Predicting Delayed Cerebral Ischemia with Quantified Aneurysmal Subarachnoid Blood Volume

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■ BACKGROUND: **The amount of blood detected on brain computed tomography scan is frequently used in prediction models for delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (aSAH). These models, which include coarse grading scales to assess the amount of blood, have only moderate predictive value. Therefore, we aimed to develop a predictive model for DCI including automatically quantified total blood volume (TBV).**

■ METHODS: **We included patients from a prospective aSAH registry. TBV was assessed with an automatic hemorrhage quantification algorithm. The outcome measure was clinical deterioration due to DCI. Clinical and radiologic variables were included in a logistic regression model. The final model was selected by bootstrapped backward selection and internally validated by assessing the optimism-corrected R^2 value, c-statistic, and calibration plot. The c-statistic of the TBV model was compared with models that used the (modified) Fisher scale instead.**

■ RESULTS: **We included 369 patients. After backward selection, only TBV was included in the final model. The internally validated R^2 value was 6%, and the c-statistic was 0.64. The c-statistic of the TBV model was higher than both the Fisher scale model (0.56; $P < 0.001$) and the modified Fisher scale model (0.58; $P < 0.05$).**

■ CONCLUSIONS: **In our registry, only TBV independently predicted DCI. TBV discriminated better than the (modified) Fisher scale, but still had only moderate value for predicting DCI. Our findings suggest that other factors need to be identified to achieve better accuracy for predicting DCI.**

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe type of stroke with a case-fatality rate of approximately 30%.[1] Delayed cerebral ischemia (DCI) in patients with aSAH is associated with mortality and poor functional outcome.[2,3] Accurate prediction of DCI is important, because patients at high risk for DCI require intensive monitoring, whereas those at low risk for DCI may be safely discharged early.[4]

Numerous factors have been associated with the development of DCI.[5] The amount of blood detected on noncontrast brain computed tomography (NCCT) scan and the patient's neurologic condition on admission are strongly associated with DCI.[6,7] These 2 parameters are often used in prediction models aiming to predict DCI; however, these models have shown poor to moderate predictive value, with an area under the receiver operator characteristic curve ranging between 0.63 and 0.66.[8,9]

The amount of blood is commonly assessed using the Fisher and modified Fisher scales.[10,11] Drawbacks of these scales are their coarseness and only moderate interobserver agreement,[12] which

Key words
- Delayed cerebral ischemia
- Prediction model
- Subarachnoid hemorrhage
- Total blood volume

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
CT: Computed tomography
DCI: Delayed cerebral ischemia
NCCT: Noncontrast computed tomography
SD: Standard deviation
TBV: Total blood volume
WFNS: World Federation of Neurosurgical Societies

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limit the potential power of amount of blood as a predictor of DCI. The Hijdra sum score is more strongly associated with DCI but is much more time-consuming to calculate and thus less practicable for use in daily practice.[13] Automatic quantitative volume measurement assesses the amount of blood more precisely, is less observer-dependent, and has strong agreement with manual delineation of hemorrhage.[14] A recent study showed a strong association between total blood volume (TBV) as measured by automatic volume quantification and DCI.[6] Therefore, our aim in the present study was to develop and validate a prediction model for DCI in patients with aSAH, including TBV as a candidate predictor, and to compare this model's predictive value with that of the (modified) Fisher scale.

