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Impaired cerebrovascular reactivity may predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Introduction: Delayed cerebral ischemia (DCI) is a major cause of disability and death after aneurysmal subarachnoid hemorrhage. The literature suggests that impaired cerebrovascular reactivity (CVR) may be a predictor for DCI; still no CVR based prediction model has been developed. Increased knowledge about possible predictors of DCI can improve patient management in high-risk patients and allow for shorter hospital stay in low-risk patients.

Method: CVR was examined in 42 patients with aneurysmal subarachnoid hemorrhage and 37 patients treated for unruptured intracranial aneurysm, using acetazolamide test with transcranial Doppler monitoring of blood flow velocities. Patients were followed for development of DCI, separated into clinical deterioration and radiographic infarction.

Results: For all patients, regardless of aneurysm rupture status, CVR was on average 5.5 percentage points lower on the ipsilateral side of aneurysm treatment. Patients with clinical deterioration due to DCI had lower CVR than patients without DCI, and the difference was larger on the contralateral side (33.9% vs. 49.2%). Two prediction models were constructed for clinical deterioration due to DCI. The area under the receiver operating characteristic curve was 0.82 in the model using established predictors, and 0.86 in the model that also included CVR.

Conclusion: Our findings support the hypothesis that impaired CVR may be an independent predictor of clinical deterioration due to DCI, and may assist in identifying patients at risk after aneurysmal subarachnoid hemorrhage. Ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of DCI development, thus highlighting the need to evaluate ipsi- and contralateral CVR separately.

1. Introduction

Delayed cerebral ischemia (DCI) is a major cause of disability and death after aneurysmal subarachnoid hemorrhage (aSAH) [1,2]. Identification of patients at high risk of developing DCI can improve patient management, and valid predictors of DCI could allow for shorter hospital stay in patients at low risk. Large amount of subarachnoid blood and poor clinical admission status are known predictors for DCI [3–7]. Other predictors, like smoking and hydrocephalus have been suggested [8]. Still, additional information is needed to make prediction more accurate.

Cerebrovascular reactivity (CVR) is often impaired in the early phase after aSAH [9–15], especially in patients with poor clinical grade [12,16–18]. Several test methods have shown reduced CVR in patients with aSAH compared with unruptured intracranial aneurysms (UIAs) [9–12,19], but this has not been confirmed for the transcranial Doppler (TCD) and acetazolamide (AZ) test (TCD-AZ test) [20]. With one exception [14], the literature suggests that impaired CVR may be associated with vasospasm and can be a potential predictor for DCI after aSAH [15–17,21–30]. However, sample sizes have been limited, methodology has varied and inconsistent and outdated definitions of DCI have been used. To our knowledge, no CVR based prediction model has yet been developed.

The main objective of this study was to assess if impaired CVR can

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be a predictor for DCI after aSAH. In adjunct, we wanted to assess the relationship between aneurysm rupture status and CVR assessed by TCD-AZ test, in order to improve understanding of CVR in this patient group.

2. Methods

2.1. Participants

Patients treated at the Department of Neurosurgery, Haukeland University Hospital between February 2011 and May 2013 were prospectively included. Inclusion criteria were: age ≥ 18 years and treatment for saccular intracranial aneurysms with endovascular coiling or surgical clipping. Exclusion criteria were: previous treatment of intracranial aneurysms, giant aneurysms treated with proximal artery occlusion, carotid stenosis (> 50%) or occlusion, lack of transtemporal bone window in TCD examination, DCI present at admission, moribund patients, and contraindications to acetazolamide.

2.1.1. Clinical, sonographic and radiographic assessment

In all patients demographics, body weight, smoking status, hypertension, aneurysm location, and treatment modality was recorded. In patients with ruptured aneurysms, the clinical status upon admission was evaluated with Glasgow Coma Scale (GCS) [31] and World Federation of Neurological Surgeons (WFNS) scale [32]. Admission computed tomographic (CT) scan was classified according to the modified CT Fisher scale [33].

Patients were monitored clinically, sonographically and radiographically for development of DCI, vasospasm and cerebral infarction. Neurological status was scored routinely three times a day, and more frequent as regarded necessary. As a pragmatic choice, sonographic examinations were performed whenever possible, in order to avoid conflicts with patient investigations or treatment. Blood flow velocities in major intracranial arteries were assessed with transcranial color-coded sonography (TCCS) using a portable Philips CX50 system (5–1 MHz sector array probe) and Lindegaard Index was calculated [34]. TCCS was performed daily and more frequent if neurological deterioration occurred. Neuroimaging, i.e. CT or magnetic resonance imaging (MRI) with or without angiography and digital subtraction angiography (DSA) was performed tailored to the clinical situation. An experienced neuroradiologist (GM) assessed all angiograms, CT and MRI scans retrospectively for vasospasm and cerebral infarctions.

2.1.2. Cerebrovascular reactivity

CVR testing was performed with acetazolamide (AZ). The AZ dose was 1000 mg for patients weighing < 80 kg, and 15 mg/kg for patients weighing ≥ 80 kg. The maximum dose was 1500 mg. CVR testing was performed after aneurysm treatment to avoid risk of (re-)rupture. Patients treated for unruptured intracranial aneurysms (UIA) were examined once, whereas patients treated for aSAH underwent serial testing during the hospital stay. The time interval between examinations was minimum 24 h. To avoid steal phenomenon and neurological deterioration, CVR testing was not performed after a patient was diagnosed with DCI. TCD was used to monitor blood flow velocities in the middle cerebral arteries (MCA) after intravenous injection of acetazolamide (AZ) [20]. Cerebrovascular reactivity was calculated as the maximum percentage change in MFV in MCA after administration of acetazolamide: CVR (%) = $[(MFV_{AZ} - MFV_{BASELINE}) / MFV_{BASELINE}] \times 100$, where $MFV_{BASELINE}$ is mean blood flow velocity before acetazolamide and MFV_{AZ} is mean blood flow velocity (maximum change) after acetazolamide. In patients with a paradoxical velocity reduction after AZ due to a steal phenomenon, CVR will be a negative value.

