Abstract

Background: The Barrow Neurological Institute (BNI) score, measuring maximal thickness of aneurysmal subarachnoid hemorrhage (aSAH), has previously shown to predict symptomatic cerebral vasospasms (CVS), delayed cerebral ischemia (DCI) and functional outcome.

Objective: We aim to validate the BNI score for prediction of above-mentioned variables and cerebral infarct and evaluate its improvement by integrating further variables which are available within the first 24 hours after hemorrhage.

Patients and Methods: We included patients from a single center. The BNI score for prediction of CVS, DCI, infarct and functional outcome was validated in our cohort using measurements of calibration and discrimination (area under the receiver operating characteristic curve [AUC]). We improved it by adding additional variables, creating a novel risk score (measured by dichotomized Glasgow Outcome Scale) and validated it in a small independent cohort.

Results: Of 646 patients, 41.5% developed symptomatic CVS, 22.9% DCI, 23.5% cerebral infarct, and 29% had an unfavorable outcome. The BNI score was associated with all outcome measurements. We improved functional outcome prediction accuracy by including age, BNI score, WFNS, rebleeding, clipping, and hydrocephalus (AUC 0.84, 95%CI 0.8-0.87). Based on this model we created a risk score (HATCH - Hemorrhage, Age, Treatment, Clinical State, Hydrocephalus), ranging 0-13 points. We validated it in a small independent cohort. The validated score demonstrated very good discriminative ability (AUC 0.84 [95%CI 0.72-0.96]).

Conclusion: We developed the HATCH-score, which is a moderate predictor of DCI, but excellent predictor of functional outcome at 1 year after aSAH.

Running title

Validation of BNI score: creating the HATCH score

Keywords

Subarachnoid hemorrhage; barrow neurological institute grade; delayed cerebral ischemia; outcome; prediction

INTRODUCTION

Subarachnoid hemorrhage is a rare form of stroke comprising 5% of all strokes with an annual incidence of 9/100,000[1]. In 85% the underlying cause is a ruptured intracranial aneurysm causing aneurysmal subarachnoid hemorrhage (aSAH)[2]. It has a 6-month case fatality of up to 60%, however more recent studies show a decreasing trend of 0.9% per year over the last decades[2-4]. Overall outcome is notably influenced by aSAH related complications such as recurrent hemorrhage, hydrocephalus (HCP), cerebral vasospasm (CVS), and delayed cerebral ischemia (DCI)[1]. Despite significant advances in acute care and surgical and endovascular treatment over the last 30 years, outcome after aSAH still remains poor[2,5]. Approximately 30% of patients develop DCI within 3-12 days after the initial hemorrhage which remains one of the leading causes for poor outcome[6-8]. Studies showed that the amount of blood on initial CT scan is associated with the development of CVS and DCI[1,2,9]. Cerebral infarct might be an even better outcome predictor than DCI[10,11]. Several prediction models are available to identify patients who are at risk for CVS and DCI[12-17]. A simple prediction tool is the Barrow Neurological Institute (BNI) score[18]. It assesses the point of maximal thickness of subarachnoid blood particularly across the cistern or fissure allocating patients into five groups[18]. It demonstrates a proportional increase in CVS risk and has proven to be superior to the more widely used Fisher scale in predicting symptomatic CVS[9,18]. Moreover, the BNI score is also a promising tool in predicting DCI and functional outcome after aSAH. A previous study has additionally demonstrated that outcome prediction by the BNI score can further be improved by adding WFNS score and age[16]. This might allow early identification of patients at risk for DCI and therefore help in selecting patients who might profit from more intensive monitoring or prophylactic treatment of DCI. Improved functional outcome prediction models will guide physicians towards more individualized decision making.

In this study we aim to externally validate the original BNI score for CVS, DCI and functional outcome prediction, followed by validation of the extended BNI score as published by Neidert et al. [16,18]. We additionally evaluate the BNI score in predicting cerebral infarct. Finally, we will investigate the improvement of functional outcome prediction by adding relevant parameters available on admission to the BNI score to ultimately create a novel risk score. We will then externally validate it in a separate collected cohort.