MATERIALS AND METHODS

Study Population

Patients were collected from a prospective aSAH registry that includes all patients with aSAH admitted to our center. For the retrospective analysis of this registry, the need for informed consent was waived by the local medical ethics committee. We included all patients from this registry admitted between December 2011 and December 2016 that met the following inclusion criteria: aSAH with admission brain NCCT available and confirmation of aneurysm suspected of rupture by computed tomography (CT) angiography, magnetic resonance angiography, or digital subtraction angiography. Patients who died within 3 days after the initial hemorrhage, patients in whom hemorrhage volume could not be segmented due to severe artifacts on admission NCCT, and patients participating in the ongoing Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage (ULTRA) trial were excluded.[15]

Clinical Data

The following clinical baseline data were collected: age, sex, history of hypertension, history of diabetes, history of cardiovascular disease, neurologic condition on admission based on the World Federation of Neurosurgical Societies (WFNS) scale, and type of aneurysm treatment (clipping, coiling, or none). The assessed outcome was clinical deterioration due to DCI, defined as the occurrence of new focal neurologic impairment or a decrease of $\geq$2 points on the Glasgow Coma Scale (with or without new hypodensity on CT) that could not be attributed to other causes, in accordance with the definition proposed by a multidisciplinary research group.[16] Patients were diagnosed with DCI by the treating neurosurgeon and were treated with induction of hypertension. The occurrence of DCI was evaluated during the course of admission. For prophylaxis against DCI, all patients received nimodipine orally (6 $\times$ 60 mg daily).

Radiologic Data

The following radiologic data were collected: TBV, Fisher grade, modified Fisher grade, aneurysm location, and aneurysm size. TBV was calculated by segmenting the amount of blood on admission NCCT with an automatic hemorrhage quantification algorithm and multiplying the number of voxels classified as blood by the voxel size.[14] The amount of blood included all subarachnoid, intraventricular, intraparenchymal, and subdural blood present on admission NCCT. In patients who experience rebleeding before treatment, the CT scan after rebleeding was used instead of the baseline scan to determine the hemorrhage volume. Rebleeding was defined as a sudden decrease in neurologic condition with an increase in hemorrhage volume on NCCT compared with a previous scan. All segmentations were checked and corrected as necessary by an experienced radiologist who was blinded to outcomes. Segmentations were corrected using ITK Snap version 3.6.0.[17] The Fisher and modified Fisher scales were graded by an experienced neurosurgeon.

Both saccular and nonsaccular (fusiform/dissection) aneurysms were included. Aneurysms were categorized as anterior or posterior circulation aneurysms. Anterior circulation aneurysms included anterior cerebral artery, anterior communicating artery, middle cerebral artery, pericallosal artery, ophthalmic artery, posterior communicating artery, and internal carotid artery aneurysms. Posterior circulation aneurysms included posterior cerebral artery, basilar artery, vertebral artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery aneurysms. Aneurysm size was defined as the maximum width or length of the aneurysm suspected of rupture.

Statistical Analysis

Variables were compared between patients who developed DCI and those who did not develop DCI using Student's *t* test for continuous normally distributed variables and the Mann–Whitney *U* test for continuous non-normally distributed variables. Dichotomous and categorical variables were compared using Fisher's exact test.

Missing Data

In our dataset, 18% of the cases had 1 or more missing variables, with a maximum of 9% missing per variable. Missing values were imputed with multiple imputation using additive regression, bootstrapping, and predictive mean matching.[18] To average the uncertainty of the imputed values, we created 20 completed datasets with imputed values.

Variable Selection

The collected variables age, sex, history of hypertension, history of diabetes, history of cardiovascular disease, WFNS grade, TBV, aneurysm location, aneurysm size, and treatment modality were considered potential predictors of DCI. The WFNS scale was dichotomized into good grade (WFNS I–III) and poor grade (WFNS IV–V). To check whether the continuous variables had a linear association with DCI, the variables were divided into deciles. In each decile of the continuous variable, the proportion of patients with DCI was assessed. If a nonlinear relationship was suspected, polynomial terms of the continuous predictor were added to the model.