2.1.3. Clinical deterioration and cerebral infarction due to delayed cerebral ischemia

All patients with aSAH, regardless of presence of ischemic symptoms or not, were given 60 mg nimodipine orally every four hours to prevent DCI [35,36]. Critically ill patients and patients with swallowing difficulties were given nimodipine as intravenous infusion 2 mg/h. Patients with severe and refractory radiographic vasospasm and clinical deterioration due to DCI were given intraarterial nimodipine [37]. Patient management was not influenced by CVR results.

We distinguished between clinical deterioration and radiographic infarction due to DCI [38,39].

Clinical deterioration ($DCI_{clinical}$) was defined as a new focal neurological impairment or ≥ 2 points reduction in Glasgow Coma Score, lasting for minimum 1 h, and not appearing immediately after aneurysm occlusion. Other causes of deterioration were excluded by clinical assessment, cerebral CT or MRI, and laboratory analyses.

Radiographic infarction ($DCI_{infarction}$) was defined as a new infarction identified on CT or MR scans during the hospital stay, within six weeks after aSAH. Infarctions present on the admission or immediate postoperative CT, and hypodensities resulting from the clipping or coiling procedure, ventricular catheter placement or intraparenchymal hematoma were not regarded as cerebral infarctions from DCI.

Angiographic vasospasm was defined as arterial narrowing present on CTA, MRA or DSA, not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia. Angiographic vasospasm was classified as none, mild (< 33% reduction in arterial diameter), moderate (34–66%) or severe (≥ 67%), and was also categorized with the Nathal grading scale [40].

Sonographic vasospasm was defined as time-averaged peak velocity (TAPV) ≥ 120 cm/s in any cerebral artery and Lindegaard index ≥ 3

Table 1
Patient, aneurysm and treatment characteristics.

	aSAH (n = 42)	UIA (n = 37)
Age, years[a]	53 ± 13	50 ± 11
Height, cm[a]	171 ± 9	169 ± 8
Weight, kg[a]	76 ± 18	77 ± 16
BMI, kg/m^2[a]	26 ± 5	27 ± 5
Female	24 (57.1)	24 (64.9)
Hypertension	19 (45.2)	18 (48.6)
Smoking		
Current	27 (64.3)	20 (54.1)
Previous	8 (19.0)	13 (35.1)
Never	7 (16.7)	4 (10.8)
Multiple aneurysm	9 (21.4)	12 (32.4)
Aneurysm diameter[a,b]	7 ± 3	7 ± 3
Location treated aneurysms		
Middle cerebral artery	12 (28.6)	17 (45.9)
ACOM, anterior complex and pericallosa	17 (40.5)	7 (18.9)
ICA, incl. ophthalmic artery and PCOM	6 (14.3)	10 (27.0)
Basilar top, cerebelli superior, PICA, VB, distal posterior	7 (16.7)	3 (8.1)
Treatment modality		
Coil	30 (71.4)	22 (59.5)
Clip	12 (28.6)	15 (40.5)
Treatment side[c]		
Left	21 (50.0)	19 (51.4)
Right	21 (50.0)	18 (48.6)

ACOM: anterior communicating artery; aSAH: aneurysmal subarachnoid hemorrhage; BMI: body mass index; ICA: internal carotid artery; PCOM: posterior communicating artery; PICA: posterior inferior cerebellar artery; UIA: unruptured intracranial aneurysms; VB: vertebrobasilar arteries.

[a] Mean ± standard deviation. All other variables are reported as n (%).

[b] Maximum diameter of the aneurysm dome. For patients with aSAH the size of the ruptured aneurysm is reported. For patients that underwent treatment for multiple UIA during the same procedure, aneurysm size was averaged.

[c] Twenty-four patients with midline aneurysms (ACOM and basilar top) were allocated to the chosen side of approach. One patient treated with combined clipping of an ACOM aneurysm and a right middle cerebral artery aneurysm in one procedure was allocated to the right side. The coiling procedure failed to adequately secure the aneurysm in one patient, so clipping was performed instead.