PATIENTS AND METHODS

Study population

We used the prospectively collected aSAH database of the Neurosurgical Department of the University Hospital Zurich, Switzerland, collected between January 2005 and December 2016. The database consisted of 721 patients. Demographic, radiological and clinical outcome data were collected using standardized forms and entered into the database of the Department of Neurosurgery. Patients without available CT on admission and those who died before day 4 were excluded from the analysis. For outcome prediction we only included patients with available GOS on follow-up. Follow-up GOS was assessed in our outpatient clinic. All patients were treated by the standard of care of our department, a highly specialized and tertiary referral center for patients with cerebrovascular diseases, which follows international guidelines at the given time[1,19,20]. Our institution does have protocols in place for the escalation of treatment and uses a 3-bolt system routinely in all patients with aSAH requiring sedation and intubation[21].
The cohort for validation of the created risk score is an independent, prospectively collected cohort of 51 consecutive patients treated in the same unit between 01/2017 and 05/2018 with available functional outcome at 1 year.

Definition of variables

Hypertension, hypercholesterolemia, and diabetes mellitus were all diagnosed if medical records or patients reported these diagnoses or if advice, lifestyle changes or drug treatment had been previously been provided. We measured clinical severity on admission using two grading systems: WFNS and Hunt and Hess[22,23]. Hyperglycemia on admission is defined as blood glucose reaching values >8mmol/l.
We defined CVS as radiologically confirmed intracranial arterial narrowing (vasoconstriction) on digital subtraction angiography, CT angiography and/or MR angiography[24]. We defined DCI as a delayed decrease of the Glasgow Coma Scale (GCS) of at least 2 points and/or new focal neurological deficit without other underlying cause[25]. Delayed cerebral infarct is defined as radiologically proven new infarcts, not occurring within 48 hours of a surgical intervention, including aneurysm coiling or clipping[15]. Rebleeding is defined as a recurrent bleed from the aneurysm. Hydrocephalus is defined as an enlargement of the ventricular system requiring intervention[26]. We used the Glasgow Outcome Score (GOS) at 1 year to assess functional outcome. We dichotomized the GOS into unfavorable (1-3) and favorable (4-5) outcome, respectively[27-32].

CT grading

An independent neuroradiologist rated all CT scans on admission to determine the maximal thickness of subarachnoid blood (diameter of blood) particularly across the cistern or fissure allocating patients to Fisher and BNI score, as well later CT scans in order to detect delayed

cerebral infarcts according to standard protocols[9,18]. Scans were reviewed by a consultant neuroradiologist. Both were blinded to the patient's clinical state.

Statistical Analysis

Statistical analysis

Categorical variables are presented as count and percentage, continuous variables as mean with standard deviation (SD). We compared groups using the Chi-square or Fisher's exact test for our binary outcome variables.

For the multivariate models for CVS and DCI we adjusted for the pre-specified variables age, sex, hypertension, smoker and BNI score based on previous studies, which are readily available on admission. For infarct we additionally pre-specified WFNS and DCI.

Validation and performance in our cohort:

We validated the BNI score for CVS prediction as originally presented[18]. We then evaluated the performance of the BNI score for DCI, infarct and functional outcome prediction in our cohort (without restricting to just Fisher 3 patients, as previously published)[16]. We calculated odds ratios (OR) for each grade of BNI score relative to the highest grade. As a final step, we additionally validated the prediction of the extended BNI score of DCI and unfavorable functional outcome as per Neidert et al[16].

Extension and risk score creation for functional outcome:

To develop a new score to predict unfavorable functional outcome, defined as GOS 1-3, we fitted a multivariate regression model based on variables that were statistically significant at the 5% level in univariate analyses, as well as with the pre-specified variables age (dichotomized into younger or older than 60 years), sex, smoker, hypertension and BNI based on previous studies. We quantified discrimination by the area under the receiver-operating characteristic curve (AUC)[33]: an AUC of 0.5 indicates no, of >0.7 acceptable, of >0.8 good, of >0.9 excellent, and of 1 perfect discriminative abilities.

