

Clinical Prediction of Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Hubert Lee

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Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

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Legend

ANN = artificial neural network
AVM = arteriovenous malformation
CSF = cerebrospinal fluid
CT = computed tomography
EEG = electroencephalogram
EVD = external ventricular drain
GCS = Glasgow Coma Scale
ICU = intensive care unit
ISUIA = International Study of Unruptured Intracranial Aneurysms
IVF = intravenous fluids
IVH = intraventricular hemorrhage
MCA = middle cerebral artery
MRI = magnetic resonance imaging
RBC = red blood cells
ROC = receiver operator characteristics
SAH = subarachnoid hemorrhage
TCD = transcranial doppler
WFNS grade = World Federation of Neurological Surgeons grade

Abstract

Objective: This study aims to derive a clinically-applicable decision rule to predict the risk of symptomatic vasospasm, a neurological deficit primarily due to abnormal narrowing of cerebral arteries supplying an attributable territory, in aneurysmal subarachnoid hemorrhage (SAH).

Methods: SAH patients presenting from 2002 to 2011 were analyzed using logistic regression and recursive partitioning to identify clinical, radiological, and laboratory features that predict the occurrence of symptomatic vasospasm.

Results: The incidence of symptomatic vasospasm was 21.0%. On multivariate logistic regression analysis, significant predictors of symptomatic vasospasm included age 40-59 years, high Modified Fisher Grade (Grades 3 and 4), and anterior circulation aneurysms.

Conclusion: Development of symptomatic vasospasm can be reliably predicted using a clinical decision rule created by logistic regression. It exhibits increased accuracy over the Modified Fisher Grade alone and may serve as a useful clinical tool to individualize vasospasm risk once prospectively validated in other neurosurgical centres.

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1.0 Background

1.1 Introduction to Symptomatic Vasospasm and Aneurysmal Subarachnoid Hemorrhage

1.1.1 What is Subarachnoid Hemorrhage?

Subarachnoid hemorrhage (SAH) is bleeding that occurs in the space where the cerebral arteries and veins course between two layers of the covering of the brain, the arachnoid and pia mater. It represents a type of hemorrhagic stroke and accounts for 3% of all strokes¹. SAH commonly arises from head injury but when spontaneous, up to 85% are due to rupture of an intracranial aneurysm, which are focal dilation in the blood vessel wall². The incidence of SAH worldwide is estimated to be 9 per 100,000 person-years, with higher rates observed in females over the age of 55 years, older age, and in Finland and Japan³. In Canada, aneurysmal SAH occurs in 11.2 per 100,000 women and 8.0 per 100,000 men⁴. Known risk factors of aneurysm rupture include female sex, personal or family history of aneurysmal SAH, hypertension, smoking, sympathomimetic substances, and high consumption of alcohol⁵. Patients typically present with a sudden onset, severe headache that can be accompanied by neck stiffness, nausea, vomiting, focal neurological deficits, loss of consciousness, and seizures.

1.1.2 Diagnosis of Subarachnoid Hemorrhage

With the suspicion of SAH, computed tomography (CT) scanning of the head is initially performed having a sensitivity of 100% for the first 6 hours from the event but reduces precipitously over the following hours to days as the hemorrhage is cleared⁶. This imaging also assesses for tracking of blood into other spaces, which can increase intracranial pressure through mass effect or blockage of cerebrospinal fluid (CSF) drainage resulting in dilation of the ventricles called hydrocephalus. If the head CT scan is normal but high clinical suspicion is

present, as is the case with delayed presentation, it is necessary to obtain CSF via a lumbar puncture. The optimal timing of collection is unknown as the breakdown product of blood, bilirubin, requires at least a few hours to develop and is the only reliable marker to distinguish true SAH from bleeding as a result of the procedure, known as a traumatic tap. Bilirubin in CSF produces a supernatant termed xanthochromia after centrifugation, which can be identified visually or with the aid of spectrophotometry⁷. Clinically, some physicians will wait 12 hours before attempting a lumbar puncture based on a study of CT-confirmed SAH patients who exhibited presence of xanthochromia in CSF by spectrophotometry 12 hours to 2 weeks after hemorrhage⁸. Aneurysms are identified or ruled out as the cause of SAH by angiography, imaging the cerebral blood vessels using intravenously or intra-arterially injected contrast medium. This can be achieved non-invasively using CT and magnetic resonance imaging (MRI) or by catheter angiography involving puncture of the femoral artery in the groin to insert a catheter to the common carotid and vertebral arteries which supply the brain. Catheter angiography is considered the gold standard for detecting intracranial aneurysms, however modern CT and MR angiography provide faster and safer alternatives with a sensitivity of 97% for aneurysms 4 mm or greater in diameter and a pooled sensitivity of 95% respectively^{9,10}.

1.1.3 Treatment of Subarachnoid Hemorrhage

SAH patients should be treated emergently in an acute care unit with neurosurgical expertise. Medical management may include airway assistance with endotracheal intubation and mechanical ventilation, cardiovascular support with vasopressors or anti-hypertensive medications, antiepileptic drugs for seizure control, an osmotic diuretic or hypertonic saline for increased intracranial pressure, and analgesia. The major neurological complications to prevent are aneurysm rebleeding, hydrocephalus, and delayed cerebral ischemia, all of which can lead to

neurological deterioration or death. The definitive prevention of rebleeding is by excluding the aneurysm from the intracranial circulation. This can be accomplished by open surgery to place a metallic clip across the base of the aneurysm (clipping) or using the intra-arterial access from catheter angiography to pack the aneurysm with detachable, platinum coils. Hydrocephalus can be temporarily managed by diverting the CSF, which is constantly produced, from the ventricle to a bedside reservoir through an external ventricular drain (EVD). Delayed cerebral ischemia will be discussed in the section on vasospasm, its main precipitant.