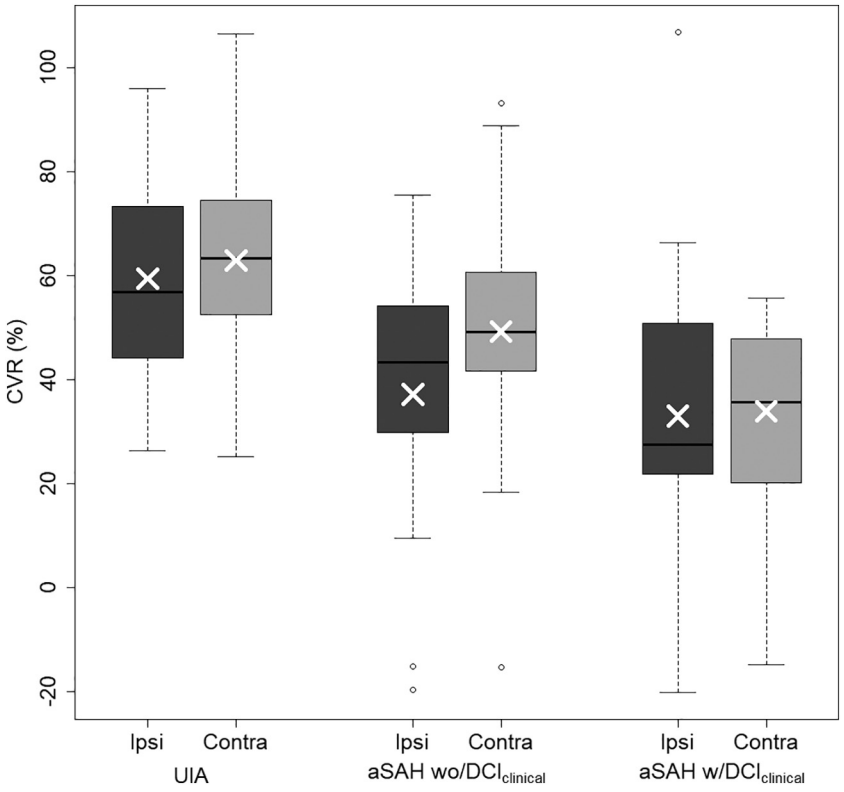

Fig. 1. Box plots comparing cerebrovascular reactivity (CVR) in patients with unruptured intracranial aneurysms (UIA), aneurysmal subarachnoid hemorrhage (aSAH) without clinical deterioration due to delayed cerebral ischemia (DCI), and aSAH with clinical deterioration due to DCI. For patients with aSAH serial measurements of CVR were performed, and the lowest measured value is presented. Ipsilateral CVR are shown in dark grey boxes, and contralateral CVR in light grey boxes. Boxes extend from the 25th to the 75th percentile. Horizontal bars represent the median, and whiskers extend to the most extreme point that is < 1.5 times the interquartile range from the box. Mean values are marked with white crosses, and outliers are depicted as points.

Table 2
Blood flow velocities and cerebrovascular reactivity in patients with ruptured vs. unruptured aneurysms.

	UIA (n = 37)	aSAH (n = 42)			
	Singel exam	First exam	Lowest value	Average of all exams	*p*-values UIA vs. aSAH
$MFV_{BASELINE}$ (cm/s)					
Ipsi	60 ± 14	57 ± 20	55 ± 19	61 ± 18	0.54, 0.25, 0.79
Contra	58 ± 14	59 ± 18	53 ± 18	60 ± 19	0.79, 0.18, 0.59
MFV_{AZ} (cm/s)					
Ipsi	94 ± 18	80 ± 28	76 ± 27	86 ± 25	0.02, 0.003, 0.15
Contra	93 ± 23	86 ± 29	79 ± 29	89 ± 29	0.25, 0.02, 0.42
ΔMFV_{AZ} (cm/s)					
Ipsi	34 ± 9	23 ± 21	18 ± 17	25 ± 17	0.004, < 0.001, 0.01
Contra	36 ± 11	28 ± 19	22 ± 15	29 ± 16	0.03, < 0.001, 0.03
CVR (%)					
Ipsi	59 ± 19	43 ± 35	33 ± 28	45 ± 30	0.02, < 0.001, 0.02
Contra	63 ± 17	48 ± 27	40 ± 23	51 ± 25	0.008, < 0.001, 0.01

[34]. Severe sonographic vasospasm was defined as TAPV ≥200 cm/s and Lindegaard index ≥6.

2.1.4. Ethics

The study was conducted in accordance with the Declaration of Helsinki (2013) of the World Medical Association, and was approved by the local ethics committee (the Regional Committees of Western Norway for Medical and Health Research Ethics, approval number 2011/144). Written informed consent was obtained from all patients or a legal representative.

2.2. Statistical analysis

We reported CVR separately as ipsilateral and contralateral values to avoid that mean values could obscure side differences [41]. Due to the wide range of reported CVR measured by TCD and AZ in healthy subjects [42–54] and patients with UIA [20], we studied CVR as a continuous variable. Effects are reported per percentage point change in CVR. Midline aneurysms were allocated according to chosen side of approach for treatment. Standard *t*-tests and multiple regression analyses (adjusted for age, sex, hypertension, smoking, aneurysm diameter and treatment modality) were carried out to examine the relationship between CVR and rupture status.

We then compared clinical, radiographical and sonographical variables of patients with and without $DCI_{clinical}$, with chi-squared or Fisher's exact test, as appropriate. Next, we assessed the predictive potential of both contralateral and ipsilateral CVR for $DCI_{clinical}$ and $DCI_{infarction}$, to decide which measure of CVR was most appropriate to use in patients with multiple measurement (first, lowest, or within-patient average of all exams). A priori, we chose the lowest or first measured CVR as the exposure (more convenient in clinical use). *t*-test was used to compare CVR in aSAH patients with and without $DCI_{clinical}$ or $DCI_{infarction}$, and to assess side differences. Simple logistic regression analyses were conducted for both $DCI_{clinical}$ and $DCI_{infarction}$ versus both within-patient average CVR and lowest measured contralateral CVR. Further, box plots were constructed, based on the lowest measured

Table 3
Characteristics of patients with aneurysmal subarachnoid hemorrhage.

	Total (n = 42[a])	Clinical DCI (*n* = 22)	No clinical DCI (*n* = 19)	p-Value
GCS on admission[b]	11 ± 4	11 ± 4	12 ± 4	0.44
WFNS				
I GCS 15	8 (19.0)	1 (4.5)	7 (36.8)	0.02[c]
II GCS 13–14, without neurological deficit	14 (33.3)	9 (40.9)	5 (26.3)	0.51
III GCS 13–14, with neurological deficit	2 (4.8)	1 (4.5)	1 (5.3)	1.00[c]
IV GCS 7–12	10 (23.8)	7 (31.8)	3 (15.8)	0.29[c]
V GCS 3–6	8 (19.0)	4 (18.2)	3 (15.8)	1.00[c]
Modified CT Fisher				
1 Thin SAH without IVH	6 (14.3)	1 (4.5)	5 (26.3)	0.08[c]
2 Thin SAH with IVH	8 (19.0)	4 (18.2)	3 (15.8)	1.00[c]
3 Thick SAH without IVH	15 (35.7)	7 (31.8)	8 (42.1)	0.72
4 Thick SAH with IVH	13 (31.0)	10 (45.5)	3 (15.8)	0.09
Hydrocephalus (during primary stay)	30 (71.4)	20 (90.9)	9 (47.4)	0.007
Cerebral infarction due to DCI	19 (45.2)	13 (59.1)	5 (26.3)	0.07
Angiographic vasospasm				
None	22 (52.4)	6 (27.3)	16 (84.2)	< 0.001
Mild	3 (7.1)	2 (9.1)	1 (5.3)	1.00[c]
Moderate	12 (28.6)	9 (40.9)	2 (10.5)	0.07
Severe	5 (11.9)	5 (22.7)	0 (0.0)	0.05[c]
Angiographic scale ad modum Nathal[d]				
No vasospasm	22 (52.4)	6 (27.3)	16 (84.2)	< 0.001
One axis	5 (11.9)	2 (9.1)	2 (10.5)	1.00[c]
Two axes	1 (2.4)	1 (4.5)	0 (0.0)	1.00[c]
Three axes	6 (14.3)	5 (22.7)	1 (5.3)	0.19[c]
Generalized/diffuse vasospasm	8 (19.0)	8 (36.4)	0 (0.0)	0.004[c]
Sonographic vasospasm[e]				
None	20 (48.8)	1 (4.8)	18 (94.7)	< 0.001
Mild to moderate	14 (34.1)	13 (61.9)	1 (5.3)	< 0.001
Severe	7 (17.1)	7 (33.3)	0 (0.0)	0.009[c]