All variables were included in a logistic regression model. Variables with limited predictive value were stepwise backward removed from the model using the Akaike information criterion. The elimination of variables was stopped when the lowest possible Akaike information criterion was reached. This process was repeated 100 times using bootstrap resampling. A bootstrap sample consists of a randomly drawn sample of subjects from the

Table 1. Baseline Characteristics

Characteristic	Total (N = 369)	No DCI (N = 256)	DCI (N = 113)	*P* Value
Age (years), mean (SD)	56.9 (12.6)	56.9 (13.3)	57.1 (0.9)	0.87
Female sex, n (%)	252 (68)	174 (68)	78 (69)	0.9
History of hypertension, n (%)	122 (36)	90 (38)	32 (31)	0.22
History of cardiovascular disease	62 (18)	47 (20)	15 (14)	0.29
History of diabetes, n (%)	23 (7)	16 (7)	6 (6)	0.82
WFNS, n (%)				0.24
I	182 (49)	135 (54)	46 (43)	
II	57 (15)	36 (15)	20 (19)	
III	13 (4)	10 (4)	3 (3)	
IV	62 (17)	40 (16)	22 (20)	
V	44 (12)	27 (11)	17 (16)	
Aneurysm location, n (%)				0.25
Anterior	300 (81)	204 (80)	96 (85)	
Posterior	69 (19)	52 (20)	17 (15)	
Aneurysm size (mm), median (IQR)	6 (4–8)	6 (4–8)	6 (4–9)	0.26
Aneurysm treatment, n (%)				0.05
Coiling	270 (73)	188 (74)	82 (73)	
Clipping	65 (18)	41 (16)	27 (24)	
Other (stent, flow diverter, pvo)	5 (1)	4 (7)	1 (1)	
No treatment	26 (7)	23 (9)	3 (3)	
Modified Fisher grade, n (%)				0.03
Grade 0	20 (5)	19 (8)	1 (1)	
Grade I	26 (7)	21 (8)	5 (5)	
Grade II	6 (2)	5 (2)	1 (1)	
Grade III	88 (24)	62 (24)	26 (23)	
Grade IV	227 (62)	148 (58)	79 (71)	
Total blood volume (mL), median (IQR)	25 (10–55)	20 (8–44)	38 (19–66)	<0.001

SD, standard deviation; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; Pvo, parent vessel occlusion.

original dataset, which is the same size as the original dataset. The bootstrapped backward selection process was repeated in each of the 20 imputed datasets. Variables that remained in the model after the backward selection procedure in more than 50% of the bootstrap samples were included in the final model.

Model Performance and Validation

Model performance was evaluated by assessing the explained variance, discriminative power, and agreement between observed outcomes and predictions. The explained variance in outcome was evaluated with the R^2 statistic, discriminative power was assessed with the c-statistic, and the agreement between observed outcomes and predictions was assessed with a LOWESS smoothed calibration plot. Model performance was internally validated by calculating the optimism-corrected R^2, c-statistic, and calibration curve using bootstrap resampling. The model was trained in each bootstrap sample and tested in the original data. The R^2, c-statistic, and model calibration were evaluated both in each bootstrap sample and in the original dataset. This process was repeated 500 times. The optimism was assessed by calculating the difference in performance of the model in the bootstrap samples and the original data. Optimism-corrected performance measures were calculated by subtracting the optimism from the performance of the original model in the original data.[19] The entire bootstrap resampling process was repeated in each of the imputed datasets, and the optimism-corrected performance measures were averaged.[20]

Comparison with (Modified) Fisher Grade

The predictive value of the TBV model was compared with that of the Fisher and modified Fisher scale models by replacing the TBV in the final model with the Fisher and modified Fisher grades. The

Table 2. Frequencies of Inclusion of Variables in the Final Predictive Model of DCI

Variable	% (SD)
Total blood volume	99 (1)
History of cardiovascular disease	48 (10)
History of hypertension	34 (9)
Aneurysm location	31 (4)
Treatment	24 (4)
WFNS	22 (4)
Aneurysm size	22 (4)
History of diabetes	20 (5)
Sex	18 (3)
Age	17 (4)

DCI, delayed cerebral ischemia; WFNS, World Federation of Neurosurgical Societies.

c-statistics of these 3 models were compared using the Delong test.

