Clinical prediction of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage

Hubert Lee, MD, MSc,¹ Jeffrey J. Perry, MD, MSc,² Shane W. English, MD, MSc,³
Fahad Alkherayf, MD, MSc, CIP, FRCSC,¹ Joanne Joseph, HBSc,⁴ Steven Nobile, BSc,⁴
Linghong Linda Zhou, BHSc,⁴ Howard Lesiuk, MD,¹ Richard Moulton, MD,¹ Charles Agbi, MBBS,¹
John Sinclair, MD,¹ and Dar Dowlathshahi, MD, PhD⁵

¹Division of Neurosurgery, The Ottawa Hospital, Ottawa; ²Department of Emergency Medicine, The Ottawa Hospital, Ottawa Hospital Research Institute, University of Ottawa; ³Department of Critical Care, The Ottawa Hospital, Ottawa; ⁴Faculty of Medicine, University of Ottawa; and ⁵Division of Neurology, The Ottawa Hospital, Ottawa, Ontario, Canada

OBJECTIVE The aim of this study was to derive a clinically applicable decision rule using clinical, radiological, and laboratory data to predict the development of delayed cerebral ischemia (DCI) in aneurysmal subarachnoid hemorrhage (aSAH) patients.

METHODS Patients presenting over a consecutive 9-year period with subarachnoid hemorrhage (SAH) and at least 1 angiographically evident aneurysm were included. Variables significantly associated with DCI in univariate analysis underwent multivariable logistic regression. Using the beta coefficients, points were assigned to each predictor to establish a scoring system with estimated risks. DCI was defined as neurological deterioration attributable to arterial narrowing detected by transcranial Doppler ultrasonography, CT angiography, MR angiography, or catheter angiography, after exclusion of competing diagnoses.

RESULTS Of 463 patients, 58% experienced angiographic vasospasm with an overall DCI incidence of 21%. Age, modified Fisher grade, and ruptured aneurysm location were significantly associated with DCI. This combination of predictors had a greater area under the receiver operating characteristic curve than the modified Fisher grade alone (0.73 [95% CI 0.67–0.78] vs 0.66 [95% CI 0.60–0.71]). Patients 70 years or older with modified Fisher grade 0 or 1 SAH and a posterior circulation aneurysm had the lowest risk of DCI at 1.2% (0 points). The highest estimated risk was 38% (17 points) in patients 40–59 years old with modified Fisher grade 4 SAH following rupture of an anterior circulation aneurysm.

CONCLUSIONS Among patients presenting with aSAH, this score-based clinical prediction tool exhibits increased accuracy over the modified Fisher grade alone and may serve as a useful tool to individualize DCI risk.

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KEYWORDS delayed cerebral ischemia; vasospasm; subarachnoid hemorrhage; aneurysm; prediction; clinical decision rule; vascular disorders

DEDELAYED cerebral ischemia (DCI) is the leading cause of preventable mortality and morbidity, accounting for 23% of deaths, 11%–15% of poor outcomes, and persistent neurological deficit in 37% of survivors.^{22,25,27} Several clinical and radiological features have been investigated as potential predictors of DCI in previous models.^{2,6,7,10,14,17,23,24} They identified neurological

grade, clot thickness, aneurysm location, cerebral blood flow (CBF), age, cardiac vital signs, CSF drainage, intracranial pressure, and serum electrolytes as important variables; however, a practical clinical tool remains to be developed. These models are limited by outdated practices, study-specific aneurysmal subarachnoid hemorrhage (aSAH) scales, cumbersome measures of intraventricular

ABBREVIATIONS aSAH = aneurysmal SAH; CBF = cerebral blood flow; DCI = delayed cerebral ischemia; DSA = digital subtraction angiography; EVD = external ventricular drainage; IVH = intraventricular hemorrhage; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; TCD = transcranial Doppler; WFNS = World Federation of Neurosurgical Societies.

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hemorrhage (IVH), institution-specific technology to measure CBF, and small sample size.

Timely diagnosis of DCI can be difficult, as the degree of arterial vessel-caliber reduction does not necessarily correlate with development of neurological symptoms. A clinical prediction rule, a mathematical tool using patient characteristics and investigation results to aid physicians in predicting DCI in aSAH, would allow early identification of patients who may benefit from aggressive prophylactic treatment, closer monitoring in an ICU, or repeat vascular imaging. Determining those at greatest risk can help reduce DCI-related poor outcomes while minimizing treatment complications and titrate ICU length of stay. The objective of this study was to derive a clinically applicable prediction rule based on routine clinical, radiological, and laboratory characteristics that identifies patients with aSAH who will develop DCI.