aSAH: aneurysmal subarachnoid hemorrhage; CT: Computer Tomography; DCI: Delayed cerebral ischemia; GCS: Glasgow Coma Score; IVH: intraventricular hemorrhage; SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurosurgical Societies score.

[a] Missing information regarding presence or absence of clinical DCI in one patient due to sedation

[b] Mean ± standard deviation. All other variables are reported as n (%)

[c] Due to few observations Fishers exact is used instead of chi-squared test

[d] The vascular axes were defined as follows: a) internal carotid artery, b) middle cerebral artery, c) anterior cerebral artery, d) vertebral artery, e) basilar artery, f) posterior cerebral artery, and g) any other arterial territory.

[e] Missing sonographic information in one patient.

iCVR and cCVR for UIA, aSAH without $DCI_{clinical}$, and aSAH with $DCI_{clinical}$.

From this, two prediction models for $DCI_{clinical}$ were created. Model I included WFNS, modified CT Fisher scale, age, sex, smoking, and hydrocephalus, all variables suspected to affect risk of $DCI_{clinical}$. Model II included all variables from Model I plus contralateral CVR. Model discrimination was assessed with area under the ROC curve (AUC), and model calibration with Hosmer-Lemeshow's C and calibration plots [55]. Results were adjusted for optimism using the bootstrapping techniques [56]. Uniformity of fit was evaluated across clinical grade (WFNS I-III vs. IV-V).

Statistical analysis was performed with R version 3.4.3 [57]. The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. Results

3.1. Patients, aneurysm and treatment

An overview of the source population is available in the online supplement (Table S1). Of 136 patients consecutively recruited during the study period, 57 were excluded, leaving a study population of 79 patients. In total, 37 patients were treated for UIA and 42 patients had aSAH (Table 1).

3.2. Cerebrovascular reactivity

In total, 101 bilateral and 20 unilateral examinations were performed. In patients with aSAH, 84 examinations were done. Median time for first exam was 3.2 (IQR 3.2; range: 1.3–15.0) days after ictus and 2.3 (IQR 2.9; range: 0.8–10.8) days after aneurysm treatment. Median time for the exam with the lowest CVR value was 5.3 (IQR 4.5; range: 1.8–20.2) days after ictus and 4.7 (IQR 3.9; range: 0.8–19.8) days after aneurysm treatment. In patients with UIA, a single examination was performed a median of 2.2 (IQR: 1.8; range: 1.1–6.2) days after aneurysm treatment.

3.3. Ruptured versus unruptured aneurysms

Patients with aSAH had lower CVR compared with patients with UIA (Fig. 1). There was no difference in baseline velocities ($MFV_{BASELINE}$) between aSAH and UIA patients (Table 2). Increase in velocity after AZ (ΔMFV_{AZ}) was however smaller in patients with aSAH, yielding lower both ipsilateral and contralateral CVR. For all patients, regardless of aneurysm rupture status, CVR was on average 5.5 percentage points lower on the ipsilateral side ($p = .04$). Regression analyses (adjustment for age, sex, hypertension, smoking, aneurysm diameter and treatment modality) confirmed that CVR was lower in patients with aSAH. Patients with UIA had a single CVR measurement, whereas aSAH patients were subject to several measurements. There are thus several approaches to calculate individual CVR: the first exam, the lowest value across exams, or the within-patient average for all exams, on both the ipsilateral and contralateral side. Using the first exam, the adjusted ipsilateral CVR was 19.6 percentage points lower in patients with aSAH ($p = .005$), and the contralateral CVR was 16.6 percentage points lower ($p = .002$). Using the lowest value across exams, the adjusted difference between the aSAH and UIA groups was 31.1 percentage points on the ipsilateral side ($p < .001$), and 23.6 percentage points on the contralateral side ($p < .001$). Using the within-patient average, CVR was 19.6 percentage points lower among patients with aSAH on the ipsilateral side ($p = .002$) and 14.7 percentage points lower on the contralateral side ($p = .004$).

3.4. Delayed cerebral ischemia and cerebral infarctions

Of 42 aSAH patients, 22 (52.4%) developed $DCI_{clinical}$. Median time from ictus to diagnosis of $DCI_{clinical}$ was 9 days (IQR 4.8, range 5–19). Furthermore, 19 patients (45.2%) developed $DCI_{infarction}$, and five patients (11.9%) developed infarctions from other causes (Table 3). Four patients with severe, refractory radiographic vasospasm and $DCI_{clinical}$ were given nimodipine intrarterially as rescue therapy and survived with $DCI_{infarction}$. In all patients, angiographic vasospasm and $DCI_{infarction}$ were located bilaterally or on the same side as the ruptured aneurysm. No patients had isolated vasospasm or infarctions on the contralateral side of the ruptured aneurysm. The overall prevalence of poor grade patients and thick bleedings was high; with WFNS grade IV-V in 42.9% of all patients with aSAH, and modified Fisher grade 3–4 in 66.7%. The proportion of patients with excellent clinical admission status (WFNS grade I) was lower ($p = .02$) and hydrocephalus was more prevalent ($p = .007$) in patients with $DCI_{clinical}$.