Sensitivity Analysis

As the predictive value of the amount of blood for DCI may decline with an increasing interval between the initial hemorrhage and CT, a sensitivity analysis was performed including only patients who underwent CT within 48 hours.[21]

Analyses were performed using SPSS version 24.0.0.1 (IBM, Armonk, New York, USA), R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria), and R packages Hmisc, bootstepAIC, rms, and pROC. Because of the sensitive nature of the data, both the data and the R code are only available on request to the authors.

RESULTS

From our prospective cohort, 436 patients were evaluated for inclusion. Sixty-seven patients were excluded, 5 because an aneurysmal source of the SAH could not be confirmed, 5 because baseline NCCT data were unavailable, 50 because of death within 3 days, and 7 because TBV measurement could not be performed due to imaging artifacts. Of the 369 patients included, 113 (31%) developed DCI. The median interval from symptom onset to baseline NCCT was 3 hours (interquartile range, 1–19 hours). Baseline characteristics are presented in Table 1. The baseline median blood volume was 38 mL in patients who developed DCI and 20 mL in those who did not develop DCI ($P < 0.001$). For the other characteristics, no statistically significant differences were observed between patients with DCI and those without DCI.

Variable Selection

TBV was selected in 99% (SD 1%) of the models after bootstrapped backward selection in all imputed datasets. The other variables were selected in <50% of the models (Table 2). TBV showed an approximately linear association with DCI up to the highest decile of blood volume, in which the occurrence of DCI

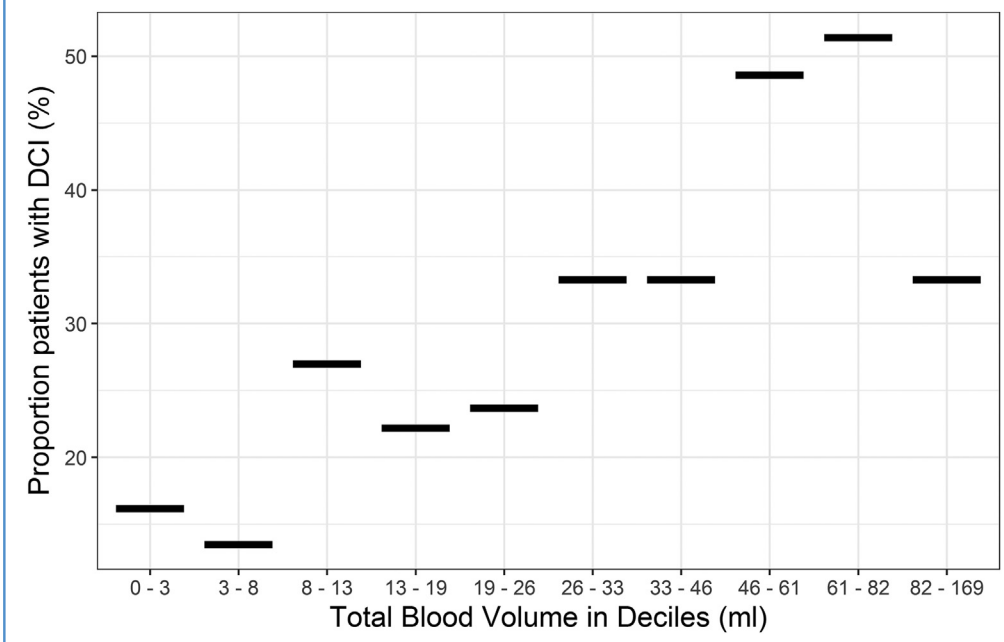

Figure 1. Plot showing the proportion of patients with delayed cerebral ischemia (DCI) in each decile of total blood volume (TBV). Each decile of TBV includes approximately 37 patients. The plot shows a fairly linear association with DCI until the highest decile of TBV, in which the risk decreases.

