Prediction Model for Three-Year Rupture Risk of Unruptured Cerebral Aneurysms in Japanese Patients

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Abstract

Objective: To build a prediction model that estimates the three-year rupture risk of unruptured saccular cerebral aneurysms.

Methods: Survival analysis using each aneurysm as the unit for analysis. Derivation data was from Unruptured Cerebral Aneurysm Study in Japan. It consists of patients with unruptured cerebral aneurysms enrolled between 2000 and 2004 at neurosurgical departments at tertiary care hospitals in Japan. The model was presented as a scoring system and aneurysms were classified into four risk grades by predicted three-year rupture risk: I, < 1%; II, 1% to 3%; III, 3% to 9%, and IV, > 9%. The discrimination property and calibration plot of the model were evaluated with external validation data. They were a combination of three Japanese cohort studies: UCAS II, the Small Unruptured Intracranial Aneurysm Verification study, and the study at Tokyo Jikei University School of Medicine.

Results: The derivation data includes 6606 unruptured cerebral aneurysms in 5651 patients. During the 11482 aneurysm-year follow-up period, 107 ruptures were observed. The predictors chosen for the scoring system were patient age, sex, and hypertension, along with aneurysm size, location, and the presence of a daughter sac. The three-year risk of rupture ranged from less than 1% to over 15% depending on the individual characteristics of patients and aneurysms. External validation indicated good discrimination and calibration properties.

Interpretation: A simple scoring system which only needs easily available patient and aneurysmal information was constructed. This can be used in clinical decision making regarding management of unruptured cerebral aneurysms.

Introduction

Unruptured cerebral aneurysms are prevalent worldwide—approximately 3 to 5 percent of the population is said to have them.[1-3] They have the potential to cause subarachnoid hemorrhage (SAH), which often results in death.[4] To circumvent this risk, the number of patients undergoing intervention on unruptured cerebral aneurysms is increasing.[5] However, these preventive treatments are not without risk; they sometimes result in neurological disability or death. Moreover, risk factors for rupture, such as larger size or location at posterior circulation, also contribute to worse treatment outcomes.[6,7] Therefore the question of whether or not to perform preventive intervention on an unruptured cerebral aneurysm at a risk of complication has always been a considerable clinical challenge.[8] A prediction model that estimates the absolute rupture risk of individual aneurysms would help direct decision making about treatment strategies for these aneurysms.

Recently, a clinically useful prediction model using comprehensive prospective cohort data from many countries was developed.[9] However, it has not undergone validation by external independent data, which is an important step toward general use of the model. It also does not account for the shape of aneurysms, which has been said to affect rupture risk.[10] It estimates the rupture risk of each patient as represented by one maximal aneurysm within the patient, although the aneurysm that ruptures is not always the largest one in the patient. Furthermore, rupture rates are different among countries; patients from some countries, most notably Japan and Finland, have a higher rate of rupture, while others experience lower rates of rupture risk.[1,11] Although differences in genetic predisposition or healthcare systems might account for the risk difference among countries, the exact reasons have yet to be elucidated. Therefore building a model for a specific country is a more conservative approach to increase the validity of a prediction model.

Our objective is to construct a prediction model with known risk factors estimating future rupture risk of each unruptured cerebral aneurysm using Japanese cohorts, and then validate this model with independent external data.

Methods

Study design

We built a prediction model that estimates three-year rupture risk of unruptured cerebral aneurysms in Japanese cohorts using Cox proportional hazard regression analysis.

Study cohorts, participants, and aneurysms

We used as data sources prospective cohort studies which were designed to follow up unruptured cerebral aneurysm in Japan.

Derivation data for constructing our model came from the Unruptured Cerebral Aneurysm Study in Japan (UCAS). UCAS consists of 5720 patients with 6697 newly diagnosed unruptured cerebral aneurysms enrolled at 283 institutions between 2000 and 2004. Patients with a modified Rankin score higher than 2 were not included. Aneurysm diagnosis was based on MR angiography, CT angiography, digital-subtraction, or conventional angiography. Follow-up data were recorded at 3, 12, and 36 months, and at 5 to 8 years if data were available. Treatment strategies depended on each patient or physician.[10]