The different approaches to CVR (first exam, lowest value and

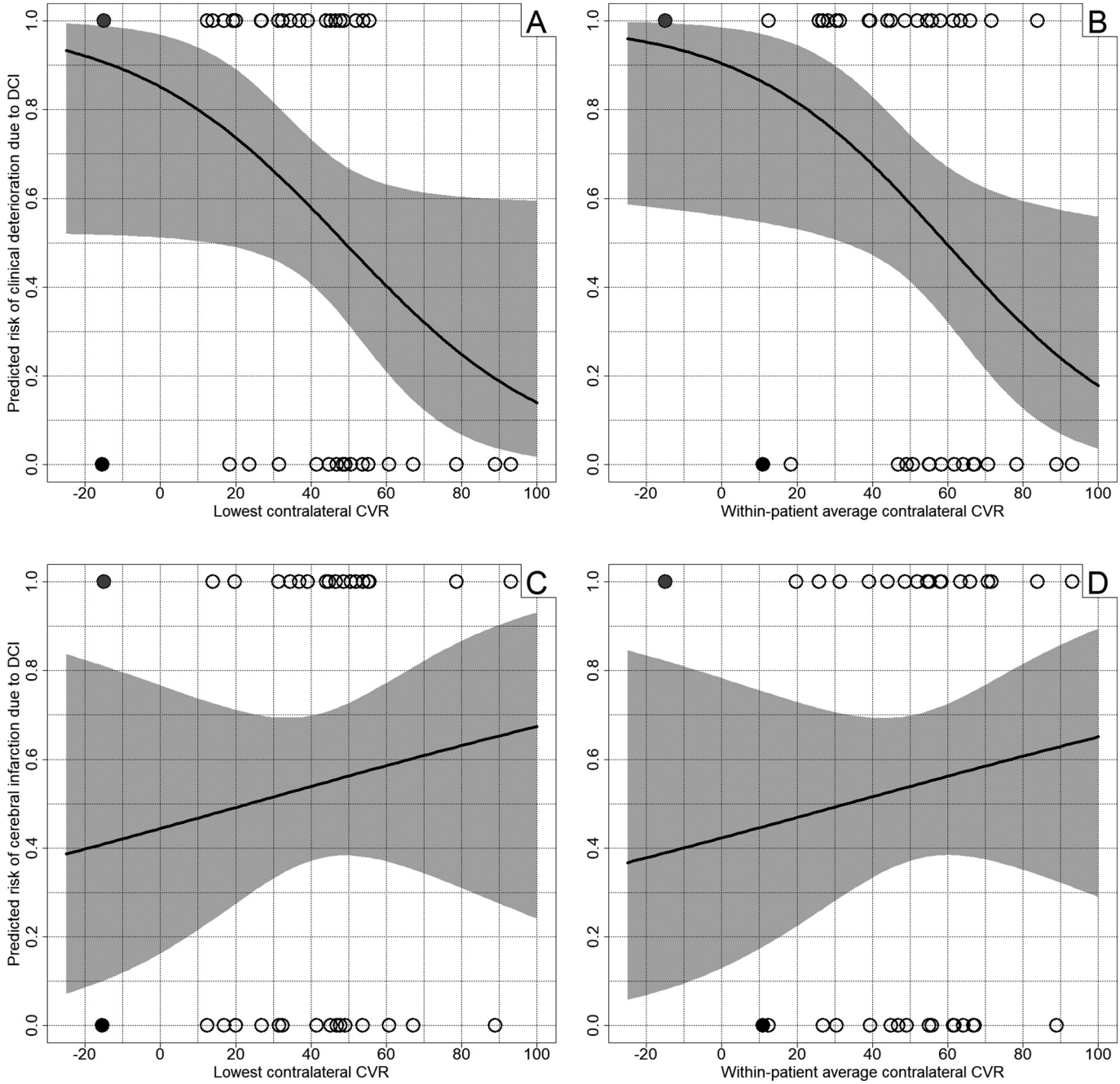

Fig. 2. Probabilities of developing clinical deterioration (A, B) and cerebral infarction (C, D) due to DCI for different CVR values, as predicted by logistic regression. CVR on the contralateral side of aneurysm treatment is used in the models, and the lowest measured CVR (A, C) and within-patient-average CVR of all exams is presented (B, D). The solid black line shows the estimated regression line. Uncertainty is indicated by the shadowed area (95% confidence band). Two patients, marked with a solid grey and black dot, had a paradoxical velocity reduction after AZ.

within-patient average) were compared for patients with and without $DCI_{clinical}$ or $DCI_{infarction}$ (Tables S2-S3). For $DCI_{infarction}$, there was no difference in ipsilateral or contralateral CVR between groups across all approaches (Table S2). For $DCI_{clinical}$ (Table S3), there was no difference in ipsilateral CVR between groups. However, the lowest contralateral CVR was lower in patients with $DCI_{clinical}$ than without (33.9% vs. 49.2%, $p = .05$) and the difference in within-patient average CVR was even larger (43.2% vs. 61.9%, $p = .02$). Differences in first-exam CVR were less apparent (44.0% vs. 56.2%, $p = .19$). Mean combined values of the right and left side masked side-differences between the groups. Fig. 1 shows box plots illustrating the difference between ipsi- and contralateral sides.