1.1.4 Outcome in Subarachnoid Hemorrhage

Case-fatality rates of aneurysmal SAH are high but range widely between studies from 8.3% to 66.76% with a median of 32.2% in the United States¹¹. This rate has declined 17% from 1973 to 2002 as result of improvements in early aneurysm treatment to prevent rebleeding. The risk of rebleeding from an unprotected aneurysm is 4% in the first 24 hours and 1.5% per day for 2 weeks with 80% of patients who experience this complication having a poor outcome^{12,13}.

Grading scales have been developed to prognosticate outcome of aneurysmal SAH patients with two that assess neurological status at the time of presentation: the Hunt and Hess and World Federation of Neurological Surgeons (WFNS) grades. The Hunt and Hess grade, shown in *table 1*, uses severity of headache, neck stiffness, neurological deficit, and alterations in level of consciousness to predict survival where increasing grade is associated with death¹⁴. While easy to administer, this scale has been criticized as subjective utilizing vague terms to distinguish between categories and poor clarity regarding the need to elevate the overall grade in the presence of systemic disease¹⁵. The WFNS grade (*see table 1*) was conceived as a result of data from the International Cooperative Aneurysm Study demonstrating the severity of headache and neck stiffness (Hunt and Hess grades 1 to 2) did not influence outcome if consciousness was

preserved¹⁵. Instead, level of consciousness (as measured by the Glasgow Coma Scale (GCS), *see table 2*) and presence of hemiparesis or aphasia were stronger determinants of death and disability.

1.1.5 Definition, Epidemiology, and Pathophysiology of Vasospasm

Vasospasm is a prolonged but self-limiting reduction in calibre of cerebral blood vessels due to abnormal smooth muscle contraction in patients after aneurysmal SAH. Its effects can be focal or diffuse, involve proximal or distal arteries, and vary in severity from mild to severe. Intracranial arterial narrowing is detected by vascular imaging in 49% to 67% of patients and referred to as angiographic vasospasm¹⁶. Its onset can be as early as 3 days after SAH, reaches peak severity at 6-8 days, and spontaneously resolves after 12-14 days¹⁷. Symptomatic vasospasm (also known as clinical vasospasm or delayed cerebral ischemia) occurs in a fraction of those experiencing angiographic vasospasm where blood flow is critically compromised triggering a cascade of molecular events involving depolarization of the cell membrane, release of excitatory neurotransmitters, and production of deleterious enzymes ultimately resulting in cell death with corresponding neurological deficits. Depending on the cerebral vascular territory affected, this can present as decreased level of consciousness, weakness, numbness, speech impairment, or cortical blindness. Approximately 50% of patients who develop angiographic vasospasm will experience symptomatic vasospasm, half of which will progress to cerebral infarcts (death of neurons due to inadequate blood supply)¹⁸. Vasospasm is a leading cause of preventable mortality and morbidity in aneurysmal SAH accounting for 23% of deaths, 11% of poor outcomes, and persistent neurological deficit in 37% of survivors¹⁹⁻²¹.

The exact mechanism by which vasospasm occurs in aneurysmal SAH is not known. It is proposed that the breakdown products of blood including oxyhemoglobin, methemoglobin, and superoxide radicals damage endothelial cells and smooth muscle cells composing the arterial wall²². This disrupts the homeostasis of factors released from the endothelium that modulate vascular tone causing endothelin-1 overproduction (a vasoconstrictor) and underproduction of nitric oxide (a vasodilator)^{23,24}. Inflammation in response to SAH causes growth and remodelling of the arterial wall which becomes thicker decreasing lumen diameter, less compliant, and less responsive to vasodilators^{25,26}.

1.1.6 Diagnosis of Vasospasm

Symptomatic vasospasm is diagnosed with observed neurological decline after exclusion of other possible explanations with a CT scan of the head and laboratory investigations (*see table 3*). If vasospasm is suspected, induced hypertension is usually administered with symptomatic improvement confirming the diagnosis. The standard for imaging vasospasm is catheter cerebral angiography, which has the benefit of providing intraluminal access for treatment. Despite this, CT angiography is becoming increasingly employed as it can be accessed rapidly, provides additional information on the brain parenchyma, new or evolving hemorrhage, and ventricular size; and is safer without the 0.5-1% risk of ischemic stroke associated with catheter access²⁷. In comparison, CT angiography is highly accurate in identifying absent (sensitivity: 95%, specificity: 96%) or severe vasospasm (sensitivity and specificity: 100%) proximally in the internal carotid, basilar, and first segments of the anterior and middle cerebral arteries when compared to catheter angiography²⁸. This is supported by a meta-analysis of 6 CT angiography studies showing a pooled sensitivity of 79.6% and specificity of 93.1% in diagnosing vasospasm across all arterial locations and severities²⁹.

Transcranial dopplers (TCDs) offer an alternative, inexpensive, bedside examination for detecting arterial narrowing using ultrasound to measure the velocity of blood flow in the proximal cerebral blood vessels through the squamous portion of the temporal bone or temporal acoustic window. It follows the Bernoulli principle where reduced vessel calibre due to vasospasm will result in increased mean blood flow velocity³⁰. The middle cerebral artery is the easiest and most reliable artery to insonate where a mean flow velocity of greater than 200 cm/s indicates severe vasospasm and less than 120 cm/s not associated with significant arterial narrowing^{30,31}.

