Development and Internal Validation of the ARISE Prediction Models for Rebleeding After Aneurysmal Subarachnoid Hemorrhage

**BACKGROUND:** Aneurysmal rerupture is one of the most important determents for outcome after aneurysmal subarachnoid hemorrhage and still occurs frequently because individual risk assessment is challenging given the heterogeneity in patient characteristics and aneurysm morphology.

**OBJECTIVE:** To develop and internally validate a practical prediction model to estimate the risk of aneurysmal rerupture before aneurysm closure.

**METHODS:** We designed a multinational cohort study of 2 prospective hospital registries and 3 retrospective observational studies to predict the risk of computed tomography confirmed rebleeding within 24 and 72 hours after ictus. We assessed predictors with Cox proportional hazard regression analysis.

**RESULTS:** Rerupture occurred in 269 of 2075 patients. The cumulative incidence equaled 7% and 11% at 24 and 72 hours, respectively. Our base model included hypertension, World Federation of Neurosurgical Societies scale, Fisher grade, aneurysm size, and cerebrospinal fluid drainage before aneurysm closure and showed good discrimination with an optimism corrected c-statistic of 0.77. When we extend the base model with aneurysm irregularity, the optimism-corrected c-statistic increased to 0.79.

**CONCLUSION:** Our prediction models reliably estimate the risk of aneurysm rerupture after aneurysmal subarachnoid hemorrhage using predictor variables available upon hospital admission. An online prognostic calculator is accessible at [https://www.evidencio.com/models/show/2626](https://www.evidencio.com/models/show/2626).

**KEY WORDS:** Aneurysmal subarachnoid hemorrhage, Intracranial aneurysm, Rerupture, Clinical prediction model

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METHODS

Study Design and Data Source

We assembled a multinational data set of patients with aSAH from 2 prospective hospital registries and 3 retrospective observational studies. The cohort included patients from prospective observational databases from the neurovascular centers from the Radboud University Medical Center Nijmegen (center 1, from January 2012 to January 2016) and Groningen University Medical Center (center 2, from January 1998 to January 2018). The retrospective observational studies come from data sets from the University Medical Center Düsseldorf (center 3, from January 2012 to January 2016), the University Medical Center Ljubljana (center 4, from January 2012 to January 2020), and the Charité University Hospital Berlin (center 5, from January 2012 to January 2017). The data set was designed to meet the conventional sample size recommendations of at least 10 to 20 events per candidate predictor variable.12 The institutional review boards approved this study and confirmed that the Medical Research Involving Human Subjects Act does not apply and that patient consent is not required. Study numbers: 2018-4939, 21.394324, 5361, EA2/230/19, and 0120-190/2018/23.

Guidelines and Data Availability

The clinical prediction model generation was in accordance to recent methodology, with reporting according to the transparent reporting of multivariable prediction model for individual prognosis or diagnosis guidelines.12-15 The data that support the findings of this study are available from the corresponding author on reasonable request.

Variable Selection

Based on the results from earlier studies, meta-analysis, and subject matter knowledge, we selected the following predictor variables that are assessable early at hospital admission and are consistently associated with outcomes for inclusion in the prediction models.2-5

Patient Characteristics

Data on patient sex, age, arterial hypertension, and clinical severity as assessed by the nonresuscitated World Federation of Neurosurgical Societies (WFNS) scale (5 category ordinal scale) at admission were included. We defined arterial hypertension as systolic blood pressure over 160 mm Hg upon admission, irrespective of pain or intracranial pressure. We retrieved the data from the patient chart.

Radiological Characteristics

Volume of subarachnoid hemorrhage on computed tomography (CT) on admission, measured by the Fisher grade (we scored thick subarachnoid hemorrhage with intracerebral or intraventricular hemorrhage as Fisher grade IV); size of the ruptured aneurysm in mm; aneurysm irregularity dichotomized into regular or irregular (ie, presence of blebs, multiple lobes or aneurysm wall protrusions) were included. Aneurysm size and irregularity as determined by local radiologists were also included.

Surgical Intervention

Cerebrospinal fluid (CSF) diversion by placement of an external ventricular or lumbar drain. The indication of CSF diversion was made by the treating physician.

Outcome Measure

We defined aneurysmal rebleeding as “CT-confirmed episodes of pre-treatment rebleeding in which any neurological deterioration or otherwise clinical suspicious events in comatose patients, such as bradycardia, sudden rise in blood pressure, or the appearance of fresh blood through ventricular drainage, prompted radiological imaging and showed an increase in blood on CT as determined by the radiologist.”16 Time to aneurysm rerupture was defined as the interval between ictus and aneurysm rebleeding.

We imputed scores for aneurysmal rerupture for 24 hours and 72 hours after ictus.