Because CVR on the ipsilateral side was similar between patients with and without $DCI_{clinical}$ and $DCI_{infarction}$, contralateral CVR was selected as the exposure variable in logistic regressions (Fig. 2). CVR did not predict $DCI_{infarction}$, but did predict $DCI_{clinical}$. For $DCI_{clinical}$, OR was 0.96 for both the lowest value (95% CI 0.93–1.00, $p = .05$) and within-patient average (95% CI 0.93–1.00, $p = .03$). This corresponds to a 4% reduction in the odds of developing $DCI_{clinical}$ per percentage point increase in CVR. Hence, $DCI_{clinical}$ risk increased with lower contralateral CVR. The risk of developing $DCI_{clinical}$ is 28.3% when the lowest CVR on the contralateral side is 75%, whereas the risk is 49.0% with CVR 50% and 70.1% with CVR 25%.

The prediction models using lowest value and within-patient

Table 4
Multivariable predictors of clinical deterioration due to delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage.

	Odds ratio (95% Confidence Interval)	
	Model I (without CVR)	Model II (with CVR)
Candicate predictors		
CVR	–	0.94 (0.89, 1.00)
Smoking (current vs. former/never)	0.33 (0.04, 2.63)	0.20 (0.01, 3.2)
Hydrocephalus	0.30 (0.02, 4.40)	0.06 (0.00, 4.0)
Established predictors		
Modified CT Fisher I-II	ref	ref
Modified CT Fisher III-IV	3.1 (0.40, 23)	2.1 (0.13, 31)
WFNS I	ref	ref
WFNS II-III	24 (0.71, 836)	3.2 (0.03, 303)
WFNS IV	69 (1.07, 4450)	31 (0.16, 5892)
WFNS V	5.9 (0.14, 251)	1.0 (0.01, 162)
Demographic characteristics		
Male sex	13 (1.14, 150)	37 (2.0, 666)
Age	0.90 (0.82, 0.99)	0.95 (0.85, 1.05)
AUC, crude	0.90 (0.80, 1.00)	0.96 (0.90, 1.00)
AUC, adjusted for optimism[a]	0.82 (0.69, 0.90)	0.86 (0.70, 0.94)

AUC: area under the receiver operating curve; CT: computed tomography; CVR: cerebrovascular reactivity; ref.: reference; WFNS: World Federation of Neurological Surgeons Scale.

[a] Adjusted for optimism with bootstrapping techniques

average were similar for $DCI_{clinical}$, even though the *p*-value for the OR was slightly lower in the second model. Still, the lowest measured CVR is more convenient to use in clinical practice, and the time of the lowest CVR reflects the typical time period for onset of DCI. The lowest value on the contralateral side was therefore chosen as the CVR predictor for $DCI_{clinical}$ in the following analyses.

In prediction Model I the area under the receiver operating characteristic curve (AUC) after correction for optimism was 0.82, and in Model II the corresponding AUC was 0.86 (Table 4). Confidence intervals for AUC for the two models were overlapping. Receiver operating characteristic curves and calibration plots are shown in Fig. 3. Hosmer and Lemeshow's C statistics were C = 15.33 (Model I), and C = 9.41 (Model II). Stratification for clinical grade (WFNS I-III vs. IV-V) did not cause any major changes in the prediction models.

Two patients had a paradoxical velocity reduction after AZ. One patient with a single contralateral CVR of −14.9% (grey dot, Fig. 2) developed both $DCI_{clinical}$ and $DCI_{infarction}$. Another patient with a negative CVR recovered without ischemic symptoms or infarction (black dot, Fig. 2). Notably, the CVR reduction was transient, with CVR of −15.4% in the first exam and 37.4% when re-tested a week later, making the within-patient average CVR 11.0%.

4. Discussion

To our knowledge, this is the first study that has used TCD and AZ to compare CVR in patients with aSAH and UIA. The study indicates that contralateral CVR may be an independent predictor for clinical deterioration due to DCI after aSAH, but CVR is not able to predict radiographic infarction due to DCI.

Various methods are used to assess CVR [58]. It is unclear if CVR results are consistent for different methodologies. Comparing results by multiple methods could elucidate potential differences, but has not been done. The TCD-AZ test is widely applied for CVR testing. The method has some advantages compared with other methods (easier set-up, reduced need for patient co-operation, high safety profile), but also some disadvantages (potential side effects, dose-dependent effects, and contraindications for AZ) [58]. We found that CVR was considerably lower in patients with ruptured aneurysms compared with patients with unruptured aneurysms and this difference appeared to be bigger on the ipsilateral side of aneurysm treatment. This is in concordance with previous CVR-studies using other vasoactive stimuli and measurement methods [9–12,19].

Since the 1970s, literature has suggested that impaired CVR may be associated with DCI after aSAH [14–17,21–30]. With the exception of one study [14], these findings are consistent across different methodologies, study designs, sample sizes, and definitions of DCI. Study sizes have however been small, and CVR has not been integrated as standard assessment after aSAH [35,59–61]. In clinical work, a CVR based prediction model of DCI would be valuable.

In our prediction models, the confidence intervals for the coefficients of the established predictors all included the value 1 by quite some margin, whereas the confidence interval for the coefficient of CVR was 0.89 to 1.00 (Table 4). Note also that 0.94 is the OR per unit change in CVR, which corresponds to an OR of about 0.54 per change of 10, and an OR of 0.05 per change of 50. Among patients in our study, CVR ranges from less than zero to > 90. Hence, contralateral CVR appears to be the strongest predictor of DCI in the model. The confidence intervals of the AUCs were overlapping, which indicates that CVR did not have additional value in the prediction of DCI after aSAH. Still, including CVR in the model caused a substantial increase of optimism adjusted AUC from 0.82 to 0.86. This warrants further investigation, especially as a more accurate prediction model for DCI is needed.

Practical considerations such as ease-of-use and patient comfort are arguments in favor of single CVR testing. Serial testing is time consuming and can be challenging due to reduced patient co-operation, postoperative intracranial air, drains and monitoring equipment in the intensive care unit. Still, DCI has a dynamic nature, the first measured CVR had very low predictive power, and serial CVR-measurements provided added information regarding the dynamic changes in CVR throughout the acute phase after aSAH.

