Early Prediction of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage
Development and Validation of a Practical Risk Chart

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Background and Purpose—To develop and validate a risk chart for prediction of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage based on admission characteristics.

Methods—For derivation of the risk chart, we studied data from 371 prospectively collected consecutive subarachnoid hemorrhage patients with a confirmed aneurysm admitted between 1999 and 2007. For its validation we similarly studied 255 patients admitted between 2007 and 2009. The predictive value of admission characteristics was tested in logistic regression models with delayed cerebral ischemia–related infarction as primary outcome. Procedure-related infarctions were not included. Performance of the models was tested by discrimination and calibration. On the basis of these models, a risk chart was developed for application in clinical practice.

Results—The strongest predictors were clinical condition on admission, amount of blood on computed tomography (both cisternal and intraventricular) and age. A model that combined these 4 predictors had an area under the receiver operating characteristic curve of 0.63 (95% confidence interval, 0.57–0.69). This model improved little by including current smoking and hyperglycemia on admission (area under the receiver operating characteristic curve, 0.65; 95% confidence interval, 0.59–0.71). The risk chart predicted risks of delayed cerebral ischemia–related infarction varying from 12% to 61%. Both low risk (<20% risk) and high risk (>40% risk) were predicted in ≈20% of the patients. Validation confirmed that the discriminative ability was adequate (area under the receiver operating characteristic curve, 0.69; 95% confidence interval, 0.61–0.77).

Conclusions—Absolute risks of delayed cerebral ischemia–related infarction can be reliably estimated by a simple risk chart that includes clinical condition on admission, amount of blood on computed tomography (both cisternal and intraventricular), and age. (Stroke. 2013;44:00-00.)

Key Words: delayed cerebral ischemia • infarction • prediction • predictor • subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage (SAH) often leads to infarctions that are a major contributor to the high case fatality and morbidity of SAH, and occurs in about one third of the SAH patients.1 Established predictors of DCI are large amounts of subarachnoid blood and poor clinical condition on admission;2–4 other potential predictors are current smoking, diabetes mellitus, presence of hyperglycemia on admission, hydrocephalus on admission, or early systemic inflammatory response syndrome.5 Previous prediction models for DCI after SAH are impractical in daily practice or not confined to data present at admission, and most are not validated.6–8 Furthermore, a risk prediction chart does not exist.

We aimed to develop and validate prognostic models based on admission characteristics to predict the risk of DCI-related infarction and to construct a risk chart that can easily be used in clinical practice. In addition, we also evaluated the risk chart for clinical deterioration owing to DCI.

Methods

Study Population
All patients were derived from the prospectively collected cohort of SAH patients admitted to our hospital. The development cohort originated from a previously described study population of patients admitted between January 1999 and June 2007.9 Three-hundred seventy-one patients met the following inclusion criteria (1) SAH confirmed by computed tomography (CT) or lumbar puncture; (2) aneurysm proven by means of CT/MR- or catheter angiography; (3) admitted within 3 days after onset; (4) at least 1 follow-up scan performed ≥24 hours after the initial scan; (5) initial CT scan available for review; (6) absence of a large intracerebral hemorrhage
with surrounding hypodensity; and (7) survival of the first 4 days after onset of SAH. The validation cohort consisted of 255 patients from the same prospectively collected cohort admitted between June 2007 and December 2009. The inclusion criteria were similar, except that patients with a large intracerebral hemorrhage were not excluded.

In the derivation cohort, the proportion of patients that could not be included because of lack of follow-up imaging was 27% compared with 8% in the validation cohort, and the proportion of patients that could not be included because of lack of the initial data was 9% compared with 3% in the validation cohort.

Delayed Cerebral Ischemia
The primary outcome measure in both cohorts was DCI-related infarction. This was assessed by 2 authors independently (N.K. de Rooij and C.J.M. Frijns) and defined as new spontaneous ischemic lesions on at least 1 follow-up scan. Only spontaneous infarctions (ie, not related to clipping or coiling of the ruptured aneurysm) within 28 days after SAH were included. Lesions caused by extraventricular drains, preexisting infarcts, and hypodensities around a hematoma or in the vicinity of the operation area were also not considered as new infarctions. Infarctions were considered to be related to treatment if new neurological symptoms occurred directly after aneurysm treatment, and an infarct was visible in the territory of the parent vessel of the aneurysm on CT within 48 hours after treatment. In case the time of development of infarction was uncertain (ie, if a new infarction was present on CT >48 hours after treatment, and the neurological state of the patient directly after treatment could not be assessed owing to sedative medication), an expert opinion was made by 2 of the authors. In this expert opinion the report of the operation or endovascular treatment was taken into account. In case of disagreement, the infarction was not counted as spontaneous infarction.