Validation:

The derived model was validated internally using bootstrap validation (with 200 bootstrap samples) and measures of predictive performance assessing calibration (calibration slope) and discrimination (measured by the AUC) were calculated[34]. Briefly, the calibration slope is a regression-based method to assess the agreement between observed and predicted values, with a calibration slope of 1 suggesting good calibration. We then validated the risk score in an independent cohort collected at a different time period at the same institution. To measure the performance of the new developed score, we used the Hosmer-Lemeshow test for calibration and AUC for discrimination[34].

Statistical analysis was performed using STATA 15 (StataCorp. 2011. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LP).

Ethical approval

The study was approved by the local ethics committee of Zurich, Switzerland. As this dataset was part of a registry approved by the local ethics committee no patient consent form was required.

RESULTS

Of 721 patients, 646 had all variables available except for treatment (clipping and coiling), as 5 patients were neither clipped nor coiled, and unfavorable outcome. Of 646 included patients, functional outcome on follow-up was available for 504 (78%) patients; 142 patients were therefore not included into the functional outcome analysis (Supplemental Figure 1). See Table 1 for baseline characteristics: mean age was 55.4 years (SD 13, range 14-88) and 432 (66.9%) were female. Overall, 268 patients developed CVS (41.5%), 148 patients developed DCI (22.9%), 152 (23.5%) delayed cerebral infarction and 146 (29.0%) had an unfavorable outcome at 1 year. The results of univariable analyses for each outcome can be seen in supplementary Tables 1-4.

Outcome prediction by the original BNI score

Prediction of CVS

Compared to the original BNI paper by Wilson et al. we had a higher rate of high BNI scores indicating a higher rate of severe bleeds (Table 1)[18]. Overall, the BNI score was associated with CVS (p=0.003). With BNI 5 as a reference group, all other BNI scores had a lower likelihood in developing symptomatic CVS (Table 2). The AUC was 0.58 (95% CI 0.54-0.62), indicating poor discriminative ability in predicting CVS (Figure 1).

The multivariable model to predict CVS was fitted with the predefined variables age, sex, hypertension, BNI score, and smoker (Supplementary Table 5). It had an overall p-value of <0.001 and showed low discriminative ability measured by an AUC of 0.64 (95% CI 0.60-0.69, Figure 2A).

Prediction of DCI

Like for CVS, DCI had higher a higher rate of BNI score 4 and 5, whereas again patients without DCI had a higher rate of BNI score 1-3 (overall p-value=0.04, Table 2). The BNI score was associated with DCI in the univariable analysis (overall p-value=0.04, Table 2 and Supplementary Table 2). The multivariate model to predict DCI was again fitted with the predefined variables age, sex, hypertension, BNI score, and smoker and had an overall p-value

of 0.004 (Supplementary Table 6). The model showed low discriminative ability measured by an AUC of 0.63 (95% CI 0.58-0.68, Figure 2B).

Prediction of infarction

Patients who developed cerebral infarcts had a higher rate of BNI score 4 and 5, whereas patients without cerebral infarcts a higher rate of BNI score 2 and 3 (overall p-value=0.03, Table 2). The multivariate model for infarction prediction was adjusted with the predefined variables. The model fit did not significantly change when removing sex and smoker and therefore these variables were not included in the final model (Supplementary Table 7). This final model had an overall p-value of <0.001 and a strong discriminative ability with an AUC of 0.84 (95% CI 0.81-0.88, Figure 2C).

Prediction of unfavorable outcome measured by the GOS at 1 year

The BNI score is significantly associated with functional outcome after aSAH (overall p-value<0.001, Table 2. For the multivariate regression we only included variables which were available within the first 24 hours. We adjusted the model with WNFS, clipping, hydrocephalus and rebleeding in addition to the predefined variables. The model demonstrated good discriminative ability with an AUC of 0.84 (95% CI 0.81-0.88).

Validation of BNI score for DCI and functional outcome sub-stratifying by Fisher 3 according to Neidert et al.[16]

The vast majority of patients (96.1%) had a Fisher score of 3. When evaluating DCI prediction sub-stratified by Fisher 3 (patients with a Fisher score of 3), there was a trend of decreasing likelihood of DCI with decreasing BNI score (Table 3). The AUC was 0.57, (95% CI 0.52-0.62) indicating poor discriminative abilities (Figure 3A). Supplemental Figure 2 demonstrates the GOS distribution by BNI score.