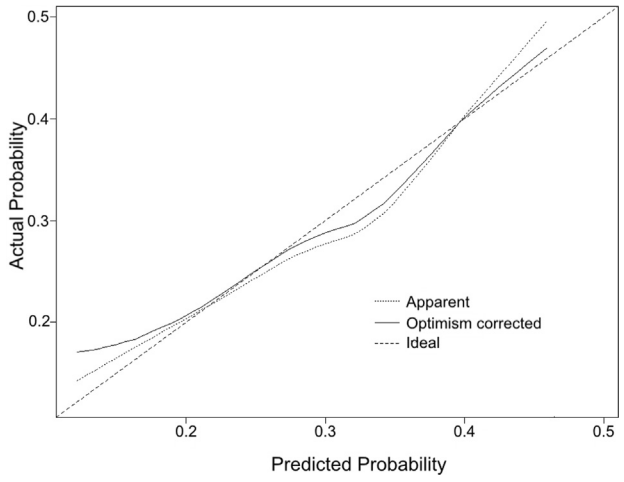

Figure 2. Calibration plot showing the predicted versus the observed probability of delayed cerebral ischemia for the final model. The dashed line shows a perfect calibration (ideal). The dotted line shows the calibration on the original data (apparent calibration). The solid line shows the optimism corrected calibration with bootstrapping.

decreased (Figure 1). Therefore, the squared and cubed TBV were added to the model.

Model Performance and Validation

The mean R^2 of the model in the imputed datasets was 8% (SD 1%). The mean c-statistic was 0.66 (SD 0.01). The calibration plot shows that the model somewhat underestimated the risk of DCI at lower risks and overestimated the risk of DCI at higher risks (Figure 2). The mean optimism-corrected R^2 was 6% (SD, 1%), and the mean c-statistic was 0.64 (SD, 0.01). The optimism-corrected calibration plot showed increased underestimation of the risk of DCI at lower risks and increased overestimation at higher risks (Figure 2).

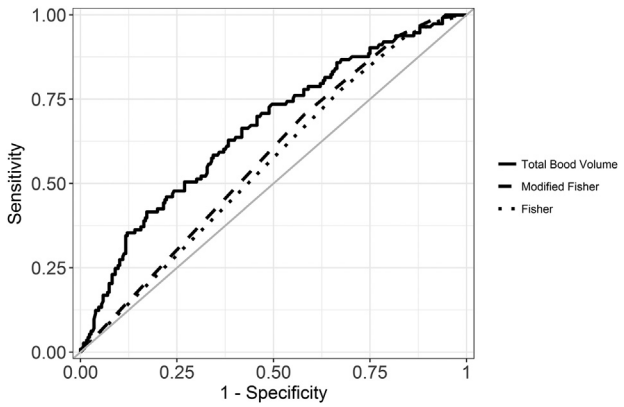

Figure 3. Receiver operator characteristic curves of the model including the total blood volume (TBV) (*solid line*), modified Fisher scale (*dashed line*), and the Fisher scale (*dotted line*). The gray line is the reference line for a noninformative model. The area under the curve is 0.66 for the TBV model, 0.58 for the modified Fisher scale, and 0.56 for the Fisher scale.

Comparison with (Modified) Fisher Grade

The c-statistics of the predictive models in which TBV was replaced by the Fisher grade and modified Fisher grade were 0.56 and 0.58, respectively. The c-statistic of the TBV model was higher than both the Fisher ($P < 0.001$) and modified Fisher ($P < 0.05$) scale models (Figure 3).

Sensitivity Analysis

After including only patients who were admitted within 48 hours after the initial hemorrhage (n = 300), the R^2 of the TBV model increased to 12% and the c-statistic increased to 0.67. The optimism-corrected R^2 and the c-statistic increased only moderately (9% and 0.66, respectively).