Overall, 52.4% of patients with aSAH in this study developed DCI. In comparison, the reported incidence of DCI is 20–35% in larger case series [1,62–70]. The high frequency of DCI may reflect the high proportion of poor grade patients in our cohort, as poor clinical grade upon admission is associated with higher risk of developing DCI. Given the high proportion of patients with large bleedings and poor clinical conditions in our study, results may not be fully valid for other populations. Still, stratification for clinical grade (WFNS I-III vs. IV-V) did not cause any major changes in the prediction model.

In a previous report we argued that ipsi- and contralateral CVR should be assessed separately, as mean values can conceal side-differences [41]. One-year follow-up study indicated that patients with unruptured aneurysms had a temporary reduction in ipsilateral CVR. The present study indicates that ipsilateral CVR is reduced also after treatment for *ruptured* aneurysms. Ipsilateral CVR reduction thus seem to occur in all patients after aneurysm treatment, regardless of $DCI_{clinical}$ status. Acknowledging this side-difference enables improved interpretation of CVR after aneurysm treatment. Aneurysm treatment in itself does not induce a substantial CVR reduction on the contralateral side, making the contralateral CVR more suitable as a predictor since any DCI-related CVR reduction will be more pronounced on this side compared with the already reduced CVR on the ipsilateral side.

In concordance with the pre-existing hypothesis that CVR can predict DCI, we found impaired CVR in patients with $DCI_{clinical}$. Surprisingly, we did not find an equivalent reduction in CVR in patients with $DCI_{infarction}$. This is quite a conundrum as one would expect impaired CVR for both categories of DCI, assuming clinical symptoms and infarctions are two time-points in a continuum of the same disease. The statistical power in our study may be insufficient to detect CVR impairment in patients with $DCI_{infarction}$. Still, as $DCI_{infarction}$ is presumably associated with more advanced ischemia one would also expect CVR impairment to be more advanced in patients with $DCI_{infarction}$ compared with $DCI_{clinical}$. However, the pathophysiology of cerebral ischemia after aSAH is multifactorial and complex [71], and it is possible that there are differences in the pathogenesis for clinical and radiographical presentations. Furthermore, we used $DCI_{infarction}$ as a dichotomous

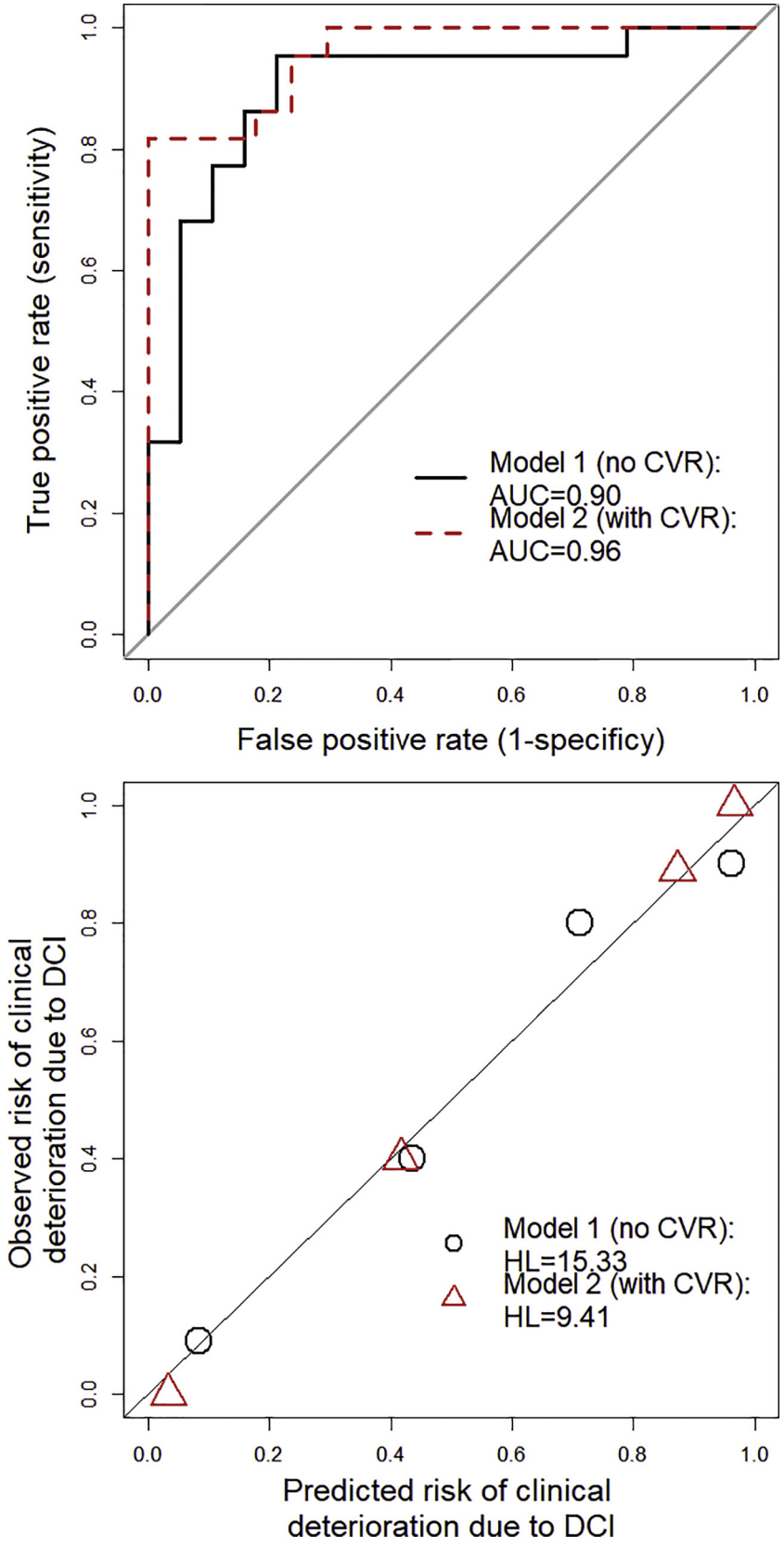

Fig. 3. Discrimination and calibration plots for predictive models with and without CVR. A, The crude receiver operating characteristic (ROC) show the discrimination of the predictive model with and without CVR, not adjusted for optimism. See Table 4. B, The plot shows the calibration (actual outcome versus predicted outcome) analyzed in four equal groups for both predictive models.