Methods

Patient Population

The health records of patients admitted between June 2002 and 2011 with subarachnoid hemorrhage (SAH) and an intracranial aneurysm were retrospectively reviewed at the Ottawa Hospital, a tertiary care institution and regional neurosurgical center. SAH was diagnosed by CT or CSF analysis demonstrating $> 5 \times 10^6/\text{L}$ red blood cells in the final test tube or xanthochromia up to 2 weeks after suspected aneurysmal rupture.^{20,21} Aneurysms were confirmed by CTA, MRA, or conventional digital subtraction angiography (DSA). Only patients older than 18 years presenting within the risk period for cerebral vasospasm were included. Death prior to day 4 post-aSAH, admission past day 14 post-aSAH, DCI at presentation, and aneurysms associated with arteriovenous malformations or of the mycotic or traumatic type were criteria for exclusion. Recruitment was completed using a validated text miner that searched radiology reports for keywords indicating aSAH and CSF analysis results within the Ottawa Hospital Data Warehouse.¹² Search results were verified individually to ensure accuracy and that the inclusion and exclusion criteria were satisfied.

Predictor Variables

Data were collected for each patient related to their comorbidities, presentation, and in-hospital course. The clinical variables included were age, sex, cardiovascular risk factors, previous intracranial hemorrhage, smoking status, illicit drug use, medications, family history of aneurysms or aSAH, presenting neurological grade, systolic blood pressure, body temperature, and unit of admission. Age was analyzed as a continuous variable and a categorical variable by decades, with ages 18–39 years and 70 years or older collapsed into single groups due to small numbers. Blood pressure and temperature were classified as continuous variables and dichotomized variables at 180 mm Hg and 38°C, respectively. Neurological grade was assessed using the World Federation of Neurosurgical Societies (WFNS) scale.

Radiological variables considered were modified Fisher grade¹³ (classified by a single investigator reviewing all

presenting CT head imaging), ruptured aneurysm location and maximum diameter, aneurysm multiplicity, hydrocephalus, and mean flow velocities recorded by transcranial Doppler (TCD) ultrasonography on days 2–14 post-aSAH. TCD results were summarized as elevated (mean flow velocity > 120 cm/sec and Lindegaard ratio > 3), normal, or not performed. Management-related variables included the modality of aneurysm treatment; use of nimodipine, prophylactic statin, antiepileptic drugs, or nicotine replacement therapy; and required external ventricular drain (EVD) placement or endotracheal intubation within 24 hours of presentation or prior to day 4 post-aSAH. Complications entered as present or absent on day 3 post-aSAH or earlier included seizures, hyponatremia, anemia, pulmonary edema, acute coronary syndrome, arrhythmia, and heart failure. The cutoffs used for hyponatremia and anemia were a serum sodium level < 135 mmol/L and hemoglobin level ≤ 100 g/L, respectively. Pulmonary edema was verified using chest radiographs. Acute coronary syndrome was considered present if clinical symptoms (chest pain, left arm pain, diaphoresis) or electrocardiogram changes accompanied elevated cardiac enzymes. The arrhythmias of interest were ventricular tachycardia, ventricular fibrillation, and supraventricular tachycardia. An echocardiogram demonstrating an ejection fraction less than 40% was required for a diagnosis of systolic heart failure.

Definition and Assessment of DCI

DCI was defined as a focal neurological deficit attributable to a detected vascular territory of intracranial arterial narrowing (angiographic vasospasm) in the absence of alternative causes. The deficit could not be present immediately after aneurysm treatment and included hemiparesis, hemiparesthesia, aphasia, apraxia, neglect, hemianopia, and decreased level of consciousness equaling a loss of ≥ 2 points on the Glasgow Coma Scale.²⁹ Changes in neurological status were determined from chart review, and arterial narrowing was diagnosed from radiology reports documenting vasospasm of all severities on CT, MR, or DSA, or elevation in TCD velocities meeting the criteria for vasospasm. Outcome assessment was divided among 3 investigators blinded to the identity of the predictor variables. Uncertainty about the outcome was adjudicated by a fourth investigator. Interrater reliability was determined based on a pilot cohort of 25 patients using the (2,1) form of the Shrout-Fleiss intraclass correlation coefficient with each rater considered a random effect.²⁶ The results from this initial evaluation period were included in subsequent analysis.