Validation data consisted of three cohort studies: UCAS II, the Small Unruptured Intracranial Aneurysm Verification (SUAVe) study, and the study at Tokyo Jikei University School of Medicine. UCAS II is another prospective cohort study independent from UCAS. In this study, 1069 patients with unruptured aneurysms were enrolled at 31 Japanese hospitals between 2006 and 2007. UCAS II also excluded patients with a modified Rankin Score greater than 2, and employed the same aneurysm confirmation modality and treatment strategy as UCAS. The study followed up patients at 3 months, 1 year, and 6

years.[12] The SAUVe study enrolled patients at 12 Japanese hospitals between 2000 and 2004. A total of 374 patients with 478 unruptured cerebral aneurysms of a diameter less than 5mm were analyzed. Patients with a modified Rankin score higher than 2 were again excluded. Aneurysms were confirmed by MR angiography, CT angiography, or digital-subtraction angiography. Follow-up data were obtained at 6, 12, 18, 24, 30, and 36 months and then annually for at least 36 months longer. Follow-ups did not involve surgical or endovascular procedures, but aneurysms that enlarged or developed blebs during the observation were managed according to each hospital's policy [13]. At Tokyo Jikei University School of Medicine, 419 patients with 529 unruptured cerebral aneurysms were enrolled between 2003 and 2006. They received conservative management without operation and were followed every 6 months with CT angiography [14]. We combined the data from these three cohorts to validate our prediction model.

Data on individual aneurysms were collected from the cohorts with each aneurysm as the unit of analysis. We included only saccular aneurysms with a diameter of 3 mm or more and excluded fusiform or dissecting aneurysms. Aneurysms with unspecified locations were also excluded. Two institutions joined both the UCAS and SUAVe studies at the same time period. In the case where a patient in these institutions was registered in both cohorts, only the data in the UCAS study were used.

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved the research protocol.

Predictor and Outcome Variables

Predictor candidate variables consisted of characteristics of patients and aneurysms. We selected them from available variables in the cohort data by referencing to current knowledge of risk factors for aneurysm rupture. Patient characteristics were: age (years old), sex (male/female), smoking (yes/never), hypertension (yes/no), diabetes (yes/no), history of SAH (yes/no), family history of SAH (yes/no), symptomatic aneurysm (yes/no), and the number of aneurysms. Aneurysmal characteristics were size (mm), location (middle cerebral artery; anterior communicating artery; internal carotid artery; internal

carotid-posterior communicating artery; basilar tip and basilar-superior cerebellar artery; vertebral artery-posterior inferior cerebellar artery and vertebrobasilar junction; or anterior cerebral artery), and daughter sac formation (yes/no). Daughter sacs were defined as irregular protrusion of the aneurysm wall. We had two continuous variables (patient age and aneurysm size) as predictor candidates, and their linearity was evaluated using restricted cubic splines and Wald tests. We transformed these continuous variables based on graphical evaluation of the relationship between the spline functions and their linear predictors.[15]

Outcome was rupture of the aneurysm. Data were also censored at the day of either surgical or endovascular treatment, death, or the last follow-up observation.

Model specification, presentation, and validation

We performed Cox proportional hazard regression using derivation data to calculate regression coefficients and hazard ratios of the predictor variables. Because some patients had multiple aneurysms, the confidence interval of regression coefficients were calculated to account for correlation within patients.[16] Interactions between age or sex and other predictors were tested. The backwards stepwise selection method was employed to reduce the number of predictors incorporated into the final model, aiming at model simplicity and a reasonable number of events per variable.[17] The significance level for removing from the model was set at $p \geq 0.20$. Proportional hazard assumptions for each predictor variable and the final model were examined by testing Schoenfeld residuals.

We employed a scoring system to present the final model. Each predictor regression coefficient was doubled and rounded to the nearest integer. We calculated the risk of rupture within three years because this was same time period planned for follow-up in the UCAS. The mean three-year rupture risk of aneurysms with the same sum of scores and their 95% confidence intervals were calculated using the baseline survival function as below:[18,19]

$$\text{Risk estimate} = 1 - S_3^{\exp(\Sigma \beta X)}$$

where S_3 is the baseline survival function at three years which corresponds to the probability of not experiencing the rupture when all covariates are zero, β is the Cox regression coefficients, and X is the individual predictor values. We further classified aneurysms into four grades according to the predicted three-year rupture risk (Grade I, < 1%; Grade II, 1% to 3%; Grade III, 3% to 9%, and Grade IV, > 9%) and drew their Kaplan-Meier survival curve.

To measure the performance of the model, we used c index to assess discrimination properties.[20] We also evaluated calibration by plotting the predicted aneurysm rupture risk of each grade and the corresponding Kaplan-Meier estimates of three-year rupture risk. Discrimination and calibration were assessed with both derivation and validation data. All tests were two-sided, with $P < .05$ considered to indicate statistical significance. Statistical analyses were performed with Stata/IC software, version 13.1 (StataCorp LP).