Alterations in volume of flow, as is the case with augmented hemodynamics induced for therapy or by autoregulatory mechanisms of the brain, can also alter flow velocity. To distinguish this, Lindegaard *et al.* compared the mean flow velocities in the middle cerebral artery and ipsilateral, extracranial internal carotid artery finding a ratio of 3 or greater supports a diagnosis of vasospasm³². Despite being convenient, TCDs suffer from relying on a good acoustic window, having low sensitivity at 58.6%, being poorly correlated with angiography for the anterior cerebral artery, and highly operator dependent^{33,34}.

1.1.7 Management of Vasospasm

The potential for rapid progression of cerebral vasospasm has led to a wealth of research invested in its prevention. Despite the promise of the anti-inflammatory effect of statins, reversal of vasoconstriction by clazosentan (endothelin receptor antagonist), and neuroprotection by magnesium sulphate, nimodipine is the only medication routinely administered and shown to decrease cerebral infarcts and positively influence clinical outcome³⁵⁻³⁹. It is a calcium channel blocker taken by mouth or by nasogastric feeding tube at a dose of 60mg every 4 hours from admission to 21 days post-hemorrhage. The mechanism by which it affects SAH is unknown,

however it does seem to drastically reduce angiographic vasospasm⁴⁰. Medical management in aneurysmal SAH patients is centered on ensuring adequate blood flow to the brain and minimizing the metabolic demands by the brain in hopes to prevent any further injury. This involves maintaining normal body temperature, normal body fluid status particularly avoiding low volumes (hypovolemia), normal to high blood pressure assuming the aneurysm is completely occluded, prevention of low blood hemoglobin and sodium levels (anemia and hyponatremia), and reducing intracranial pressure with an EVD^{5,18,41}.

The occurrence or strong suspicion of symptomatic vasospasm requires prompt elevation of blood pressure to increase cerebral blood flow as the arteries have lost the ability to self-regulate their diameter to sustain adequate oxygen and nutrient delivery to the brain tissues. The major concerns regarding this therapy are heart failure causing build-up of fluid in the lungs (pulmonary edema), worsening of swelling in the brain elevating intracranial pressure, rebleeding from an unsecured aneurysm, and bleeding into areas of established infarct. One or more these complications occur in about 25% of patients⁴⁰. These risk are greatest amongst patients with advanced age and pre-existing cardiopulmonary disease. High blood pressure appears to be safe with concomitant unruptured intracranial aneurysms as demonstrated by one study enrolling 21 SAH patients with additional unsecured, unruptured aneurysms who underwent induced hypertension with systolic blood pressures above 180 mmHg for 7 days without aneurysmal rupture⁴². Once a systolic blood pressure of 200 mmHg or cerebral perfusion pressure of 80 mmHg (the pressure within cerebral arteries) is reached without resolution of neurological symptoms, the treatment is considered failed. In such cases or those unable to

tolerate hemodynamic augmentation, endovascular management through a femoral artery puncture is required.

Currently accepted endovascular therapies include mechanical dilation from within the lumen of the blood vessel by angioplasty and selective arterial injection of medications to relax smooth muscles in the artery wall⁵. Angioplasty involves threading a wire into the cerebral arteries experiencing vasospasm to guide a balloon catheter up to the sites of arterial stenosis for inflation. Neurological improvement following balloon angioplasty varies from 62-86% with a complication rate of 1-5%, the most feared being vessel rupture^{43,44}. Commonly used intra-arterial vasodilators include milrinone, fasudil, papaverine, nicardipine, and verapamil^{40,44,45}. Their effects may be transient with 23% experiencing recurrence of vasospasm requiring re-treatment with repeat intra-arterial milrinone infusion or balloon angioplasty in a study by Fraticelli *et al*⁴⁵.

1.2 Prediction of Vasospasm, A Review of the Literature

1.2.1 The Fisher and Modified Fisher Scales

Risk factors associated with vasospasm in aneurysmal SAH have been studied intensively with amount of subarachnoid blood at hospital presentation being consistently predictive of its occurrence⁴⁶⁻⁵⁰. This was recognized by Fisher *et al.* who developed the Fisher grading scale to identify SAH patients at high risk based on the thickness and distribution of SAH on CT in a cohort of 47 cases (*see table 4*)⁴⁶. Absence of subarachnoid hemorrhage on CT (Grade 1) was associated with low rates of angiographic vasospasm (4 out of 11 patients) and no cases of symptomatic vasospasm. Thicker SAH with increasing grade resulted in a greater proportion

experiencing this complication where all patients having thick SAH on CT (Grade 3) developed angiographic vasospasm and a majority (23 of 24) had severe vasospasm with attributable neurological deficit. The risk with hemorrhage being predominantly intraventricular or intracerebral (Grade 4) was more similar to Grade 2 than 3.

While commonly used by neurosurgeons in clinical practice, the Fisher scale is limited by the measurements representing outdated imaging-based rather than true thickness, not accounting for the additive risk of simultaneously having thick subarachnoid and intraventricular blood, and being weakly related to neurological deterioration due to vasospasm^{40,48,51}. This inspired the modified Fisher grading scale, which classifies SAH on CT by thickness (Grade 1 or 2 compared to Grade 3 or 4) and presence or absence of intraventricular extension (Grade 1 compared to 2 and Grade 3 compared to 4, *see table 3*)⁵⁰. The revised scale demonstrates a stronger correlation to symptomatic vasospasm than the original with a 28% increase in odds of occurrence per scale grade. It is also more intuitive as the risk of developing vasospasm increases with each grade, 24% (Modified Fisher Grade 0 or 1) to 40% (Modified Fisher Grade 4), rather than peaking at Grade 3 and decreasing for Grade 4 as seen in the original Fisher scale. The key limitation is the subjective dichotomization of thin and thick SAH as no formal definition was provided or used during its derivation.