Data Collection and Statistical Analysis

We thoroughly checked all data for consistency. A few issues were queried with the responsible investigator, and all were resolved. For continuous data, we show means, standard deviations, and ranges. For categorical data, we used counts and percentages.

Model Development

The mixed-effects Cox regression was used to develop a clinical prediction model estimating aneurysmal rebleeding before aneurysm closure. Patients who received treatment for aneurysm closure were considered censored. Age and aneurysm size were kept as continuous predictor variables in the analysis to avoid loss of prognostic information.17,18 In addition, we explored nonlinearity for the association of age and aneurysm size with aneurysmal rebleeding using restricted cubic splines.17,19 Missing values were assumed to be missing at random, and multiple imputation was performed using the multiple imputation by chained equations algorithm.17,20 Missing values were imputed 5 times; we performed statistical analyses on the 5 imputed data sets and pooled the results using the Rubin rules. The modeling procedure consisted of 2 models: a base model and an extended model adding aneurysm irregularity to the base model. We estimated hazard ratios with 95% CIs as measures for association of the predictor variables with aneurysmal rebleeding.

Model Performance

The quality of the prediction model was assessed by evaluating discrimination and clinical utility.12 The Harrell concordance statistic (c-statistic) was used to quantify the discriminative ability.17,21 The model discrimination indicates how well the constructed prediction model classifies between those with and those without aneurysmal rebleeding. An uninformative model will have a c-statistic of 0.5, whereas a model with perfect discrimination will have a c-statistic equaling 1.0.17 The c-statistic for prognostic models typically ranges from 0.60 to 0.85.22 In addition, the clinical utility of the prediction model was quantified using decision curve analysis. Decision curves graph the net benefit of using the prediction model for decision making against various relevant risk thresholds. The net benefit is conveyed in units of true positives per person and calculated by the difference in benefits (true-positive results) and costs (false-positive results), weighted by the relative harms and benefits. The net benefit of the developed prediction models is compared with each other and to 2 default treatment strategies: intervention for all and intervention for none.

Model Validation

We developed the models using all available data from the cohorts. The internal validation from our models was analyzed with the bootstrapping procedure (1000 samples), and we calculated the optimism-corrected model performance measures.13 We refrained from an internal-external cross-validation procedure because of the low event rate in most individual patient cohorts.
Model Presentation
Using nomograms, an individual patient’s rebleeding probability was predicted at 24 hours and 72 hours after ictus. We used R software version 3.5.2 (R Foundation for Statistical Computing) for all descriptive and prediction modeling analyses. The significance level was set at 5% for all analyses.

RESULTS
Study Population
After imputation, the combined patient cohorts included 2075 complete cases and 269 rebleeding events before aneurysm closure. The median patient age was comparable across the different centers, ranging from 52 to 56.5 years. Approximately two-thirds of the patients were female. Table 1 shows the distributions of predictor variables in the 5 centers, including the number of missing data per predictor. For two-thirds of the patients, data on aneurysmal irregularity were not available. To address this, we have performed a sensitivity analysis restricted to patients with an observed value for aneurysm irregularity and observed similar results compared with estimating a model using all patients (data not shown).

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<th>3 (N = 194)</th>
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<th>5 (N = 113)</th>
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<td>Time (h)</td>
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<td>16.3 (8.50, 38.0)</td>
<td>15.0 (6.00, 24.0)</td>
<td>5.00 (2.4, 24.1)</td>
<td>3.00 (9.00, 64.0)</td>
<td>29.0 (13.8, 72.0)</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; WFNS, World Federation of Neurosurgical Societies.

*Irregularity is completely missing for center 2. The P-value is calculated excluding center 2.

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time of ictus (Supplemental Digital Content [S3], Figure, http://links.lww.com/NEU/D209).

**Model Development**

Age and aneurysm size could be modeled well assuming a linear association. Age, patient sex, and hypertension were predictors with a relative minor impact in the prediction model (Table 2). Because of a low number of patients in the WFNS 3 and Fisher 1 categories, we merged these patient groups with the WFNS 2 and Fisher 2 categories, respectively. High WFNS scores at admission were statistically significantly associated with aneurysmal re-bleeding. Similarly, patients with greater volumes of subarachnoid...
hemorrhage on admission CT and patients with a larger aneurysm size and those in need of acute CSF diversion before aneurysm closure were found to be at higher risk of rebleeding. The direction of the predictor effects was the same for the extended prediction model, which showed a significant predictor effect for aneurysm irregularity (hazard ratio = 2.73 [1.44-4.15], Table 2).