Results

Participants and aneurysms

Characteristics of participants and aneurysms are summarized in Table 1A and 1B. A total of 6606 aneurysms in 5651 participants in the derivation data were eligible and analyzed for model construction. 107 ruptures were observed during a total follow-up time of 11482 aneurysm-years, and the overall rupture rate was 0.93 per 100 aneurysm-years. Among the 25 ruptures observed in patients with multiple aneurysms, 5 (20%) did not occur at the largest aneurysms in the patient. The validation data consisted of 1661 aneurysms in 1460 participants. 33 ruptures were observed during a total follow-up time of 3475 aneurysm-years, and the overall rupture rate was 0.95 per 100 aneurysm-years. Although almost all predictor variables were fully available, the SUAVe study lacked information about daughter sacs, meaning that 14.9% of the validation data on daughter sacs were missing. It also did not differentiate internal carotid-posterior communicating arteries from internal carotid arteries. To fill in the missing data, we employed single imputation method using a regression model made from the validation data.

Prediction model

As a result of linearity assessment, patient age data were dichotomized and aneurysmal size was logarithmically transformed (Fig 1A and 1B). Interactions between age or sex and other predictors were insignificant and not further considered. Hazard ratios of each predictor variable are shown in Table 2. Predictors kept in the final model by stepwise selection were age, sex, hypertension, aneurysmal size, location, and presence of daughter sac, as they all had a statistically strong association with a high possibility of rupture. Schoenfeld residual testing did not reject the proportional hazard assumption. The prediction model is presented as a scoring system in Table 3 and 4. The three-year probability of rupture corresponding to scores calculated by Table 3 is displayed in Table 4. For example, the total score for a 5mm saccular aneurysm with a daughter sac in an anterior communicating artery in a 65 year old female who has hypertension is: 0 (Size) + 1 (Daughter sac) + 3 (Location) + 0 (Age) + 1 (Sex) + 1 (Hypertension) = 6 points, which corresponds to a 3.7% estimated rupture risk in three years. Scores are classified into four grades: Grade I, 0 to 3 points; Grade II, 4 to 5 points; Grade III, 6 to 8 points; and Grade IV, 9 points or larger. The Kaplan-Meier survival curve of each grade is shown in Fig 2.

Validation of the model

As for discrimination, the c index was 0.815 for the derivation data. Calibration plotting for the derivation data indicates a strong correlation between predicted and observed probability of rupture (Fig 3). When they were assessed with an external validation dataset, the c index fell slightly to 0.803 but the calibration plot continued to show a good correlation (Fig 4). To evaluate the effect of data imputation, we performed a sensitivity analysis with a model that did not contain aneurysms with imputed predictors. The results showed similar discrimination properties and a similar calibration plot.

Discussion

We constructed an externally validated prediction model for the three-year rupture risk of unruptured cerebral aneurysms derived from Japanese prospective cohorts. Three-year rupture risk ranged from less than 1% to over 15%, depending on patient and aneurysm characteristics. Our model only contains basic characteristics of patients and aneurysms as predictor variables, thus it could be easily adopted to clinical practice. Our model also has substantial discriminatory power. Its calibration plot demonstrates a strong concordance between predicted risk and observed proportion of rupture. This is shown even in the external validation data, which warrants general use of the model. We handled each aneurysm as a unit of analysis, thereby enabling us to predict the rupture risk of each aneurysm, not of each patient. This is important because among the patients in our data with multiple aneurysms who experienced a rupture, 20% did not experience the rupture at their largest aneurysm. Some studies which analyzed rupture risk per patient reveal that multiplicity raises the risk,[4,13] but it could be explained by the cumulative risk of each aneurysm. The overall rupture risk of the patients who have two or more aneurysm would be the summation of each individual aneurysm rupture risk.

Data sources for our model were confined to Japanese cohorts. Rupture risk is higher in Japan than in other countries, with Finland being one exception.[11] The reasons for this have not been clarified, therefore our restriction can contribute toward decreasing the effects of unmeasured or unknown confounders. If we combine more heterogeneous cohorts, it can be applied to a wider population. However we must be careful in using such a model, as a model made from multiple cohorts with different rupture risk profiles would not ideally fit a particular population. We aimed at higher internal validity and generalizability to our target population by choosing homogeneous cohorts. In fact, our external validation which used independent data from the derivation data for model construction indicated a strong correlation between predicted rupture risks and observed three year rupture probabilities. Moreover, when we calculate the 5-year rupture risks of the aneurysms in UCAS II using the model previously reported by Greving et al, they tend to be lower than the observed rupture probabilities especially among Grade III and Grade IV