1.2.2 Clinical Prediction Models and Decision Rules for Symptomatic Vasospasm

The Modified Fisher grading scale offers a simple and useful prognostication tool in aneurysmal SAH. However, a clinical prediction model assimilating the contributions of other factors associated with symptomatic vasospasm including age, history of hypertension or diabetes, cigarette smoking, neurological grade at presentation, hydrocephalus, and hyperglycemia, has yet

to be adopted clinically to improve identification of high risk patients^{49,52,53}. A review of the literature identified 6 previously published models predicting symptomatic vasospasm after aneurysmal SAH (*see table 5*)⁵⁴⁻⁵⁹. The search strategies employed can be found in *appendix A* and *figure 1* illustrates the screening process with reasons for article exclusion in accordance with the preferred reporting times for systematic review and meta-analysis protocol (PRISMA-P)⁶⁰. These models are not suitable for clinical practice owing to methodological limitations such as small sample size, overly restrictive inclusion criteria, and absence of external validation. Practice protocols were also non-representative with derivation when aneurysms were secured in a delayed fashion by surgical clipping, quantifying SAH thickness with study-specific scales, and use of cerebral blood flow monitoring not widely available.

1.2.2.1 Adams (1987) and Hijdra (1988)

The first attempt at creating a prediction rule was by Adams *et al.* using multivariate logistic regression shortly after the introduction of the Fisher grading scale⁵⁴. The population used stands as one of the largest at 934 patients from the International Cooperative Study on Timing of Aneurysm Surgery, a multicenter research initiative to identify the optimal timing of treating aneurysms as the standard practice at the time was delayed intervention at 7 to 14 days post SAH to reduce the risk of vasospasm and death. Amount of SAH on presenting CT, neurological grade based on consciousness and orientation, and antifibrinolytic use were identified as important predictors of symptomatic vasospasm. While this rule succeeds in distinguishing low and high risk patients, it is not applicable to the current management of aneurysmal SAH as ruptured aneurysms are now secured within 48 hours of presentation with endovascular coiling as a primary modality of treatment that was not available to patients in the derivation population. Antifibrinolytics have also fallen out of use along with early, non-surgical prevention of

rebleeding. Hijdra et al's model, which includes SAH thickness on admission CT, presence of intraventricular hemorrhage (IVH), and tranexamic acid (an antifibrinolytic) use, suffers from these same shortcomings⁵⁵.

1.2.2.2 Qureshi (2000) – Symptomatic Vasospasm Risk Index

Qureshi *et al.* proposed a symptomatic vasospasm risk index adding aneurysms of the anterior cerebral or internal carotid artery and early elevation of mean flow velocity (≥ 110 cm/sec) in the middle cerebral (MCA-MFV) artery by TCD to improve prediction⁵⁶. A convenient point system is devised with a minimum score of 4 (one per variable) and maximum score of 10 corresponding to post-test probabilities of 13% and 65% respectively. The authors demonstrate that the sum contribution of the four variables has greater accuracy in risk stratification than thickness of SAH on CT or TCD velocities alone, however area under the receiver operator characteristics (ROC) curve was 68% suggesting discrimination was somewhat poor. The grading of SAH thickness was study-specific rather than based on the validated Fisher grading scale and does not account for intraventricular extension, which was found to be a significant predictor in this study during univariate analysis and by others in multivariable analysis^{49,50}. Moreover, their use of MCA-MFV by TCD does not incorporate the Lindegaard ratio preventing distinction between vasospasm and an augmented hemodynamic state, such as with induced hypervolemia, as the cause of elevation.

1.2.2.3 Gonzalez (2007) – Vasospasm Probability Index

TCDs are easy to perform at the bedside however their utility in guiding clinical management is best when velocities are less than 120 cm/s (negative predictive value = 94%) or 200 cm/s or greater (positive predictive value = 87%) in the middle cerebral artery⁶¹. In these ranges, this imaging tool can accurately indicate the absence or presence of significant angiographic

vasospasm. Nevertheless, a strong correlation between TCD mean flow velocities and symptomatic vasospasm has not been found^{61,62}. Gonzalez *et al.* recognized this issue subsequently deriving the Vasospasm Probability Index incorporating cerebral blood flow as measured by a bedside portable unit using the xenon clearance technique⁵⁷. Dividing the measured TCD velocity by the cerebral blood flow from the ipsilateral hemisphere produced the spasm index which had a sensitivity of 73.1% and specificity of 84.4% in diagnosing symptomatic vasospasm when elevated above 3.5. In combination with the Hunt and Hess grade and Fisher grade, the resulting index achieves a high area under the ROC curve of 92.9%. The importance of cerebral blood flow in predicting symptomatic vasospasm in aneurysmal SAH is clear however the technology used in this study is not widely available and whether flow as measured by CT, MRI, or portable near infrared spectroscopy can be interchangeably applied remains to be shown. Their use of Fisher Grade 4 as the reference for SAH thickness is confusing as it represents neither the lowest nor highest risk group.