Logistic Regression

The associations between the chosen predictor variables and DCI were characterized by univariate analysis using the chi-square or Fisher exact test and 2-sided t-test for categorical and continuous variables, respectively. Only those variables available at the time of presentation up to day 3 post-aSAH were considered. Candidate variables meeting a conservative p value < 0.20 underwent multivariate logistic regression using stepwise backward selection, and

those reaching statistical significance ($p < 0.05$) were retained. Odds ratios with corresponding 95% confidence intervals were calculated describing the contribution of each predictor to the occurrence of DCI. Model fit was assessed using the Hosmer-Lemeshow test and its discrimination determined by receiver operating characteristic (ROC) curve analysis. The area under the ROC curve of the derived model was compared to the performance of the modified Fisher grade alone. All analyses were performed using SAS software (version 9.4, SAS Institute Inc.).

Using accepted methods, a risk score was developed based on the estimated beta coefficients from the final multivariate logistic regression model.²⁸ The smallest coefficient was assigned as the constant for the point system representing a point of 1. Values for the remaining risk factors were assigned by dividing the associated beta coefficient by the point system constant and rounding to the nearest 0.5. The estimated risk of DCI associated with each point total was calculated using the methods described by Sullivan et al. and the corresponding sensitivity and specificity for each score cutoff were determined.²⁸

Results

From the cohort of 568 aSAH patients identified by the text miner, 463 were included in this study. The most common criterion for exclusion was death prior to day 4 post-aSAH, accounting for 75 (71.43%) of the excluded patients. Two unruptured aneurysms undergoing endovascular coiling complicated by intraoperative rupture were included and analyzed, as they met predefined inclusion criteria. It was not possible to perform a meaningful sensitivity analysis comparing spontaneous to iatrogenic ruptured aneurysms due to small numbers.

The mean age $\pm$ SD at presentation was 56.0 ± 13.2 years, and the majority of patients were female (70.2%). Almost half the patients had a history of hypertension and current smoking (46.0% and 48.0%, respectively). Neurological grade at presentation was generally good, with 50.5% of patients having WFNS grade I and only 13.2% having WFNS grade V. Thick SAH with IVH was observed on CT in 41.7% of patients, corresponding to a modified Fisher grade 4; 14.5% SAHs were modified Fisher grade 3, 17.9% were modified Fisher grade 2, and 25.9% were modified Fisher grade 1 or 0. Lumbar puncture was used to diagnose 27 patients whose CT scan was negative for SAH. Anterior circulation aneurysms predominated at 82.5%. TCD ultrasonography was only performed in 34.6% of patients, with 3.9% demonstrating elevated velocities. A greater proportion of aneurysms underwent endovascular coiling (57.0%) than surgical clipping (43.0%). CSF diversion via EVD placement was required by 31.3% patients.

Angiographic vasospasm was detected by CTA, MRA, DSA, or TCD ultrasonography in 57.7% of patients, of whom just over one-third exhibited attributable neurological symptoms. The resulting overall incidence of DCI in this cohort was 21.0%. The distribution of clinical features, radiological findings, treatments, and complications between those who developed DCI and those who did not is detailed in Table 1. While just under 50% of patients

TABLE 1. Demographic, clinical, and radiological characteristics of 463 patients presenting with aSAH

Characteristic	Pts w/ Delayed Cerebral Ischemia (n = 97)	Pts w/o Delayed Cerebral Ischemia (n = 366)	p Value
Demographics			
Age, yrs			
Mean	54.62 ± 11.56	56.35 ± 13.58	0.25
<40	7 (7.2)	39 (10.7)	0.15
40–49	26 (26.8)	80 (21.9)	
50–59	34 (35.1)	107 (29.2)	
60–69	20 (20.6)	67 (18.3)	
≥70	10 (10.3)	73 (20.0)	0.22
No. of females	73 (75.3)	252 (68.9)	
Comorbidities			
Hypertension	42 (43.3)	171 (46.7)	0.55
Hypercholesterolemia	11 (11.3)	53 (14.5)	0.43
Diabetes	7 (7.2)	32 (8.7)	0.84
Coronary artery disease	10 (10.3)	35 (9.6)	0.85
Stroke	2 (2.1)	16 (4.4)	0.39
Connective tissue disorder	2 (2.1)	2 (0.6)	0.19
Sickle cell disease	0 (0.0)	1 (0.3)	>0.99
Current smoker	51 (52.6)	171 (46.7)	0.30
Cocaine/amphetamine use	2 (2.1)	7 (1.9)	>0.99
Previous hemorrhage (SAH/ICH/IVH)	2 (2.1)	10 (2.7)	>0.99
Family history of aneurysms or SAH	9 (9.3)	39 (10.7)	0.85
Home medications			
Statin	9 (9.3)	56 (15.3)	0.14
Antiplatelet	11 (11.3)	60 (16.4)	0.22
Anticoagulant	1 (1.0)	10 (2.7)	0.47
Clinical features at presentation			
WFNS grade			0.02
I	35 (36.1)	199 (54.4)	0.33
II	18 (18.6)	44 (12.0)	
III	8 (8.3)	15 (4.1)	
IV	20 (20.6)	63 (17.2)	
V	16 (16.5)	45 (12.3)	
Mean systolic blood pressure, mm Hg	161 ± 34.63	157.5 ± 30.18	0.95
Mean temperature, °C	36.23 ± 0.92	36.22 ± 0.96	0.01
ICU admission	45 (46.4)	120 (32.8)	
Radiological findings			
Modified Fisher grade			<0.0001
0/1	11 (11.3)	109 (29.8)	0.01
2	8 (8.3)	75 (20.5)	
3	21 (21.7)	46 (12.6)	
4	57 (58.8)	136 (37.2)	