aneurysms, although their model accommodates Japanese high baseline rupture risk (This validation only used UCAS II as external data, because aneurysms in SUAVe and Tokyo Jikei University School of Medicine were included in the data source for their model. We set a 5-year time horizon because we can only calculate 5-year rupture risk from their model, while the time horizon for the main study is 3-year; see Fig 5). This indicates our model is more precisely calibrated and produces more accurate estimates among Japanese patients. Thus a model based on each individual population could be seen as more suitable for prediction than a model based on heterogeneous populations. Circumstances in Japan where unruptured cerebral aneurysms are rigorously investigated in cohort studies allowed this analysis. Japanese cohorts have unique characteristics regarding the detection process of unruptured aneurysms. Among our derivation data, 91% of aneurysms were not causing symptoms and were detected incidentally. This can be partly explained by the brain health check-up system (called 'brain dock') available nationwide in Japan.[21] There are around 600 accredited facilities in Japan which provide brain MRI scans to detect asymptomatic brain disease. Therefore our model would be useful in predicting the rupture risk of aneurysms identified incidentally.

In terms of patient characteristics, our model incorporated age, sex, and hypertension. Those aged 70 years and over are at a high risk of rupture in our model. Age has been pointed out as a risk factor for rupture, but both positive and negative effects have been reported.[11,13,22,23] There might be high risk aneurysms in younger populations, but our study includes less than 2% of patients below 40 years old, thus has limited power to predict rupture risk in young patient groups. In the majority of previous studies, aneurysms were identified in female patients significantly more than male patients.[1] While the exact reason for this sex predisposition is unknown, female sex was a significant predisposing factor in forming cerebral aneurysms and was also identified as a predictor that raises the probability of rupture.[11,24] Hypertension has been pointed out as a risk factor for rupture of unruptured aneurysms as well as for aneurysmal SAH in the general population.[13,25-27]

Several aneurysm characteristics were associated with rupture risk and included in our model. Larger size has frequently been shown to be a risk factor for rupture and is significantly associated with rupture in our model as well. As for aneurysm location, our results are consistent with previous findings that internal carotid artery aneurysms have a lower risk, while those of the anterior communicating artery, internal carotid-posterior communicating artery, or basilar artery have a higher risk. Our model enables estimation based on more detailed location information than previous models. Furthermore, our model contains daughter sac as a predictor. The importance of aneurysm shape on rupture risk has been increasingly demonstrated in the literature and this association is supported by both morphologic and epidemiologic studies.[10,28,29] Our model reflects this knowledge, with the presence of a daughter sac increasing the rupture risk by almost 1.5 times.

As compared to the model by Greving et al, our model lacks prior SAH as a risk factor. However, it does not seriously affect risk prediction for Japanese patients because most of the aneurysms are incidentally found at 'brain dock' and almost all of the patients do not have history of SAH in Japanese cohorts. On the other hand, only our model contains female sex and daughter sac as risk factors. Therefore their model produces lower estimates when predicting rupture risks for aneurysms associated with a daughter sac, which is found in approximately 20% of all aneurysms in Japanese cohorts, or the aneurysms in female patients, which account for two-thirds of cases. This may degrade the reliability of their model in predicting rupture risk of Japanese cerebral aneurysms.

It is clinically important to quantify each aneurysm's absolute rupture risk using prediction models. More and more aneurysms are being repaired in advance and the financial burden of treatment is also increasing.[5] In Japan, over 16000 surgical or intravascular interventions are performed on unruptured aneurysms annually.[30] We always weigh careful observation against preventive treatment when we face unruptured cerebral aneurysms in clinical practice, since aneurysm rupture could result in serious neurological dysfunction or death, while treatment such as clipping or coiling might also lead to

complications including disability.[6,7,31] Aneurysms classified as grade I in our model are considered to have minimal rupture risk, while grade IV aneurysms have substantial risk of SAH in three years. Whether interventions should be performed on grade II or III aneurysms will likely be a topic of debate. In making this decision we also account for patient preference, medical personnel expertise, environment, cost, and other factors. The ability to quantify rupture risk using the best available evidence is the first step to achieve this end.[32,33] Our results would make it possible to guide patients and medical personnel through the complex web of relevant factors.

Our model has several limitations. First, validity in populations outside Japan remains to be elucidated. The Japanese population carries around 3 times higher rupture risk compared to the populations in other countries like US, Canada, or European countries excluding Finland.[9,11] For this reason, our model prediction value would likely be higher than the true rupture probabilities in those populations, though we should await validation studies in those populations before making any definitive conclusions. In application to other populations, differences in the rupture rate and the risk factors among populations should be taken into consideration. Second, estimated rupture rates might be rather low relative to actual rates. Follow-ups were censored at the date of intervention; therefore those with a high possibility of rupture could tend to be censored. However, since evidence about rupture risk factors already exists, it would have been unethical to leave aneurysms with seemingly high risk of rupture without intervention. Furthermore, neurosurgeons can preferably treat smaller aneurysms because they have lower risks of complication accompanied by treatment.[8] As a result, this bias could be offset.