1.2.2.4 Dumont (2011) – Artificial Neural Network

Dumont *et al.* investigated artificial neural networks (ANN) as an alternate means to logistic regression in the prediction of symptomatic vasospasm occurrence with the reported advantage of greater flexibility in estimating complex, non-linear associations⁵⁸. The authors used factors previously published by Adams *et al.* and Qureshi *et al.* in addition to age, gender, EVD placement, and surgical clipping or endovascular coiling^{54,56}. The resulting ANN out-performed the original models (area under the ROC curve = 0.96 (ANN), 0.93 (Adams), 0.90 (Qureshi)) when applied prospectively to 22 patients, however from the same centre as the derivation cohort. Despite validation, this model is not ready for clinical use particularly in other neurosurgical centers; a sentiment shared by the authors in their discussion. This is due to the

network's synthesis from a small sample size and lack of subsequent reproduction in another cohort of SAH patients. It does serve as a promising platform upon which a more intricately designed AAN trained on a large, prospective population may be created.

1.2.2.5 Roederer (2014)

The approach taken by Roederer *et al.* also differed from traditional vasospasm models employing routinely collected but seldom associated variables of CSF drainage volume, blood pressure, heart rate, intracranial pressure, and blood levels of glucose and sodium collected during the first 3 days post-SAH⁵⁹. The choice of measures available within 3 days of hemorrhage, as compared to Qureshi *et al.*'s TCD velocities recorded up to 5 days after hemorrhage, is most ideal as it precedes the typical onset of symptomatic vasospasm⁵⁶. Together, these automated features had greater predictive ability (area under the ROC curve = 0.54) than the previously established factors of SAH thickness on CT, neurological grade, and TCD velocities (area under the ROC curve = 0.34). This model's automated-data driven nature is appealing as it stands to improve practice without additional clinician work, however, their inclusion of only high Fisher grades (3 and 4) and defining symptomatic vasospasm as angiographic arterial narrowing necessitating endovascular therapy limits the population in which it can be directly applied.

1.3 Methodological Standards for Clinical Decision Rules

Clinical decision rules are tools that aid diagnosis, prognosis, or predicting patient response to treatments by weighing the contribution of clinical history, radiological findings, and laboratory results⁶³. To guide derivation, criteria have been established to ensure their accuracy and reliability⁶⁴⁻⁶⁶. The need for a rule should firstly be assessed to determine if potential for

improvement in patient care exists. Another important factor is willingness of physicians to implement the rule, which is dependent on their perception of its usefulness and the complexity of its components.

Development of a clinical decision rule should begin by clearly defining the outcome of interest to ensure it is reliably diagnosed and relevant^{29,64}. Investigators assessing the outcome should be blinded to the identity of the predictors and likewise, investigators collecting the predictors should be blinded to the occurrence of the outcome^{63,65}. This is to prevent bias in recording of the data particularly if predisposed to subjectivity. Candidate clinical variables should be comprehensive, selected based on factors already used by physicians in decision making and those that have a biologically-conceivable association to the outcome^{29,64}. These predictors have the greatest utility if they are readily available at the time of presentation or early during hospitalization, easily reproducible between clinicians, and present in a sufficient proportion of patients studied. An adequate sample size is crucial, typically at least 10 outcome events per predictor variable in multivariate logistic regression, to prevent over-fitting the rule to the study population limiting its external validity⁶⁷.

Once derived, the clinical decision rule is considered level 4 evidence requiring prospective validation in a separate population and evidence of improved patient outcomes prior to clinical application⁶⁵. This ensures the predictor-outcome relationships inherent to the rule are real and relevant to other populations while evaluating the ease of use by clinicians in everyday practice. Even when rules are accurate in theory, complexity rendering them difficult to remember or reliably applied can lead to poor adoption. Successful implementation and demonstration of

meaningful healthcare cost savings due to widespread utilization of a clinical decision rule are necessary to alter clinical practice and ultimately improve patient outcomes⁶³.

1.4 Candidate Predictor Variables for Symptomatic Vasospasm from the Current

Literature

Although first proposed by Fisher *et al.*, the amount and distribution of subarachnoid blood on initial CT remains the strongest risk factor for developing symptomatic vasospasm in aneurysmal SAH patients^{46,49,50,52,54,56}. The Modified Fisher grading scale highlights the contribution of IVH while providing a more logical scale where the odds of occurrence increase with grade level⁵⁰. Subsequent models should not only incorporate this as a component but also demonstrate improved performance over the scale alone. Other clinical, radiological, laboratory, and management characteristics predictive of symptomatic vasospasm have been investigated and are reviewed below.

1.4.1 Clinical Features

The contribution of age to vasospasm is controversial with evidence to support and disprove its influence^{49,56,68-70}. These findings appear to be dependent on whether it is analyzed as a continuous or categorical variable and if the outcome definition requires the presence of cerebral infarctions on CT. Charpentier *et al.* found that the incidence of symptomatic vasospasm was reduced with age greater than 50 years after controlling for possible confounding by neurological grade, SAH thickness, treatment modality, operator experience, fever, low blood pressure, and high blood glucose⁶⁹. Similarly, Macdonald *et al.* demonstrated an inverted, U-shaped relationship where patients age 40 to 59 years were at maximal risk⁴⁹. It is hypothesized that atherosclerosis in elderly cerebral vessels may be less susceptible to pathological narrowing in

aneurysmal SAH. Only one study has shown higher incidence with age less than 35 years, however their outcome was generally favourable⁷⁰.