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Characteristic	Pts w/ Delayed Cerebral Ischemia (n = 97)	Pts w/o Delayed Cerebral Ischemia (n = 366)	p Value
Radiological findings (<i>continued</i>)			
Location			0.002
Posterior circulation	7 (7.2)	74 (20.2)	
Posterior communicating artery	17 (17.5)	63 (17.2)	
Internal carotid artery	6 (6.2)	37 (10.1)	
Middle cerebral artery	29 (29.9)	68 (18.6)	
Anterior cerebral artery	3 (3.1)	14 (3.8)	
Anterior communicating artery	35 (36.1)	110 (30.1)	
Mean diameter of ruptured aneurysm, mm	6.61 ± 3.69	7.27 ± 4.06	0.15
No. of pts w/ multiple aneurysms	29 (29.9)	124 (33.9)	0.46
Mean total no. of aneurysms	1.47 ± 0.91	1.49 ± 0.88	0.86
Hydrocephalus	54 (55.7)	173 (47.3)	
TCD ultrasonography (SAH day 3 or prior)			0.14
Elevated	7 (7.2)	11 (3.0)	
Normal	31 (32.0)	111 (30.3)	
Not performed	59 (60.8)	244 (66.7)	
Treatment			
Surgical clipping*	47 (49.5)	147 (41.3)	0.15
Endovascular coiling*	48 (50.5)	209 (58.7)	
Nimodipine	97 (100.0)	361 (98.6)	0.59
Statin	49 (50.5)	141 (38.5)	0.03
Antiepileptic drug	94 (96.9)	343 (93.7)	0.32
Nicotine replacement therapy	4 (4.1)	16 (4.4)	>0.99
Complication (SAH day 3 or prior)			
EVD placement	39 (40.2)	106 (29.0)	0.03
Seizures	20 (20.6)	52 (14.2)	0.12
Intubation	41 (42.3)	113 (30.9)	0.03
Pulmonary edema	12 (12.4)	48 (13.1)	0.85
Cardiac	10 (10.3)	33 (9.0)	0.70
Hyponatremia (<135 mmol/L)	16 (16.5)	54 (14.8)	0.67
Anemia (≤100 g/L)	21 (21.7)	76 (20.8)	0.85

ICH = intracerebral hemorrhage; pts = patients.

* Twelve aneurysms did not undergo occlusive treatment due to poor neurological condition.

were discharged home from the hospital, the case fatality rate of aSAH was 14.3%. Those who acquired DCI had a marginally higher mortality rate at 16.5% (no DCI: 13.7%) and substantially reduced discharge home, 38.1% (no DCI: 52.5%).

Interrater Reliability

The percentage agreement among the 3 outcome assessors for the pilot aSAH cohort was 85.3%. An identical diagnosis by all assessors occurred in 20 of 25 cases. The Shrout-Fleiss intraclass correlation coefficient was 0.84 (95% CI 0.71–0.92), indicating good interrater reliability in identifying DCI.

Logistic Regression

A total of 14 variables were significantly associated with DCI at $p < 0.20$ (Table 1). These included age, history of connective tissue disorder, home statin use, WFNS grade, ICU admission, modified Fisher grade, aneurysm location, aneurysm diameter, early elevated TCD velocities, modality of aneurysm treatment, statin prophylaxis, EVD placement, seizures prior to admission, and early intubation. TCD ultrasonography results did not undergo further analysis, as there was a great amount of missing information, with 303 patients who did not undergo this examination.