In conclusion, we constructed a scoring system which predicts three-year rupture risk of unruptured cerebral aneurysms. It contains sex, age, hypertension, size and location of aneurysm, and daughter sac as predictor variables. It is easily utilized in clinical practice to assist decision making when patients and medical staff have to confront the presence of unruptured cerebral aneurysms.

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Authorship:

A.M., N.S., Y.S., I.D., T.T., K.N., K.H., S.M., T.K., and K.H. conceived the study concept. S.T., A.M., and T.N. participated in the design of the study. A.M., T.I., T.Y., H.T., Y.M., M.S., M.Y., N.S., Y.S., I.D., T.T., K.N., K.H., S.M., T.K., and K.H. collected data. S.T. and T.N. analyzed and interpreted the data. S.T., A.M., and T.N. drafted and edited the manuscript. A.M. had full access to all the data in the study and takes responsibility of the data and the accuracy of the data analysis. All the authors have approved the final manuscript. We thank Mr. Joe Collver for manuscript editing assistance.

Potential Conflicts of Interest:

T.I. reports grants Stryker and Siemens, personal fees from Stryker, outside the submitted work. H.T. reports grants from FUJIFILM and NTT docomo, outside the submitted work. Y.M. reports grants from Stryker and Siemens, personal fees from Stryker, Asahi Intecc, and Kaneka, outside the submitted work. K.H. reports personal fees from Kanto Neurosurgical Hospital, outside the submitted work. Other authors have nothing to report.

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Figure legends

Figure 1. (A) Relationship between patient age and linear prediction. Line indicates restricted cubic spline with five knots (Wald test: P < .001). Dots indicate linear predictions of individual aneurysms based on categorization adopted in the final model. (B) Relationship between aneurysmal size and linear prediction. Line indicates restricted cubic spline with five knots (Wald test: P < .001). Dots indicate linear predictions of individual aneurysms based on logarithmic transformation adopted in the final model.

Figure 2. Kaplan-Meier Survival Estimate According to Risk Grades
Aneurysms are classified into four risk grades according to the predicted three-year rupture risk (Grade I, < 1%; Grade II, 1% to 3%; Grade III, 3% to 9%, and Grade IV, > 9%)

Figure 3. Calibration Plot for Derivation Data
Labels indicate risk grade according to Table 4.White dots indicate the relationship between mean predicted aneurysm rupture risk of each grade and corresponding observed Kaplan-Meier estimates of rupture risks with their 95% confidence intervals (vertical lines). Black dots indicate the relationship between mean predicted aneurysm rupture risk in deciles and corresponding observed Kaplan-Meier estimates of rupture risks. Diagonal dashed line indicates perfect concordance between predicted risk of rupture and observed possibility of rupture.

Figure 4. Calibration Plot for Validation Data
Labels indicate risk grade according to Table 4. White dots indicate the relationship between mean predicted aneurysm rupture risk of each grade and corresponding observed Kaplan-Meier estimates of rupture risks with their 95% confidence intervals (vertical lines). Black dots indicate the relationship between mean predicted aneurysm rupture risk in deciles and corresponding observed Kaplan-Meier estimates of rupture risks. Diagonal dashed line indicates perfect concordance between predicted risk of rupture and observed possibility of rupture.

Figure 5. Calibration plot for external validation comparing our model with the model by Greving et al. (2014)
Labels indicate risk grade according to Table 4. White dots indicate the relationship between mean 5-year aneurysm rupture risk of each grade predicted by our model and corresponding observed Kaplan-Meier estimates of rupture probabilities. Black dots indicate the relationship between mean 5-year aneurysm rupture risk of each grade predicted using the model by Greving et al. and corresponding observed

Kaplan-Meier estimates of rupture probabilities. Diagonal dashed line indicates perfect concordance between predicted risk of rupture and observed possibility of rupture.

Figure 1.