**Model Performance and Internal Validation**

The apparent c-statistics of the developed prediction models were promising with the extended model having the highest discriminative ability: c-statistic 0.80 and optimism corrected c-statistic 0.79. Bootstrapping identified a heuristic shrinkage factor of 0.95 and 0.94 for the base model and extended model, respectively (Table 2).

Sensitivity analysis (leaving out center 2 from the model development) showed that the coefficients of the predictor variables were in the same direction and, overall, were largely unchanged (data not shown). The calibration plot shows that the agreement between the observed and predicted rebleeding rates is satisfactory (Supplemental Digital Content [S4], Figure, http://links.lww.com/NEU/D209).

**Assessment for Clinical Utility**

Figure 2 shows the net benefit gain for the 2 models compared with default strategies. The net benefit (number of true positives — odds of the risk threshold x false positives) is calculated across a range of threshold probabilities. If the net benefit is higher compared with the default strategies, a strategy to identify high-risk patients using the model is better.23 The developed prediction models had greater net benefit than the default strategies at threshold probabilities roughly ranging from 5% to 35%.

**Model Presentation**

We developed nomograms for the base and extended model to predict an individual patient’s risk for several time periods (Figures 3 and 4). In addition, we created an online prognostic calculator based on the model algorithms including error margins (95% CI for prediction). It is accessible at https://www.evidencio.com/models/show/2626, Supplemental Digital Content (S5), Table. http://links.lww.com/NEU/D209, provides the baseline hazard and predictor coefficients for the different models to allow for independent external validation studies.

**DISCUSSION**

**Key Results**

We have developed prediction models for Aneurysmal Rebleeding after Subarachnoid Hemorrhage (ARISE), based on predictor items assessable upon hospital admission. The models predict the risk of rebleeding within 24 or 72 hours after ictus and show a good performance; the optimism-corrected c-statistic for internal validation for the base and extended model is 0.77 and 0.79, respectively.

By pooling data from 5 cohort studies, we were able to include 2075 patients of whom 269 suffered aneurysmal rerupture. Our risk score comprises well-established risk factors for aneurysm rebleeding and includes hypertension, WFNS scale, Fisher grade,
aneurysm size, CSF drainage before aneurysm closure, and aneurysm irregularity.

**Limitations**

Clinical documentation in the cohorts was accurate. Nevertheless, data values from our database were missing, most notably for aneurysm irregularity, which we used to develop the extended model. However, the multiple imputation by chained equations algorithm is a widely used method to address missing data, and the sensitivity analysis yielded comparable results. The extended model represents a slight improvement over the base model. However, the base model could be used to eliminate this uncertainty.

In addition, inter-rater reliability could influence baseline characteristics of patients with aSAH such as aneurysm size or irregularity. Differences in local treatment protocols can lead to diverse indications for CSF diversion. Another possible source of bias is the different time epochs between the cohorts as critical care, and blood pressure management protocols have evolved over time. We cannot rule out that we have missed or wrongly classified some instances of aneurysmal rebleeding. Such misclassification might have resulted in less accurate predictions, and the overall risk of rebleeding might be higher if events have been missed. In practice, timing of treatment may be influenced by a number of factors that may also affect outcome, such as their time of hospital admission. However, the analysis could not detect a selection bias based on the time of hospital admission; this type of bias might confound the risk estimation of re-rupture. Similarly, the time between ictus to aneurysm repair confounds the risk of rebleeding.

Our cohort represents a large series of patients in whom timing of treatment was as recommended by both the European and American guidelines. Moreover, our study could not control for the proportion of individuals who suffered aneurysmal rebleeding or died from such before hospital admission.

**Interpretation**

It remains uncertain which patients are most likely to benefit from early treatment. Although it is suggested that early aneurysm repair (<24 hours) reduces the likelihood of poor outcome, no benefit has been found for treatment <24 hours compared with treatment within 48 or 72 hours.1,1 Moreover, some studies suggest possible harm from early treatment.7,24 The models show a discrimination similar to established clinical prediction models.25,26 Our prediction models can serve to (1) provide clinicians with an indication of those patients at increased risk of aneurysmal rerupture. The prediction models are developed for the first 24 and 72 hours after aneurysm rupture, but this risk cannot be extrapolated over the further clinical course because the risk of rebleeding is not constant over time. However, because most events take place early after ictus, the clinical significance of later rebleeding prediction is low.1 In addition (2), the models can identify patients for a new study on the timing of aneurysm repair to classify those patients for whom the benefits of emergency aneurysm closure might outweigh the potentially increased risks of emergency aneurysm treatment.

However, before further clinical application, eg, defining a threshold for decision making and use in clinical guidelines, it is essential that future efforts empirically evaluate the predictive performance of our prognostic prediction model in data sets that
were not used to develop the model. Internal validation, even with bootstrapping, will likely overestimate the power of our model. Furthermore, evidence must be provided that the use of the decision rule based on the prediction model leads to benefits in rebleeding rates and improved patient outcome in comparison with the current standard of care.