In the validation cohort, we additionally assessed clinical deterioration owing to DCI as secondary outcome measure. It was defined as decreased Glasgow coma scale of at least 2 points lasting >2 hours or a new focal deficit with exclusion of other causes (rebleed, hydrocephalus, epilepsy, metabolic, or infectious causes) and was assessed by the same 2 authors independently.

Data Collection
The following admission data were recorded: age, sex, current smoking status, history of hypertension, history of cardiovascular disease (including stroke, myocardial infarction, and peripheral vascular disease), diabetes mellitus, presence of any loss of consciousness, clinical condition on admission, amount of blood on CT, presence of enlarged ventricles on CT, and blood levels for glucose and hemoglobin. Restricted cubic spline functions and graphs were used to determine whether continuous variables (age, glucose, and hemoglobin) could be analyzed as linear terms or required transformation. Missing values of patient characteristics were imputed by means of regression imputation. Logistic regression analysis was performed with DCI-related infarction as outcome variable. All candidate predictors were included in a multivariable logistic regression model (irrespective of their univariate association with DCI) and were excluded step by step if the Wald test had a P value of >0.20.

Model Performance
We evaluated both discrimination and calibration of the 3 models. The discriminative performance was described by an area under the receiver operating characteristic curve (AUC) with a corresponding 95% confidence interval (CI). Calibration was assessed with the Hosmer and Lemeshow test and visually with a calibration plot, plotting the observed outcomes versus predicted risks over quintiles of risks.

Internal Validation
We internally validated our model with bootstrapping techniques where in each bootstrap sample the entire modeling process was repeated to correct for overestimation. This resulted in a shrinkage factor for the regression coefficients. The bootstrap procedure was also used to assess the AUC corrected for overoptimism. The corrected AUC may be considered as an estimate of discriminative ability expected in future similar patients.

Model Presentation
On the basis of these risk prediction models, we constructed a risk chart displaying absolute risks of DCI-related infarction in SAH patients according to the absence or presence of the independent predictors. Also, we classified our patients into 3 risk groups of DCI-related infarction: low risk (<20%), average risk (20%–40%), and high risk (>40%) and represented the risk classification in a color scheme.

Validation
We evaluated both discrimination and calibration of the risk chart in the validation cohort and assessed the number of patients with low or high risk of DCI-related infarction. In addition, we performed similar analyses with the second outcome measurement (clinical deterioration owing to DCI) to assess whether our risk chart was also useful for prediction of clinical DCI.

Results
The baseline data of the development and validation cohorts are presented in Table 1. DCI-related infarction occurred in 110 patients (30%) of the development cohort and 52 patients (20%) of the validation cohort. In the validation cohort, clinical deterioration owing to DCI occurred in 57 patients (22%).

Prognostic Models
The multivariable models for prediction of DCI-related infarction are presented in Table 2. The strongest predictors were clinical condition on admission (WFNS), amount of cisternal and intraventricular blood on CT, and age. For the combination of these 4 predictors (model I), the AUC after correction for optimism was 0.63 (95% CI, 0.57–0.69). Adding smoking and hyperglycemia (model II) contributed little, the
AUC after correction for optimism was 0.65 (95% CI, 0.59–0.71). Model III had no additional predictive value. Receiver operating characteristic curves and calibration plots for model I and II are given in Figure 1. Hosmer and Lemeshow tests were nonsignificant (P = 0.377 in model I, and P = 0.548 in model II).

**Risk Chart**

Because the first model had almost the same discriminatory performance as the second model (AUC 0.63 versus 0.65 with overlapping 95% CIs), we developed a risk chart on the basis of the first model with 4 instead of 6 variables. The risks of