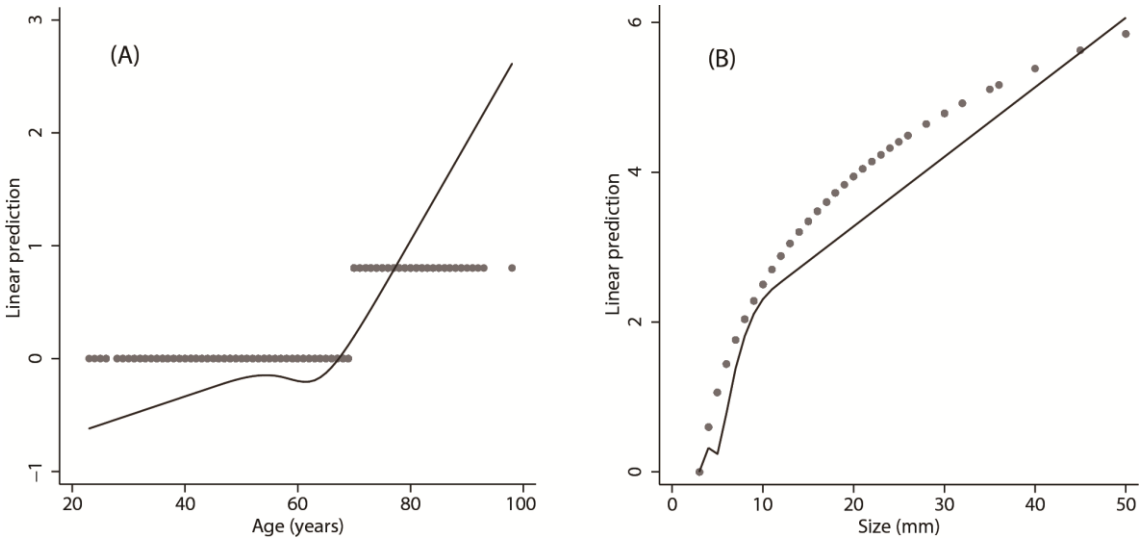
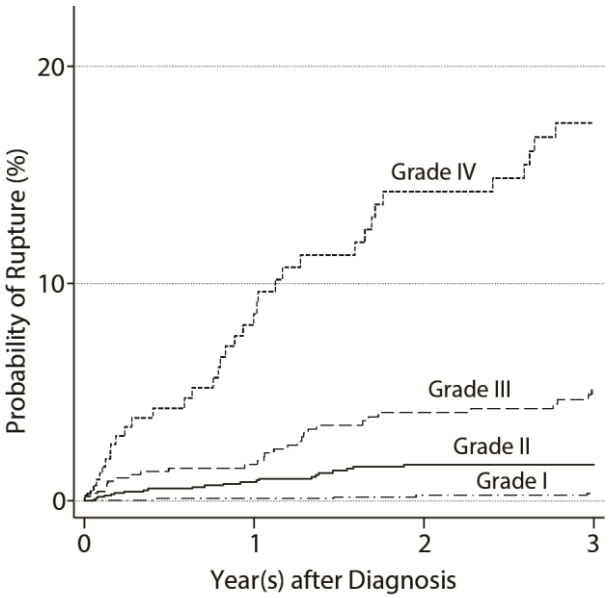


Figure 2.



No. at Risk

Grade IV	456	180	142	95
Grade III	1141	576	502	326
Grade II	2433	1229	1081	713
Grade I	2576	1348	1213	806

Figure 3.

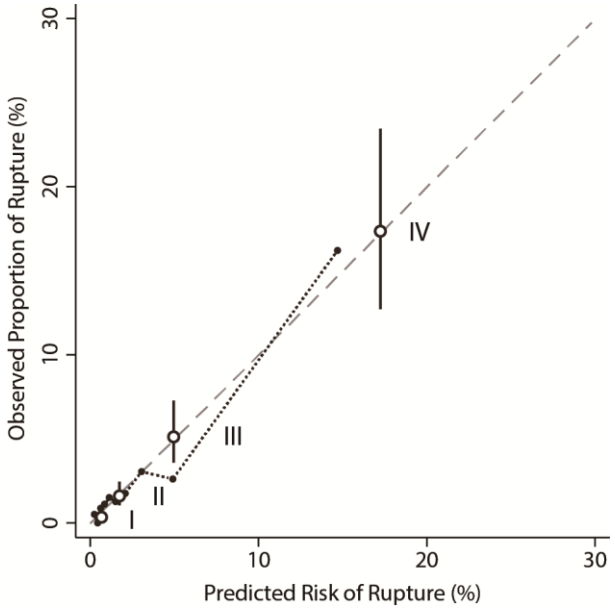


Figure 4.