**FIGURE 3.** Nomogram for the base model to predict an individual patient’s risk for aneurysmal rerupture before treatment for 24 and 72 hours after ictus. To use the nomogram, first give each variable a score on its points scale. Then, add the scores for all variables to obtain the total score and draw a vertical line from the total point row to estimate the 24-hour and 72-hour rebleeding risk. CSF, cerebrospinal fluid; WFNS, World Federation of Neurosurgical Societies.

**FIGURE 4.** Nomogram for the extended model, to predict an individual patient’s risk for aneurysmal re-rupture prior to treatment for 24 and 72 hours after ictus. To use the nomogram, first give each variable a score on its points scale. Then, add the scores for all variables to obtain the total score and draw a vertical line from the total point row to estimate the 24-hour and 72-hour rebleeding risk. CSF, cerebrospinal fluid; WFNS, World Federation of Neurosurgical Societies.
Generalizability

The predictors in our model are well defined and easily determined upon admission. The cohort contains a relatively large number of patients from which the model was derived, indicating sufficient power and includes patients from several different countries, which may improve the external validity. However, clinical integration should not be considered until the ability to produce accurate predictions among patients drawn from different, but related, populations is verified in one or more external validation studies.

CONCLUSION

Our prediction model for aneurysmal rebleeding within 24 and 72 hours after ictus provides the clinician with a good starting point for clinical decision making on timing of aneurysm repair and an evidence-based approach for patient selections in future trials. Routine clinical integration should not be considered until its accuracy is verified in external validation studies.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES


Supplemental digital content is available for this article at neurosurgery-online.com.

Supplemental Digital Content (S1). Table. Patient characteristics. Patient population stratified by time of aneurysm closure after ictus.

Supplemental Digital Content (S2). Figure. Cumulative event rate. Aneurysmal rerupture in hours after ictus stratified according to the respective medical center.

Supplemental Digital Content (S4). Figure. Timing of treatment. Distribution of delay (hours) between ictus and aneurysm closure during the day (24 hours total), stratified according to medical center.

Supplemental Digital Content (S4). Figure. Calibration plots for the base and extended model. The plots show the observed outcomes vs the predicted outcomes. The dotted line shows the line of perfect calibration. The open dots indicate the actual outcome (probability of rebleeding) by deciles of risk. The vertical lines correspond to the 95% CI.

Supplemental Digital Content (S5). Table. Predictors for the base and extended model. Coefficients and baseline hazards of the prediction models.

COMMENTS

The authors developed the Aneurysmal Rebleeding after Subarachnoid hEmorrhage prognostic model to predict aneurysm rebleeding after SAH within the first 24 and 72 hours using a multinational study sample of 2075 patients emanating from both prospectively-maintained and
retrospective registries. The predictive factors are relatively well-described in previous natural history studies and include hypertension, World Federation of Neurosurgical Societies Scale, Fisher grade, aneurysm size, cerebrospinal fluid diversion, and aneurysm irregularity. The model was able to achieve good discrimination and acceptable calibration and has the potential to provide clinical utility if external validation is achieved. The authors have also incorporated the model into an online web-based platform, which will greatly facilitate subsequent validation efforts by outside investigators and potentially clinical adoption once external validity is confirmed. As the study utilized a multinational cohort of aneurysm patients, a greater likelihood of model generalizability is expected.

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The authors aim to predict the risk for the early cerebral aneurysm re-rupture in relation to specific patient profiles at the time of their hospital admittance. However, should we also discuss the model’s relation to the patient-specific prognosis. Should we urgently treat the poorest grade patients with highest grade SAH potentially also having a higher risk for re-rupture? For such patients, one may argue that it is reasonable to do a short conservative follow-up at the ICU and proceed to invasive treatment only if relevant clinical improvement is noted. Therefore, treating the aneurysm or the patient is also worth a discussion. The general recommendations based a randomized studies already in the late 80s favor early procedures to prevent early re-bleedings and should be readily available in dedicated tertiary neurovascular units. Preferably, the treatment should be provided in less than 24 hours if not already during the same day of ictus. The endovascular era together with the general recommendation to centralize expertise means that more and more ruptured aneurysms are treated by endovascular means, and this should also be done even during the late hours. One may ask if it would be worthwhile to reduce some hours from the patients’ waiting time and what would that affect in contrast to minimizing errors in diagnostics, and referral/transportation delays, and optimizing the preprocedural treatment at the intensive care unit. In a single patient but also in larger series improving accuracy and effectiveness in all these details must have a positive effect in the outcome.

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