After fitting the variables significant from univariate analysis into an initial multivariable model, only age, modified Fisher grade, and aneurysm location remained predictive of DCI (Table 2). For age, being younger than 40 years and 60–69 years did not reach significance when compared to age ≥ 70 years. Similarly, modified Fisher grade 2 in relation to grade 1 had a p value > 0.05 . The Hosmer-Lemeshow test of the multivariable model did not show evidence of poor fit ($p = 0.82$). Discrimination was acceptable with an area under the ROC curve of 0.73 (95% CI 0.67–0.78), greater than the modified Fisher grade alone (0.66 [95% CI 0.60–0.71]).

DCI Score Derivation

The smallest estimated coefficient, 0.23 from the relationship between modified Fisher grade 2 and grade 1, was assigned a point equivalence of 1 and used as the score constant from which the point values for the remaining covariate categories were designated (Table 2). This resulted in a score containing 3 clinicoradiographic variables totaling 0–17 points and associated with an estimated risk of DCI of 1%–38% (Table 3). Figure 1 illustrates the sensitivities and specificities for all possible score cutoffs.

Discussion

Factors Predictive of DCI

We derived a clinical decision rule to predict DCI using 3 predictors: age, amount of SAH on presentation, and ruptured aneurysm location. This decision rule achieves improved estimation of an individual's DCI risk beyond the modified Fisher grade alone. A recently proposed risk chart identified age dichotomized at 55 years as an important prognostic factor.⁷ We characterize this risk between decades in a contemporary study population where endo-

TABLE 2. Multivariable logistic regression model predicting DCI in aSAH and derivation of the DCI score

Predictor	Estimated β Coefficient	SE	Estimated OR	95% CI	p Value	Points = β Coefficient/B
Intercept	-4.42	0.6636			<0.0001	
Age, yrs						
<40	0.85	0.59	2.34	0.74–7.36	0.15	4
40–49	1.20	0.45	3.33	1.39–7.97	0.007	5
50–59	1.18	0.43	3.22	1.40–7.42	0.006	5
60–69	0.69	0.46	1.99	0.82–4.87	0.13	3
≥ 70	Reference					0
Modified Fisher grade						
0/1	Reference					0
2	0.23	0.50	1.26	0.48–3.34	0.64	1
3	1.49	0.42	4.46	1.96–10.13	0.0004	6
4	1.70	0.37	5.45	2.62–11.33	<0.0001	7
Aneurysm location						
Anterior	1.26	0.43	3.54	1.51–8.29	0.004	5
Posterior	Reference					0

B = constant for the point system (0.23 from modified Fisher grade 2).

vascular coiling is increasingly prevalent. Dumont and colleagues' artificial neural network also included age; however, the variable "age" was entered with presumed importance and its individual contribution is difficult to interpret.¹⁰ A 2013 systematic review concluded "inconsistent evidence" from studies supporting greater risk in younger patients,³ with increasing age,³⁰ or no difference with age.^{8,23} Macdonald and colleagues' description of DCI risk peaking for ages 40–59 years mirrors our findings.¹⁸ Senescent intracranial arteries become increasingly stiff with reduced elasticity from vessel wall thickening, increased thickness-to-radius ratio, and collagen fiber formation.^{15,16} This, along with atherosclerosis, may render elderly patients more resistant to vasospasm with the ability to maintain luminal patency in the setting of restricted CBF. Why younger patients experienced lower rates of DCI is uncertain but perhaps reflects an increased resilience to ischemia and preservation of autoregulation. This is suggested by the loss of association between the reversibility of neurological deterioration secondary to angiographic vasospasm and severity of vessel narrowing with increasing age where cardiorespiratory comorbidities are increasingly prevalent.³¹

The amount of initial SAH has a robust association to DCI regardless of its classification.^{2,10,14,17,23} The modified Fisher grade, which we demonstrated to independently increase susceptibility to DCI with higher grade, has only been studied in other models when collapsed into thin or thick SAH despite improved prognostication by incorporating IVH status.^{4,6,7,13} De Rooij and colleagues' risk chart recognized the contribution of IVH, quantifying it using the Hijdra score.⁷ This score's complexity comprises overall feasibility and is likely the reason it was removed in the VASOGRADE, a subsequent external validation study.⁶ A multivariate analysis of 218 aSAH patients demonstrated the modified Fisher grade to be a significant risk factor for DCI with an OR of 2.99 (95% CI 2.05–4.35).³⁰ We

did not find a difference between modified Fisher grades 1 and 2, representing the absence or presence of IVH accompanying thin SAH. Only 8 cases of grade 2 aSAH were associated with DCI, resulting in insufficient power. EVD placement prior to day 4 post-SAH did significantly alter the influence of having a modified Fisher grade 4 versus grade 3 aSAH when included in the multivariable model such that the grades' odds ratios were practically equivalent, negating the importance of IVH. If true, the deleterious effects of hemorrhagic products in CSF can be minimized by enhanced clearance through CSF drainage. Omission of EVD placement from the final prediction rule