| Table 1. Baseline Characteristics of the Participants In the Development and Validation Cohort |
|-----------------------------------------------|-----------------------------------------------|
| Year of admission to our hospital           | Development Cohort                             |
|                                               | Validation Cohort                              |
| No. of patients                              | January 1999–June 2007                        |
|                                               | June 2007–December 2009                       |
| Mean number of patients per year (range)     | 371                                           |
| DCI-related infarction                        | 102 (86–99)                                   |
| Clinical deterioration caused by DCI         | 52 (20%)                                      |
| Women                                        | Not registered                                |
| Age, median years (range)                    | 55 (18–85)                                    |
| History of hypertension                      | 102 (27%)                                     |
| History of vascular disease                  | 53 (14%)                                      |
| History of diabetes mellitus                 | 16 (4%)                                       |
| Current smoking                              | 193 (52%)                                     |
| Glucose on admission: median (range), mmol/L  | 7.4 (3.6–22.5)                                |
| Clinical condition on admission: WFNS scale  | 7.2 (3.7–15.8)                                |
| I: GCS, 15                                   | 149 (40%)                                     |
| II: GCS, 13–14 without focal deficit         | 88 (24%)                                      |
| III: GCS, 13–14 with focal deficit           | 30 (8%)                                       |
| IV: GCS, 7–12                                | 53 (14%)                                      |
| V: GCS, 3–6                                  | 51 (14%)                                      |
| Amount of blood: modified Fisher 0 and 1: No/Thin SAH and no IVH | 29 (8%)                                      |
| 2: Thin SAH with IVH                          | 18 (5%)                                       |
| 3: Thick SAH and no IVH                      | 111 (30%)                                     |
| 4: Thick SAH with IVH                        | 213 (57%)                                     |
| Amount of blood: Hijdra scale                |                                               |
| Hijdra Cisternal, median (range)             | 24 (0–30)                                     |
| Hijdra Ventricles, median (range)            | 24 (0–12)                                     |
| Site of the aneurysm                          |                                               |
| Posterior communicating artery               | 88 (24%)                                      |
| Internal carotid artery                       | 18 (5%)                                       |
| Medial cerebral artery                        | 49 (13%)                                      |
| Anterior communicating artery                | 143 (39%)                                     |
| Pericallosa artery                            | 10 (3%)                                       |
| Basilar or vertebral artery                  | 44 (12%)                                      |
| Posterior inferior cerebral artery            | 11 (3%)                                       |
| Other                                         | 8 (2%)                                        |
| Treatment of the aneurysm                    |                                               |
| No treatment                                  | 47 (13%)                                      |
| Coiling                                       | 142 (38%)                                     |
| Clipping                                      | 182 (49%)                                     |
| Other treatment (stent, embolization)         | 0 (0%)                                        |

DCI indicates delayed cerebral ischemia; GCS indicates Glasgow coma scale; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; and WFNS, World Federation of Neurological Surgeons Scale.

*Missing data in 10% of the patients.
developing DCI-related infarction ranged from 12% in an older patient with good clinical condition on admission (WFNS I), and no or thin amount of cisternal and intraventricular SAH on the initial CT, to 61% in a younger patient with poor clinical condition on admission (WFNS V), and large amounts of cisternal and intraventricular blood on the initial scan (Figure 2). A low risk of DCI-related infarction was predicted in 87 patients (23%), an average risk in 203 patients (55%), and a high risk in 81 patients (22%).

Validation
The AUC for the risk chart in the validation group was 0.69 (95% CI, 0.61–0.77) for DCI-related infarction (Figure 3A), and 0.66 (95% CI, 0.58–0.74) for clinical deterioration owing to DCI. Outcomes in the validation cohort were systematically better than those predicted ( Hosmer and Lemeshow test was P=0.003; Figure 3B). For clinical deterioration owing to DCI, the overestimation of the risk chart was slightly lower than for DCI-related infarction (data not shown). A low risk of DCI-related infarction was predicted in 55 patients (22%), an average risk in 203 patients (55%), and a high risk in 42 patients (16%; Table 3).

Discussion
We developed a practical risk chart to predict absolute risks of DCI in individual patients with SAH, based on 4 predictors that can easily be retrieved on admission. The model categorizes ≈20% of the patients to have a low risk (<20% risk) and another 20% to have a high risk of DCI (>40% risk). Validation confirmed that the discriminative ability was adequate (AUC, 0.69).