Women are known to have a higher prevalence of aneurysms (75% of the included patients from the International Study of Unruptured Intracranial Aneurysms (ISUIA))⁷¹ in addition to a 1.24 times incidence of SAH compared to men³. A recent study suggests that this difference may be attributable due to smoking imposing a more deleterious effect on women⁷². Despite these findings, sex does not appear to be related to the occurrence of symptomatic vasospasm.

Several pre-existing comorbidities have exhibited strong associations to symptomatic vasospasm development including hypertension, diabetes mellitus, current smoking, and cocaine use^{53,69,73-75}. Ohman *et al.* found cerebral infarcts on CT in 63.8% of those with prior history of hypertension but only 45.5% in those without⁶⁸. This difference remained significant even when prophylaxis with nimodipine was accounted for. Hypertension may render the brain less resilient to ischemia due to damage of the arterial wall structure and impaired function. The effects of chronic microvascular disease from diabetes mellitus has similarly been shown to increase risk in SAH patients even when glycemic control was similar to that of non-diabetics⁷⁵. Hyperglycemia on its own during hospital admission was also a significant contributor in studies by Charpentier *et al.* and de Rooij *et al.* Cigarette smoking and aneurysmal rupture are well-known to be positively correlated, and fittingly, it has also proven to be a risk factor for symptomatic vasospasm^{2,73}. Weir *et al.* merged data from 4 North American and 1 European randomized controlled trials of tirilazad and nicardipine forming a cohort of 3500 patients in which they found smokers had a 22% increased odds of vasospasm⁷³. A systematic review from 2013 offers

further support for these three cardiovascular risk factors increasing the risk of delayed cerebral ischemia with pooled odds ratios of 1.5 [95% confidence interval (CI): 1.3-1.7] for hypertension, 6.7 [95% CI: 1.7-26] for diabetes mellitus, and 1.2 [95% CI:1.1-1.4] for current smokers⁵³.

Cocaine is a potent vasoconstrictor whose use has been linked to several cerebrovascular diseases such as vasculitis, intracerebral hemorrhage, and rupture of intracranial aneurysms^{76,77}.

Conway *et al.* investigated its association to symptomatic vasospasm finding cocaine users experienced clinically relevant vessel narrowing twice as often corresponding to an odds ratio of 3.9 [95% CI: 1.7-8.6]⁷⁴.

Neurological grade at presentation has been recognized to prognosticate outcome in aneurysmal SAH, as demonstrated by the Hunt and Hess and WFNS grading scales, but is also associated with symptomatic vasospasm^{49,54,56,70}. Poor neurological condition following aneurysm rupture is undoubtedly related to occurrence of vasospasm due to the presence of greater amount of SAH. Yet, there are a few studies, all of which use the WFNS grading scale, that fail to show such a relationship^{47,48,55}. It is unlikely these studies suffered from significant misclassification as the scale uses GCS and presence or absence of motor deficit, both of which have clearly defined objective criteria (*see tables 1 and 2*). A recent systematic review also revealed good inter-rater reliability where 81% of studies had a kappa greater than 0.7 and all 9 studies with an intraclass correlation coefficient reported values greater than 0.75⁷⁸.

1.4.2 Radiological/Laboratory Features

Aneurysm location was first identified as an important determinant of symptomatic vasospasm by Qureshi *et al.* with a higher incidence observed amongst those originating from the anterior cerebral or internal carotid arteries⁵⁶. The protective effect of posterior circulation aneurysms

was confirmed specifically for posterior cerebral artery aneurysms in a separate study investigating the role of leukocytosis in aneurysmal SAH⁷⁹. Fisher *et al.* similarly found that anterior cerebral artery was involved in more cases of vasospasm amongst Grade 3 patients compared to the middle cerebral artery⁴⁶. Contrary to these findings, a systematic review of delayed cerebral ischemia predictors included a number of studies as evidence against the role of aneurysm location^{53,69,80,81}. One multivariate analysis has shown aneurysm size (13mm or greater) to be a significant predictor of vasospasm⁴⁹.

Roederer *et al.*'s model was the first to incorporate laboratory values demonstrating their potential as predictors. The relationship between hemoglobin level and occurrence of symptomatic vasospasm was recently investigated revealing reduced incidence when concentrations were between 110-120 g/L after controlling for Hunt and Hess neurological grade and Fisher Grade⁸². Correction of anemia (low hemoglobin level) in SAH should be performed with caution as blood transfusions have been associated with angiographic vasospasm and poor outcome⁸³. Hyponatremia (low blood sodium level) is another common complication in aneurysmal SAH typically secondary to cerebral salt wasting, an endocrine disorder of excess excretion of sodium by the kidneys following brain injury. A systematic review of hyponatremia in aneurysmal SAH concluded low serum sodium levels were associated with increased risk of symptomatic vasospasm, however whether this metabolic abnormality is due to hemodynamic augmentation therapies used to treat vasospasm or even a result of cerebral infarction remains uncertain. Interestingly, one study identified an increased risk amongst WFNS Grade 4 or 5 only when the onset of hyponatremia was after day 5⁸⁴.