TABLE 3. Estimated risk of DCI based on the point total from the DCI score

Point Total	Estimate of Risk (%)	Risk Group
0	1.2	Low
1	1.5	
3	2.4	
4	3.0	
5	3.7	
6	4.6	
7	5.8	Moderate
8	7.2	
9	8.9	
10	10.9	
11	13.4	
12	16.3	
14	23.7	High
15	28.2	
16	33.1	
17	38.4

FIG. 1. Sensitivity and specificity of the delayed cerebral ischemia score for all point cutoffs. Figure is available in color online only.

stems from the possibility that the modified Fisher grade influences EVD insertion, allowing a change of a patient's risk score in real time, if included.

Ruptured posterior circulation aneurysms were less likely to precipitate DCI than anterior circulation aneurysms. Qureshi and colleagues' risk index also identified anterior cerebral and internal carotid artery aneurysms as high-risk features.²³ The relationship between aneurysm location and DCI has previously been investigated. Posterior cerebral artery aneurysms were protective against DCI with an OR of 0.05 (95% CI 0.01–0.41).¹⁹ Abla et al. determined that rupture of vertebral and basilar artery aneurysms resulted in the second and third lowest mean SAH maximum thickness behind pericallosal artery aneurysms.¹ While this association with SAH thickness could explain our observed difference in DCI incidence, it is doubtful, as the proportion of aSAHs classified as modified Fisher grades 3 and 4 was comparable between locations (anterior: 56.5%, posterior: 54.3%).

Incidence of DCI and Proposed Clinical Decision Rule

The DCI score estimates the risk to be 1.2% in a ≥ 70 -year-old patient with thin to absent SAH, no IVH, and a posterior circulation aneurysm. A patient 40–59 years old with thick SAH, IVH, and an anterior circulation aneurysm is at highest risk, estimated at 38.4%. This range differs from Qureshi and colleagues' point-based risk index due to differing incidence.²³ When all risk factors are present in both scores, the probability of developing DCI almost doubles.²³ Our observed rate falls in the lower end of the range (20% to 43.2%) from previously published prediction models whose outcome definitions varied.^{2,6,7,10,14,17,23,24} Reduced diagnosis of DCI may have resulted from the requirement for attributable angiographic vasospasm. However, the artificial neural network of Dumont et al. used an identi-

cal outcome definition, resulting in 39 cases (35%).¹⁰ The lowest incidence was observed in de Rooij and colleagues' validation cohort—20%—where radiographic evidence of infarction was required.⁷ The incidence of DCI has decreased from 32.5% in studies published prior to 1994 to 28.5% in studies published between 1994 and 2009, during which aSAH management has changed, affecting complication rates and outcome.⁹ With calcium channel blocker prophylaxis (nimodipine or nicardipine) in 32 publications, this proportion declined to 22%. Nimodipine administration in this study occurred in all but 3 patients, explaining the lower incidence as well as suggesting efficacy of this prophylactic agent. A recent study investigating the role of aneurysm location on aSAH outcomes similarly found neurological deterioration with angiographic vasospasm in 22% of patients who all received nimodipine.¹ It is recognized that our definition of DCI potentially missed cases precipitated by mechanisms other than proximal arterial narrowing, including microvascular vasospasm, microthromboembolism, and cortical spreading ischemia.

The current practice in aSAH management is to monitor all patients as high risk for DCI, particularly until after the peak onset period for vasospasm of 6–8 days after aSAH. The VASOGRADE and de Rooij and colleagues' risk chart identified predictors (age, initial neurological grade, thickness of SAH, and IVH) available at the time of presentation with the same aim as this study for early risk stratification to tailor patient monitoring, treatment, and disposition.^{6,7} Classifying age into decades and the addition of aneurysm location in our model improved discriminative performance with a greater area under the ROC curve (0.73 [current study] vs 0.63 [de Oliveira Manoel et al.⁶] vs 0.63 [de Rooij et al.⁷]). In choosing a score cutoff, clinicians are more likely to accept over-diagnosing DCI, as missed cases can lead to serious morbidity or even mortality. A DCI score of ≤ 9 is proposed to represent a low-

risk group having less than half the estimated risk ($< 10\%$) of developing DCI and high sensitivity near or at 100% for scores lower than 7. Sensitivity approaches specificity at a score of 14, where the estimated risk (28.2%) begins to exceed the population incidence, suggesting scores ≥ 15 to be a high-risk group.