The largest amount of prognostic information consisted of a set of 4 predictors: clinical condition on admission, amount of cisternal and amount of intraventricular blood on CT, and age. A recent study found exactly the same predictors (good clinical condition on admission, small amounts of extravasated blood, and older age) to be associated with a low risk of DCI. However, because the authors chose to predict 100% absence of
DCI risk, the cut-off points needed for that prediction applied to only 12 (4%) of their 307 patients. Another study reported thickness of clot, high flow on transcranial Doppler, clinical condition (Glasgow coma scale<14), and ruptured aneurysm in the anterior and carotid circulation as main predictors. The definition of DCI used was ambiguous (including clinical symptoms like headache, stiff neck, or low-grade fever as symptoms of DCI), and it was not possible to make a prediction on admission, because also transcranial Doppler measurements until day 5 were included in the model. In a small series of 68 patients, a high AUC of 0.90 was found, but this model included technical demanding factors (ie, Lindegaard ratio using cerebral blood flow evaluation with Xenon clearance technique) that are not commonly available in SAH patients. In yet another study, the authors designed an artificial neural network. From the 15 variables included in their model, the majority was similar to our study variables, but they also added variables that were not yet available on admission, like elevated transcranial Doppler velocities until day 5, aneurysm treatment modality, and ventricular drainage. They found an extremely high AUC of 0.96. Till now, the approach of designing an artificial neural network is controversial owing to its proneness to overfitting. Thus, to our knowledge, we developed the first risk chart for prediction of DCI using easily retrievable data available on admission.

Figure 2. Predicted probabilities of delayed cerebral ischemia after subarachnoid hemorrhage (SAH) for each combination of the main 4 independent predictors present on admission. A, Based on the Modified Fisher scale. Thick clot, modified Fisher 3 and 4. B, World Federation of Neurological Surgeons Scale (WFNS) represents the clinical condition on admission. WFNS I, Glasgow coma scale (GCS) 15; WFNS II/III, GCS 13 to 14 (with or without focal deficit); WFNS IV, GCS 7 to 12; and WFNS V, GCS 3 to 6. C, Dichotomized at the median of the intraventricular Hijdra scale. Thick blood, intraventricular Hijdra scale of at least 3. In other words, in case at least 1 of the 4 ventricles was completely filled with blood; or in case at least 3 of the 4 ventricles contained a spot/sedimentation of blood; or at least 1 of the 4 ventricles was partly filled with blood and another contained sedimentation.

Figure 3. Discrimination and calibration plot of the risk chart in the validation cohort. A, The receiver operating characteristic (ROC) curve shows the discrimination of the risk chart (Model I) in prediction of delayed cerebral ischemia (DCI)–related infarction in the validation cohort. B, The plot shows the calibration of the risk chart (actual outcome versus predicted outcome) in the validation cohort for DCI-related infarction. For clinical deterioration owing to DCI, the numbers of observed DCI were slightly higher in the first 3 groups.

Though the discriminative performance of the risk chart was validated adequately, a limitation of our study is the systematic overestimation of the risk of DCI in our validation cohort. This miscalibration is caused by the lower incidence of DCI in the validation cohort, which may largely be explained by 2 time-dependent differences between the 2 cohorts. The first is an overall tendency to perform follow-up imaging to assess aneurysm occlusion. This implicates a larger proportion of patients without clinical deterioration that undergo follow-up imaging, and thus dilutes the number of patients with DCI. The second is the larger proportion of patients undergoing coiling in the validation cohort. These patients invariably
undergo follow-up imaging to assess aneurysm occlusion over time, which increases the proportion of patients without DCI. Moreover, several studies suggest that coiling is associated with a lower risk of DCI compared with clipping.20,21 Interobserver variability as an explanation of the lower percentage of DCI-related infarction is not likely because in both cohorts it was assessed by the same 2 authors using exactly the same definition. Although ideally the risk estimation should be as accurate as possible, in clinical practice the overestimation in our study is of less concern than an underestimation would have been. A second limitation is that the AUC of <0.70 may seem to be low. However, besides accuracy of discrimination (high AUC), the practical value of a model depends on other items, such as the potentials for extrapolation, relevance of the outcome, and usability of the model.22 The Framingham risk model, for instance, discriminates only moderately in certain (sub)populations with an AUC of slightly >0.70, but is nonetheless widely used.23 One of the strengths of our study is that we developed several models in a large cohort of SAH patients and also validated our findings. Analyses were performed using up-to-date methods for the development of prognostic models, using backward elimination, shrinkage factors, and correction for overoptimism. We used predictors that are well known from the literature.

Finally, we developed a simple practical risk chart that can easily be used on admission to predict absolute risks of DCI in individual patients with SAH. Before application of the risk chart in clinical practice, it should be externally validated in another hospital setting, preferably in another healthcare system. The predicted risk may tailor treatment. Patients predicted to have a high risk probably should stay longer on an intensive or medium care unit, whereas patients with a low risk may be discharged to a regular ward early. Also, time of mobilization (with the risk of drop in blood pressure and DCI) could differ between patients with high or low risk. For the use of antifibrinolytics, the estimated risk of DCI could also be taken into account.

Disclosures

None.

References


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