variable, not taking into account the size or severity of the infarction. For ethical reasons, moribund patients and patients with increased ICP were excluded (Table S1), this probably reduced the number of patients with severe infarctions that was tested and left a higher proportion of minor infarctions in the studied population. Additional studies with larger study sample and more comprehensive radiographical examinations including assessment of infarction size could help clarify if impaired CVR is associated with $DCI_{infarction}$ or not.

There are limitations to our study. The study population is small, although the number of patients ($n = 42$) is higher than in other neurosonological studies (median $n = 27$, range 18–34) [14,16,19,22,30,72,73]. Further limitations are the lack of external validation of the prediction model. We did not examine patients according to a rigid time schedule. To better compare the aSAH and UIA groups, and overcome the dynamic nature of CVR over time, CVR should ideally have been examined in all patients at the same time intervals after treatment. All patients underwent cerebral imaging with CT and/or MRI after aneurysm treatment. Among 42 patients with aSAH, 17 were only evaluated with CT/CTA during their primary hospital stay. Still, MRI was performed in the majority of patients during follow-up. Of the 39 patients alive after one year, 36 underwent MRI; two were tourists and lost to follow-up; and one patient declined to take the exam due to claustrophobia. We used a well-known classification system for cerebral infarction [74,75]. Still, the attribution of infarction etiology after aSAH is difficult and not easily validated [76], and one cannot be certain whether infarctions are related to DCI or not. To avoid misclassifying procedure-related infarcts as vasospasm-induced, CT and MRI scans should be performed between 24 and 48 h after aneurysm occlusion. This was only done in 33 of 42 patients. The diagnosis of sonographic vasospasm and clinical deterioration due to DCI was set without blinding of CVR-results. Ideally, the AZ doses should have been bodyweight-based in all patients in the study, not only in patients weighing ≥80 kg. Still, the recommended AZ dose of 13 to 18 mg/kg [46,77] was achieved in 91.7% of CVR tests. We used different brands of AZ, yet no difference in CVR has been found when the three manufacturers were compared [41].

A strength of our study is the methodology. Unlike the majority of previous studies [14,15,17,21–29], we used standardized definitions of DCI separated into clinical and radiographic findings [38,39]. We performed serial testing, which is better adjusted to the dynamic nature of vasospasm and DCI. We also tested CVR in patients treated for UIA to increase our general understanding of CVR in patients with intracranial aneurysms. One sonographer (MLB) performed all ultrasound examinations and CVR-tests to reduce operator variability. One neuroradiologist (GM) diagnosed angiographic vasospasm and cerebral infarction, unaware of the patient's clinical and sonographic status.

Central drawbacks with regards to clinical use is that CVR testing is time consuming and that a number of patients experience side effects related to AZ, like headache, flushing, nausea or paresthesia [20]. Still, potential side effects are usually transient and well tolerated [78]. Results are promising, but does not provide firm confirmation that impaired CVR predicts DCI. There are still unresolved issues, and it is too soon to recommend routine use of CVR in clinical practice. Results needs to be externally validated, and the conundrum regarding CVRs relation to $DCI_{infarction}$ needs to be investigated. If validation studies confirm our findings, CVR testing may assist clinicians in early identification of patients who may benefit from aggressive prophylactic treatment, closer monitoring, or repeat vascular imaging. Determining those at greatest risk can help reduce DCI-related poor outcomes while minimizing treatment complications and titrate length of stay in an intensive care unit.

Pretreatment CVR testing could assess potential effects on CVR caused by aneurysm treatment itself. Still, patients were not examined prior to treatment because of the potential risk of causing aneurysm (re-)rupture, and to avoid delay in the acute treatment of a ruptured aneurysm. CVR can be assessed at an earlier time in patients with UIA with assumed low rupture risk and no planned treatment, but this will not give any information about the status of cerebrovascular integrity immediately before aneurysm treatment or rupture. We did not take into account variations of intracranial pressure (ICP) or systemic blood pressure in patients with aSAH. AZ does not cause major changes in systemic blood pressure [43,79], but may lower ICP by reducing cerebrospinal fluid secretion [80]. AZ may also *increase* ICP by cerebral vasodilation [81] and may not be well suited for patients with increased ICP. These high-risk patients are closely monitored for development of DCI and AZ testing might be of less importance. In less severe cases, however, improved prediction of DCI is highly useful, and can assist medical and logistic decision making.

5. Conclusions

Impaired CVR on the contralateral side may be an independent predictor of $DCI_{clinical}$, and may assist in identifying patients in need of closer observation after aSAH. An ipsilateral CVR reduction occurs in all patients after aneurysm treatment, regardless of $DCI_{clinical}$ status, highlighting the need to consider ipsilateral and contralateral CVR separately. This study underscores the value of serial CVR measurements, and future studies aiming to investigate the relationship between CVR and DCI after aSAH should take this into account. Our prediction model can be useful in clinical practice, but needs to be validated.

Author contribution statement

Study conception and design: Bøthun, Helland, Thomassen. Acquisition of data: Bøthun, Helland, Moen. Analysis and interpretation of data: All. Drafting of manuscript: Bøthun, Haaland. Critically revising the article: All. Reviewed submitted version of manuscript: All. Statistical analysis: Haaland. Study supervision: Bøthun, Helland, Thomassen.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116539.

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