Study Limitations

The major limitation of this study is its retrospective nature, which may have led to diagnosis misclassification of DCI, failure to identify important comorbidities, and precluded standardization of CBF monitoring. While this could contribute to the lower incidence of DCI observed, it remains within the expected range when considering newer studies implementing routine nimodipine administration.⁹ The proportions for cardiovascular risk factors, hypertension and diabetes specifically, were also consistent with those of previous studies (hypertension: 25%–44%,¹⁸ diabetes: 3%–9%).¹¹ Patients whose altered neurological status was successfully treated medically were potentially at risk of misclassification as not experiencing DCI, which could alter the observed association of certain predictors with DCI. This situation would be conceivably rare, attributable only to transient arterial narrowing or alternate etiologies to vasospasm. Lastly, a high percentage of our cohort presented with good neurological grade, known to be associated with reduced risk of developing DCI.^{6,7,23} This skewed distribution, although similarly observed in other studies investigating presenting neurological grade as a risk factor, could have reduced power in our outcome analysis and may explain why WFNS grade did not remain significant in the multivariate logistic regression model.^{5,6,8} Prior to clinical use, our proposed rule requires prospective evaluation in multiple institutions to capture variability in practice and aSAH populations.

Conclusions

Clinical and radiographic features available early in the presentation of aSAH can be used to reliably predict the onset of DCI. These risk factors include amount and distribution of SAH on initial CT, age, and ruptured aneurysm location. Their combined contributions in our proposed clinical decision rule improved predictive value over SAH thickness as classified by the modified Fisher grade, the only prognostic factor currently widely used in the management of this disease. It suggests patients 40 to 59 years old with a ruptured anterior circulation aneurysm and thick SAH are at high risk and should be considered for more aggressive monitoring in an ICU setting with frequent cerebrovascular imaging. Once prospectively validated in other neurosurgical centers, this rule may prove clinically useful to individualize DCI risk in aSAH patients.

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References

1. Abila AA, Wilson DA, Williamson RW, Nakaji P, McDougall CG, Zabramski JM, et al: The relationship between ruptured aneurysm location, subarachnoid hemorrhage clot thickness, and incidence of radiographic or symptomatic vasospasm in patients enrolled in a prospective randomized controlled trial. *J Neurosurg* **120**:391–397, 2014
2. Adams HP Jr, Kassell NF, Torner JC, Haley EC Jr: Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: influences of clinical condition, CT results, and anti-fibrinolytic therapy. A report of the Cooperative Aneurysm Study. *Neurology* **37**:1586–1591, 1987
3. Charpentier C, Audibert G, Guillemin F, Civit T, Ducrocq X, Bracard S, et al: Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. *Stroke* **30**:1402–1408, 1999
4. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Cope land D, et al: Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke* **32**:2012–2020, 2001
5. Crobbedu E, Mittal MK, Dupont S, Wijdsicks EFM, Lanzino G, Rabinstein AA: Predicting the lack of development of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Stroke* **43**:697–701, 2012
6. de Oliveira Manoel AL, Jaja BN, Germans MR, Yan H, Qian W, Kouzmina E, et al: The VASOGRADE: a simple grading scale for prediction of delayed cerebral ischemia after subarachnoid hemorrhage. *Stroke* **46**:1826–1831, 2015
7. de Rooij NK, Greving JP, Rinkel GJE, Frijns CJM: Early prediction of delayed cerebral ischemia after subarachnoid hemorrhage: development and validation of a practical risk chart. *Stroke* **44**:1288–1294, 2013
8. de Rooij NK, Rinkel GJE, Dankbaar JW, Frijns CJM: Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. *Stroke* **44**:43–54, 2013
9. Dorsch N: A clinical review of cerebral vasospasm and delayed ischaemia following aneurysm rupture. *Acta Neurochir Suppl* **110**:5–6, 2011
10. Dumont TM, Rughani AI, Tranmer BI: Prediction of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage with an artificial neural network: feasibility and comparison with logistic regression models. *World Neurosurg* **75**:57–63, 25–28, 2011
11. Dumont T, Rughani A, Silver J, Tranmer BI: Diabetes mellitus increases risk of vasospasm following aneurysmal subarachnoid hemorrhage independent of glycemic control. *Neurocrit Care* **11**:183–189, 2009
12. English SW, McIntyre L, Fergusson D, Turgeon A, Sun C, dos Santos MP, et al: Enriched administrative data can be used to retrospectively identify all known cases of primary subarachnoid hemorrhage. *J Clin Epidemiol* **70**:146–154, 2016
13. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al: Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery* **59**:21–27, 2006
14. Gonzalez NR, Boscardin WJ, Glenn T, Vinuela F, Martin NA: Vasospasm probability index: a combination of transcranial Doppler velocities, cerebral blood flow, and clinical risk factors to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg* **107**:1101–1112, 2007
15. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K: Stiffness and elastic behavior of human intracranial and extracranial arteries. *J Biomech* **13**:175–184, 1980
16. Hegedüs K, Molnár P: Age-related changes in reticulin fibers and other connective tissue elements in the intima of the major intracranial arteries. *Clin Neuropathol* **8**:92–97, 1989
17. Hijdra A, van Gijn J, Nagelkerke NJ, Vermeulen M, van