When evaluating unfavorable outcome sub-stratified by Fisher 3, the BNI score was associated with unfavorable outcome (overall p-value <0.001). This association was linear with declining BNI score (Table 3). The AUC for the sub-stratified BNI score association analysis was 0.64 (95%CI 0.59-0.7, Figure 3B). Next, we validated the score proposed by Neidert et al. by adding WFNS and age to BNI score. This led to a slight improvement in the discriminative abilities of predicting unfavorable outcome by increasing the AUC 0.79 (95% CI 0.74-0.83, Figure 3C).

Creation of risk score for functional outcome prediction and independent validation

As ultimately the prediction of the three other outcome variables results in the prediction of functional outcome and due to the promising results above, we created a point-based risk score for GOS prediction at 1 year due to the importance of predicting functional outcome. Since sex, smoker and hypertension did not significantly predict unfavorable outcome and their exclusion

did not significantly change the model (data not shown) or its discriminative ability (AUC 0.84 (95% CI 0.8-0.88, Figure 4). Thus, the final model contained following variables: age, BNI score, WFNS, clipping, hydrocephalus, and rebleeding (Table 4)

From this we created a point-based risk score for GOS prediction at 1 year, the HATCH score, which stands for: Hemorrhage (BNI score and rebleeding), Age (≤60 versus >60 years of age), Treatment (coiling versus clipping), clinical state measured by the WNFS and Hydrocephalus. We assigned points to each of the six independent predictors based on the strength of association (regression coefficients) with the outcome. A higher score is associated with an increased risk of unfavorable outcome with the maximum score of 13 points yielding a risk of 98.3% (Table 5). See supplemental Figure 3 demonstrating HATCH vs risk of unfavorable outcome.

In a final step we validated the risk score in a separate cohort of 51 patients from the same department. Due to the small size of the validation cohort we combined the score into four categories: 0-4, 5-6, 7-8 and 9-12. The discriminative ability for unfavourable outcome prediction at 1 year, measured by the AUC, was 0.84 (95% CI 0.72-0.96, Figure 5) indicating good discriminative ability. Calibration, as assessed by the Hosmer-Lemeshow test, however, was poor (p=<0.001). In particular, there was poor agreement between the observed and expected event rates for groups 5-6, although performance in the other groups was acceptable.

DISCUSSION

We successfully validated the original BNI score for the prediction of CVS, DCI, cerebral infarct and unfavorable outcome as well as the BNI score sub-substratified by Fisher 3 score, as proposed by Neidert et al. and their extended BNI score. We then created a new risk score, the HATCH score, for unfavorable outcome prediction based on variables present within 24 hours of admission – BNI score and rebleeding, age, treatment, clinical state and hydrocephalus - and validated it in a separate cohort showing good discriminative ability with an AUC of 0.84.

Our study has several strengths. The included sample size is relatively large and comes from a prospectively collected database in a tertiary referral center. The definition of variables has been made according to previous guidelines and consensus[25]. The HATCH score only uses variables which are available within 24 hours of admission making it applicable in the very early stages of this disease. It also offers the opportunity of a further extension of the score during the course of the disease.

Our study also has limitations: despite the cohort being collection prospectively, the analysis was conducted retrospectively. A prospective approach is preferred as a focus on the outcome

variables of interest can particularly reduce missingness. Multiple imputation would be a great tool to overcome this problem, however, it is not a generally advised method for imputation of outcome variables. Also, a direct comparison to the previously published validation by Neidert et al., including their extended score, is limited: they used the modified Ranking Scale (mRS) as opposed to the GOS for functional outcome measurement. Additionally, 22% were lost to follow-up and therefore had no functional outcome available. Another important limitation is that although discriminative ability of the HATCH score was good in the independent validation cohort, calibration was poor, most likely due to the small sample size. The validation cohort of 51 individuals can only be considered exploratory due to the small number of patients. Finally, the recruitment period of 11 years could lead to bias due to potentially improved outcome over time. We did investigate the differences of mortality as well as unfavorable outcome over the years and they did not differ significantly (data not shown).