DISCUSSION

In this study we aimed to develop a prediction model for DCI, using TBV as one of the candidate predictors among other clinical and radiologic variables. TBV was the sole independent predictor of DCI selected for inclusion in the final model in our dataset. The other variables did not add to the predictive value of TBV alone. TBV discriminated better than the Fisher and the modified Fisher scales; however, TBV still discriminated only moderately between patients who developed DCI and those who did not develop DCI.

Numerous studies have investigated associations between risk factors and DCI[5]; however, few have developed and validated prediction models for DCI. Two recent models, of which one applied internal validation techniques, included TBV assessed on the modified Fisher scale and WFNS grade on admission as predictors of DCI.[8,9] WFNS grade was not an independent predictor of DCI in our dataset. As such, TBV may have a stronger association than WFNS grade with DCI. In our study, TBV predicted DCI better than both the Fisher and modified Fisher scales. However, the TBV model has a similar c-statistic as these 2 recently published models, suggesting that TBV may have a similar predictive value as the predictors included in those models.

Although the amount of blood was predictive of DCI, it should not be included as a linear predictor in a model, given that the risk of DCI decreases again after a certain threshold. Therefore, we added polynomial terms of TBV to the model. This nonlinear relationship is most likely caused by an increased risk of coma or death in patients with a large TBV. Patients with a larger TBV are at higher risk of in-hospital death, which prevents them from developing DCI.[2] Furthermore, patients with a larger TBV who remain alive may be in a comatose state, in which it is difficult to diagnose clinical deterioration due to DCI.

Our study confirms that the amount of blood plays a role in the development of DCI.[6] However, TBV explained only 6% of the variation in DCI. This did not increase substantially after including only patients who underwent a CT scan within 48 hours after the initial hemorrhage. This suggests that other factors not considered in this model may play a role in the development of DCI.

An important factor may be the location of the blood. Blood volumes at different locations in the brain may have different

associations with DCI.[22] Considering location-specific blood volumes separately in a model may increase the predictive value. The precise pathophysiology of DCI is not clear, and thus various other predictors of DCI may be considered.[23] A systematic review identified smoking as a possible predictor of DCI.[5] Other recent studies have suggested that white blood cell count on admission, extent of cerebral edema, and diffusion tensor imaging parameters as potential predictors of DCI.[24-26]

An important strength of our study is the use of automatic hemorrhage segmentation techniques to assess the TBV. This resulted in a more precise measurement of the blood volume compared with coarse grading scales. However, the automated method requires manual correction and needs further optimization before it can be used in a clinical setting. Furthermore, classification of blood location currently cannot be performed automatically and thus was not considered in our model. Automatic calculation of location-specific blood volumes is challenging due to deformation of the brain in the presence of a large intraparenchymal hematoma and difficulty differentiating between intraparenchymal and Sylvian fissure hematoma on NCCT.[27]

Another strength of the study is the availability of prospectively collected registry data, which allowed us to build a DCI prediction model on a representative aSAH population of The Netherlands. We used a strict definition of DCI, as only patients who met the criteria by a multidisciplinary research group were classified as DCI.[16] However, even when using a strict definition of DCI, the diagnosis remains difficult, especially in comatose patients. Therefore, there may be some degree of uncertainty regarding the diagnosis in some patients. The number of included patients may be limited for the development of a prediction model; however, a minimum number of 10 cases of DCI per variable was still met.

TBV provides an indication of which patients are at high risk for DCI but does not discriminate well enough for use in clinical practice. Therefore, we decided not to validate the current set of predictors in an external population. Future studies should aim to develop better-discriminating prediction models by researching other predictors besides the frequently used WFNS score and blood volume.

CONCLUSIONS

In our prospective registry of patients with aSAH, only quantified TBV was independently predictive of DCI. TBV discriminated better than both the Fisher scale and the modified Fisher scale but still was only moderately predictive of the development of DCI. Although TBV plays a role in the development of DCI, other factors need to be identified to achieve better accuracy for DCI prediction models.

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