1.5 Study Rationale

Timely diagnosis of symptomatic vasospasm can be difficult as the degree of vessel-caliber reduction does not necessarily correlate with development of neurological symptoms as some patients with moderate vasospasm develop infarcts while others with severe vasospasm remain asymptomatic. There are also multiple competing diagnoses in aneurysmal SAH patients that can manifest with similar clinical features including hydrocephalus, intracranial hemorrhage, cerebral edema, seizures, electrolyte abnormalities, infection, and cardiac dysfunction. A clinical decision rule using patient characteristics and the results of investigations to aid physicians predict symptomatic vasospasm would allow early identification of patients who may benefit from aggressive prophylactic treatment, closer monitoring in an intensive care unit, or repeat vascular imaging. Patients with a higher probability of developing this complication, as determined by such a rule, would be ideal candidates for emerging pharmacological agents aimed to prevent vasospasm and improve tolerance of brain tissue to ischemia. Clazosentan, an antagonist of the vasoconstrictive endothelin receptor, has been shown to reduce vasospasm-related morbidity and all-cause mortality in a phase III double-blind, randomized controlled trial³⁶. The neuroprotectant, NA-1, reduced the number of ischemic infarcts in a phase II study of patients undergoing endovascular embolization of cerebral aneurysms⁸⁵. Increased ICU length of stay also has a dramatic impact on health care expenditure with hospitalization accounting for 85% of the cost associated with aneurysmal SAH patients during their first year⁸⁶. Expediting transfer of patients who are low risk for symptomatic vasospasm from an ICU setting has potential for significant cost savings. Accurate assessment of symptomatic vasospasm risk will improve management and potentially overall outcome in aneurysmal SAH patients.

1.6 Study Objectives

1.6.1 Primary Objective

The primary aim of this study was to derive a clinically-applicable decision rule using logistic regression and recursive partitioning from a large aneurysmal SAH cohort based on routine clinical, radiological, and laboratory characteristics that identified patients who would develop symptomatic vasospasm.

1.6.2 Secondary Objectives

In addition to prediction rule derivation, other objectives included:

- Determine the incidence of symptomatic vasospasm amongst aneurysmal SAH patients at a single neurosurgical center
- Identify important clinical, radiological, or laboratory features that are independent predictors of symptomatic vasospasm
- Compare the accuracy and ease of use of the final multivariate logistic regression and recursive partitioning decision rules

2.0 Methods

2.1 Study Design

This study is a historical cohort study reviewing the paper and electronic health records of a single institution.

2.2 Study Population

Patients presenting directly or by referral from another hospital with SAH in the presence of an intracranial aneurysm seen on angiography were reviewed. Recruitment occurred at The Ottawa Hospital, Civic Campus, a tertiary care neurosurgical centre with a catchment area encompassing all of eastern Ontario, western Quebec, and extending north through Sudbury up to Nunavut. SAH was diagnosed radiographically by the presence of blood in the subarachnoid space on computed tomography (CT) or by cerebrospinal fluid (CSF) analysis. A positive CSF analysis was defined as greater than $5 \times 10^6/L$ red blood cells in the final test tube or existence of xanthochromia, a yellow precipitant due to hemoglobin breakdown, up to 2 weeks after suspected aneurysmal rupture⁸⁷. CSF evidence of SAH was included due to reduced sensitivity of CT imaging for SAH within a few days post-ictus whereas xanthochromia can persist for up to 2 weeks⁸⁸. Aneurysms were confirmed for all patients by CT angiography, MR angiography, or conventional catheter cerebral angiography.

2.2.1 Inclusion Criteria

All patients 18 years or older were eligible for inclusion if their presentation included both of the following conditions:

1. SAH demonstrated on CT brain or CSF obtained by lumbar puncture up to 2 weeks after a sudden onset, severe headache that was positive for xanthochromia or contained $>5 \times 10^6$ RBCs/L
2. At least 1 angiographically proven intracranial aneurysm

2.2.2 Exclusion Criteria

Patients were excluded if they presented outside the risk period for cerebral vasospasm or with neurological symptoms attributable to cerebral vasospasm (the outcome). Aneurysms as a result of infection, trauma, or augmented blood flow secondary to an arteriovenous malformation were also excluded as they are thought to represent a different disease. The specific criteria used were:

1. Death prior to the 4th day after SAH
2. Presentation past the 14th day after SAH
3. Evidence of symptomatic vasospasm at presentation
4. Aneurysms that are associated with an arteriovenous malformation or of the mycotic or traumatic type

2.3 Patient Recruitment

Recruitment occurred from a cohort of non-traumatic SAH patients managed between June 2002 and June 2011 at the Ottawa Hospital, Civic Campus. They were previously identified retrospectively using a validated text miner that searched the text of laboratory and radiology reports within the Ottawa Hospital Data Warehouse with keywords indicating the presence of an aneurysm and SAH⁸⁹. This data warehouse stores information from every inpatient encounter including individual demographics, investigation results, procedure reports, and hospital metrics. Unique identifiers were used to preferentially select data for CT, MRI, and catheter angiograms

of the brain as well as CSF analysis results. This method was calibrated to eliminate false negatives achieving a sensitivity of 96.5% [95% confidence interval (CI): 94.8-97.8%] and specificity of 40.3% [95% CI: 38.1-42.6%]. Search results were verified individually to ensure accuracy and that the inclusion and exclusion criteria were satisfied.

2.3.1 Sample Size

The incidence of symptomatic vasospasm ranges from 20-40% amongst SAH patients who survive to hospitalization⁹⁰. Examining the populations from previously published models aiming to predict this complication reveals its occurrence in 26.5 to 43.2%^{54,56-59,91}. Assuming an average event rate of 35%, a sample size of 355 (124 events) was determined necessary to achieve a target sensitivity of 100% with a 95% confidence interval (CI) of 97-100% using the Wilson score method⁹². This value fell well below the total of 632 cases of primary SAH in the cohort identified by *English et al.* to be used for recruitment, increasing the likelihood this study would achieve appropriate power⁸⁹.