Our findings are consistent with previous findings[10,16,35]. The BNI score significantly and successfully predicts CVS, DCI, cerebral infarct and functional outcome[18,25]. Based on a previous study demonstrating the potential of BNI score being included in a simple risk score we created the HATCH score[16]. Compared to the extended BNI score by Neidert et al., however, we created a risk score including all Fisher grades. Key feature of the HATCH score is the focus on only variables present within 24 hours of admission. The HATCH score demonstrates good discriminative ability (AUC of 0.84), accurately discriminating patients into high or low risk for unfavorable functional outcome. Despite the small size of the independent validation cohort, the score demonstrated good discriminative ability measured by an AUC of 0.84.

Despite a large enough sample size to achieve adequate power, the BNI score was only a moderate predictor of DCI. However, it is indeed a strong and statistically significant predictor of functional outcome. Further factors such as age, WFNS, rebleeding, clipping, and hydrocephalus easily improve its predictive ability. In our cohort, patients who were clipped had a lower chance of good outcome. Although we cannot conclusively explain this finding, this might be either due to the invasiveness of the surgery or a potentially higher-grade hemorrhage. Many scoring systems already exist with the aim of predicting different complications as well as functional outcome after aSAH[5,9,16-18,36-42]. The advantage of the HATCH score lies in its composition by radiological as well as clinical and interventional variables which are available right on admission or within 24h. Compared to other scoring systems this enables clinicians to predict functional outcome very early during the course of the disease which is especially important in guiding families and carers in decision making

processes. Most importantly, all of the included variables will be available in respective centers and do not need any deviation from the standard of care. It is further strengthened by the fact that it was successfully externally validated and also externally validated the BNI and extended BNI score. This indicates that the HATCH score can be generalized. The extended BNI score described by Neidert et al. demonstrates an improvement in predicting functional outcome and a good discriminative ability also in our cohort. However, this could be influenced by the fact that some of our patients overlapped with the cohort used by Neidert et al.[43]. Although only some patients overlap, these two cohorts are not two fully independent cohorts.

A previous study noted that clinical parameters are better in predicting outcome and radiological parameters do not improve their prediction abilities[10]. In our cohort, the BNI score was equally effective in predicting CVS and DCI, but the WFNS was better in predicting cerebral infarct and functional outcome substantiating these previous findings.

CONCLUSION

The newly created and easy-applicable HATCH score is a moderate predictor of DCI, but excellent predictor of functional outcome at 1 year after aSAH and demonstrating good discriminative abilities. Due to only a small sample size in the independent validation cohort, this score requires validation in a larger independent cohort to confirm our results.

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FIGURE LEGEND

Figure 1) AUC for prediction of CVS by Fisher grade according to Wilson et al.,
Figure 2A) AUC for prediction of CVS by age, sex BNI score, and hypertension, 2B) AUC for prediction of DCI by age, sex BNI score, and hypertension, 2C) AUC for prediction of infarction by age, BNI score, WNFS, DCI and hypertension
Figure 3A) AUC for prediction of DCI by BNI score sub-stratified by Fisher grade 3 according to Neidert et al,3B) AUC for prediction of unfavorable outcome by BNI score sub-stratified by Fisher grade 3, 3C) AUC for prediction of unfavorable outcome by BNI score, WFNS score and dichotomize age (below and above 60 years) sub-stratified by Fisher grade 3.
Figure 4) AUC for prediction of unfavorable outcome by BNI score, rebleeding, age, clipping, WNFS, and hydrocephalus
Figure 5) AUC for prediction of unfavorable outcome using the HATCH score in the validation dataset

SUPPLEMENTARY DATA LEGEND

Supplemental Figure 1, Flowchart
Supplemental Figure 2, GOS distribution by BNI score
Supplemental Figure 3, Graph demonstrating the HATCH score vs risk of unfavorable outcome
Supplemental Tables 1-7, 1) Univariable analysis for outcome CVS, 2) Univariable analysis for outcome DCI, 3) Univariable analysis for outcome cerebral infarction, 4) Univariable analysis for outcome unfavorable outcome, 5) Multivariable model for creation of a risk score for prediction of CVS, 6) Multivariable model for creation of a risk score for prediction of DCI, 7) Multivariable model for creation of a risk score for prediction of cerebral infarct