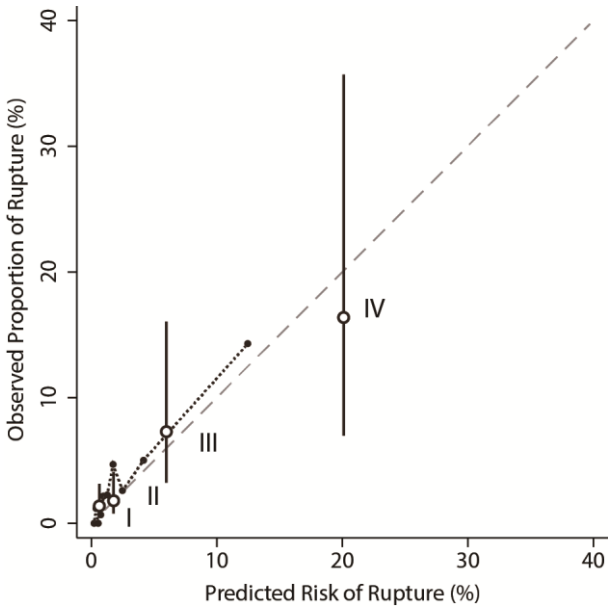
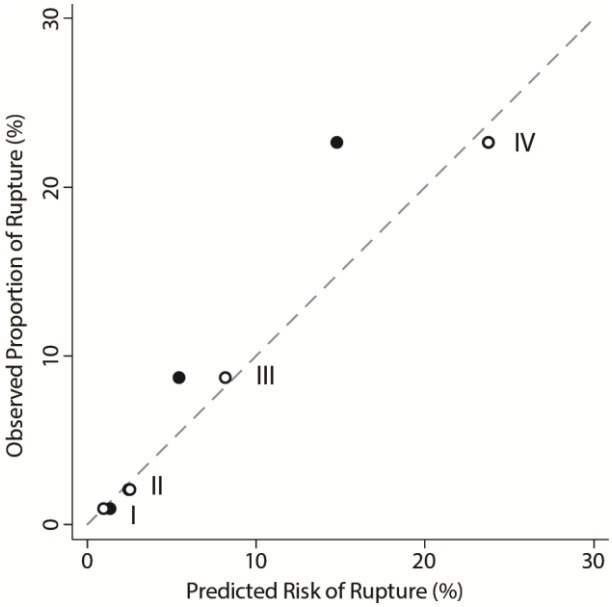


Figure 5.



Tables

Table 1A. Characteristics of Patients

	Derivation Data	Validation Data			
Characteristics	UCAS (n=5651)	UCAS II (n=921)	SUAVe (n=221)	Jikei (n=318)	Total (n=1460)
Age, mean (SD), years	62.5 (10.3)	61.6 (10.0)	62.0 (10.3)	60.8 (10.9)	61.5 (10.2)
Female, No. (%)	3759 (66.5)	619 (67.2)	139 (62.9)	215 (67.6)	973 (66.6)
Hypertension, No. (%)	2449 (43.3)	416 (45.2)	104 (47.1)	120 (37.7)	640 (43.8)
Diabetes, No. (%)	350 (6.2)	NA[a]	NA[a]	NA[a]	NA[a]
Smoking, No. (%)	950 (16.8)				
History of SAH, No. (%)	185 (3.3)				
Family history of SAH, No. (%)	731 (13.0)				
Symptomatic aneurysm, No. (%)	169 (3.0)				
Multiple aneurysms, No. (%)	777 (13.7)	117 (12.7)	26 (11.8)	32(10.1)	175 (12.0)

[a] Data for diabetes, smoking, history of SAH, family history of SAH, and symptomatic aneurysm in validation cohorts were not collected because they were not used in the final model.

SAH, subarachnoid hemorrhage; NA, not applicable.

Table 1B. Characteristics of Aneurysms

	Derivation Data	Validation Data			
Characteristics	UCAS (n=6606)	UCAS II (n=1057)	SUAVe (n=247)	Jikei (n=357)	Total (n=1661)
Size, No. (%), mm					
3 ≤ size < 7	4924 (74.5)	762 (72.1)	247 (100.0)	304 (85.2)	1313 (79.0)
7 ≤ size < 10	1003 (15.2)	209 (19.8)	0 (0.0)	24 (6.7)	233 (14.0)
10 ≤ size < 20	600 (9.1)	81 (7.7)	0 (0.0)	21 (5.9)	102 (6.1)
20 ≤ size	79 (1.2)	5 (0.5)	0 (0.0)	8 (2.2)	13 (0.8)
Location, No. (%)					
MCA	2425 (36.7)	384 (36.3)	95 (38.5)	50 (14.0)	529 (31.9)
ACOM	1037 (15.7)	158 (15.0)	30 (12.2)	46 (12.9)	234 (14.1)
ICA	1245 (18.9)	253 (22.2)	89 (36.0)	126 (35.3)	425 (25.6)[a]
IC-PCOM	1037 (15.7)	154 (14.6)		57 (16.0)	236 (14.2)[a]
BA	445 (6.7)	64 (6.1)	20 (8.1)	36 (10.1)	120 (7.2)
VA	123 (1.9)	11 (1.0)	4 (1.6)	11 (3.1)	26 (1.6)
ACA	294 (4.5)	51 (4.8)	9 (3.6)	31 (8.7)	91 (5.5)
Daughter sac, No. (%)	1256 (19.0)	258 (24.4)	NA	36 (10.1)	325 (19.6)[a]
Total follow-up time, Aneurysm-years	11482	1712	850	913	3475
Rupture, No. (%)	107 (1.6)	13 (1.2)	5 (2.0)	15 (4.2)	33 (2.0)