- Crevel H: Prediction of delayed cerebral ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. **Stroke** **19**:1250–1256, 1988
18. Macdonald RL, Rosengart A, Huo D, Karrison T: Factors associated with the development of vasospasm after planned surgical treatment of aneurysmal subarachnoid hemorrhage. **J Neurosurg** **99**:644–652, 2003
 19. McGirt MJ, Mavropoulos JC, McGirt LY, Alexander MJ, Friedman AH, Laskowitz DT, et al: Leukocytosis as an independent risk factor for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. **J Neurosurg** **98**:1222–1226, 2003
 20. Perry JJ, Stiell IG, Sivilotti MLA, Bullard MJ, Emond M, Symington C, et al: Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. **BMJ** **343**:d4277, 2011
 21. Perry JJ, Stiell IG, Sivilotti MLA, Bullard MJ, Hohl CM, Sutherland J, et al: Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. **JAMA** **310**:1248–1255, 2013
 22. Proust F, Hannequin D, Langlois O, Freger P, Creissard P: Causes of morbidity and mortality after ruptured aneurysm surgery in a series of 230 patients. The importance of control angiography. **Stroke** **26**:1553–1557, 1995
 23. Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN, Ulatowski JA: Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. **Crit Care Med** **28**:984–990, 2000
 24. Roederer A, Holmes JH, Smith MJ, Lee I, Park S: Prediction of significant vasospasm in aneurysmal subarachnoid hemorrhage using automated data. **Neurocrit Care** **21**:444–450, 2014
 25. Ropper AH, Zervas NT: Outcome 1 year after SAH from cerebral aneurysm. Management morbidity, mortality, and functional status in 112 consecutive good-risk patients. **J Neurosurg** **60**:909–915, 1984
 26. Shrout PE, Fleiss JL: Intraclass correlations: uses in assessing rater reliability. **Psychol Bull** **86**:420–428, 1979
 27. Solenski NJ, Haley ECJ Jr, Kassell NF, Kongable G, Germanson T, Truskowski L, et al: Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. **Crit Care Med** **23**:1007–1017, 1995
 28. Sullivan LM, Massaro JM, D'Agostino RB Sr: Presentation of multivariate data for clinical use: The Framingham Study risk score functions. **Stat Med** **23**:1631–1660, 2004
 29. Vergouwen MDI, Vermeulen M, van Gijn J, Rinkel GJE, Wijdeveld EF, Muizelaar JP, et al: Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. **Stroke** **41**:2391–2395, 2010
 30. Yin L, Ma CY, Li ZK, Wang DD, Bai CM: Predictors analysis of symptomatic cerebral vasospasm after subarachnoid hemorrhage. **Acta Neurochir Suppl** **110**:175–178, 2011
 31. Yoshimoto Y, Kwak S: Age-related multifactorial causes of neurological deterioration after early surgery for aneurysmal subarachnoid hemorrhage. **J Neurosurg** **83**:984–988, 1995

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Author Contributions

Conception and design: Lee, Perry, English, Alkherayf, Lesiuk, Moulton, Agbi, Sinclair, Dowlathshahi. Acquisition of data: Lee, Joseph, Nobile, Zhou, Dowlathshahi. Analysis and interpretation of data: Lee, Perry, English, Alkherayf, Lesiuk, Moulton, Agbi, Sinclair, Dowlathshahi. Drafting the article: Lee. Critically revising the article: Lee, Perry, English, Alkherayf, Dowlathshahi. Reviewed submitted version of manuscript: Lee, Perry, Dowlathshahi. Approved the final version of the manuscript on behalf of all authors: Lee. Statistical analysis: Lee, English, Dowlathshahi. Administrative/technical/material support: Lee. Study supervision: Perry, Dowlathshahi.

Supplemental Information

Previous Presentations

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Correspondence

Hubert Lee: The Ottawa Hospital, Ottawa, ON, Canada. hulee@toh.on.ca.