[a] Numbers include imputed data.

MCA, middle cerebral artery; ACOM, anterior communicating artery; ICA, internal carotid artery; IC-PCOM, internal carotid-posterior communicating artery; BA, basilar tip and basilar-superior cerebellar artery; VA, vertebral artery-posterior inferior cerebellar artery and vertebrobasilar junction; ACA, anterior cerebral artery; NA, not available.

Table 2. Results of Cox Proportional Hazard Regression Analysis

	Univariate Analysis	Multivariate Analysis
Variable	HR (95% CI)	Adjusted HR (95% CI)
70 ≤ Age, years	2.23 (1.52-3.27)	1.29 (0.88-1.89)
Female	1.36 (0.89-2.10)	1.52 (0.99-2.35)
Hypertension	1.67 (1.14-2.45)	1.29 (0.88-1.90)
Diabetes	0.86 (0.38-1.92)	Omitted[a]
History of SAH	0.94 (0.30-2.91)	Omitted[a]
Family history of SAH	0.74 (0.39-1.41)	Omitted[a]
Smoking	0.70 (0.38-1.28)	Omitted[a]
Symptomatic	4.16 (2.15-8.05)	Omitted[a]
Logarithm of Size	7.99 (6.01-10.6)	7.31 (5.34-9.99)
Location		
ICA	Reference	Reference
MCA	2.13 (0.92-4.90)	2.39 (1.03-5.56)
ACOM	4.24 (1.82-9.88)	4.25 (1.79-10.1)
IC-PCOM	5.57 (2.45-12.7)	4.25 (1.89-9.58)
BA	4.92 (2.01-12.1)	3.41 (1.40-8.27)
VA	2.74 (0.57-13.2)	1.46 (0.31-6.90)
ACA	1.33 (0.28-6.38)	1.73 (0.34-8.71)
Daughter sac	3.09 (2.07-4.61)	1.48 (0.98-2.24)
Multiple aneurysms	0.82 (0.52-1.28)	Omitted[a]

[a] Omitted as a result of stepwise selection.

HR, hazard ratio; ICA, internal carotid artery; MCA, middle cerebral artery; ACOM, anterior communicating artery; IC-PCOM, internal carotid-posterior communicating artery; BA, basilar tip and basilar-superior cerebellar artery; VA, vertebral artery-posterior inferior cerebellar artery and vertebrobasilar junction; ACA, anterior cerebral artery.

Table 3. Scores for Rupture Risk Factors

Risk Factor	Score
Age, years	
< 70	0
70 ≤	1
Sex	
Male	0
Female	1
Hypertension	
No	0
Yes	1
Size, mm	
3 ≤ size < 7	0
7 ≤ size < 10	2
10 ≤ size < 20	5
20 ≤ size	8
Location	
ICA	0
ACA or VA	1
MCA or BA	2
ACOM or IC-PCOM	3
Daughter sac	
No	0
Yes	1

ICA, internal carotid artery; ACA, anterior cerebral artery; VA, vertebral artery-posterior inferior cerebellar artery and vertebrobasilar junction; MCA, middle cerebral artery; BA, basilar tip and basilar-superior cerebellar artery; ACOM, anterior communicating artery; IC-PCOM, internal carotid-posterior communicating artery.

Table 4. Three-Year Probability of Rupture Corresponding to Sum of Scores from Table 3

Sum of Scores	Probability of Rupture in Three Years, % (95% CI)	Grade (Predicted Risk)
0	0.2 (0.2-0.3)	I (< 1%)
1	0.4 (0.2-0.7)	
2	0.6 (0.2-1.5)	
3	0.9 (0.2-2.4)	
4	1.4 (0.5-3.8)	II (1% to 3%)
5	2.3 (0.8-6.3)	
6	3.7 (1.3-10)	III (3% to 9%)
7	5.7 (2.1-16)	
8	7.6 (2.7-21)	
9≤	17 (6.4-40)	IV (> 9%)