2.4 Predictors

2.4.1 Predictor Selection and Literature Review

To help guide predictor choice, a comprehensive search of Medline, EMBASE, and the Cochrane Library database using an OVID interface was conducted looking for previously established models to predict symptomatic vasospasm. The search strategy employed controlled vocabulary, including the National Library of Medicine's medical subject headings (MeSH) and keywords related to the concepts of SAH, intracranial aneurysms, vasospasm, and clinical prediction rule. No filters were placed on study methodology or year of publication, however,

only publications in the English language were considered. This peer-reviewed process was created with the guidance of neurosurgeons, neuro-intensivists, neurologists, and emergency physicians. Variables employed in the identified studies were included in the current derivation process. This provided the framework upon which additional potential predictors of symptomatic vasospasm were incorporated. These were identified through interviews with practicing neurosurgeons and review of relevant references from previously published models.

2.4.2 Variables Collected

Data were collected for each patient related to their past medical history, presentation, and in-hospital course (*see data collection form in Appendix C*). The clinical variables included were patient age, gender, history of cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, coronary artery disease, stroke, connective tissue disorder, or sickle cell disease), history of intracranial hemorrhage (subarachnoid, intracerebral, or intraventricular), smoking status, use of illicit drugs (amphetamine or cocaine), medication use (statin, antiplatelet, or anticoagulant), family history of aneurysms or SAH; presenting neurologic grade, systolic blood pressure, and body temperature (in Celsius); date of SAH on admission, and unit of admission. Age was analyzed as a continuous variable and categorical variable by decades, except ages 18-39 years and 70 years or older, which were collapsed into single groups due to the few number of patients within those decades. Systolic blood pressure and temperature were classified as continuous variables and dichotomized variables about 180 mmHg and 38 degrees Celsius respectively. Neurological grade was assessed using the World Federation of Neurological Surgeons (WFNS) scale, which accounts for level of consciousness and presence of motor deficits (*see table 1*)¹⁵.

Radiological variables considered were thickness of SAH (by the modified Fisher grade, *see table 3*); ruptured aneurysm location and maximum diameter (in millimeters); aneurysm multiplicity, presence or absence of hydrocephalus, and mean flow velocities recorded by TCD for the anterior, middle and posterior cerebral arteries days 2 to 14 after SAH. The TCD results were summarized as elevated, normal, or not performed and only those performed 3 days post-SAH or earlier were entered for prediction. An elevated TCD was defined as a mean flow velocity greater than 120 cm/second or a Lindegaard Ratio (mean flow velocity in the middle cerebral artery divided by the mean flow velocity in the extracranial internal carotid artery) greater than 3 corresponding to moderate to severe angiographic vasospasm³².

Management-related variables included modality of aneurysm treatment (surgical ligation or endovascular embolization); use of nimodipine, prophylactic statin, anti-epileptic drugs, nicotine replacement therapy, prophylactic induced hypertension, or prophylactic induced hypervolemia; and need for external ventricular drainage (EVD) or endotracheal intubation within 24 hours of presentation or prior to day four post-SAH. Induced hypertension was defined as administration of intravenous fluids (IVF), vasopressors, or colloids to maintain a MAP greater than 65 mmHg or systolic blood pressure greater than 140 mmHg. Induced hypervolemia corresponded to an IVF infusion rate greater than 100 ml/hour. Initiation of hypertension or hypervolemia was considered prophylactic if it occurred at least 24 hours prior to the manifestation of neurological symptoms.

Complications entered as present or absent day three post-SAH or earlier included hyponatremia, anemia, pulmonary edema, and any cardiac event (acute coronary syndrome, arrhythmia, or heart

failure). Seizures were diagnosed based on clinical manifestations with or without electroencephalogram confirmation and classified as prior to/on presentation, during hospitalization or both. The cut-offs used for hyponatremia and anemia were a serum sodium level less than 135 mmol/L and serum hemoglobin level less than or equal to 100 g/L respectively. The serum sodium and hemoglobin levels on day 3 post-SAH were recorded for all patients. Pulmonary edema was verified using chest radiographs. Acute coronary syndrome was considered present if clinical symptoms (chest pain or left arm pain, diaphoresis) or electrocardiogram (ECG) 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.

2.4.3 Predictor Variable Assessment

The predictor variables were assessed by a single investigator (the author) through retrospective chart review. While it is recommended that this occur without knowing the outcome status of the patient, this was not possible given that both predictor and outcome information co-existed within the same body of text in the patient's medical record^{64,65}. The impact on the validity of the subsequently derived clinical decision rule is felt to be small as all but one of the variables were objectively determined, inputted directly from the chart and not requiring analysis by the assessor. Only SAH thickness was assigned a modified Fisher grade based on the author's (a senior neurosurgery resident) interpretation of the patient's CT head imaging. In addition, a majority of these variables were collected during the first three days post-SAH when the outcome was unlikely to occur.

2.5 Outcome

2.5.1 Definition

The outcome of interest, symptomatic vasospasm, was defined as a focal neurological deficit attributable to the vascular territory of intracranial, intradural arterial narrowing (angiographic vasospasm) in the absence of potential alternative causes⁹³. The focal neurological deficit could not be present immediately after aneurysm treatment and includes hemiparesis, hemiparesthesia, aphasia, apraxia, neglect, hemianopia, and decreased level of consciousness equalling a loss of 2 or more points on the Glasgow Coma Scale (GCS, *see table 2*). Arterial narrowing was diagnosed based on radiology reports documenting visualization of vasospasm of all severities on CT, MR, or catheter cerebral angiography or TCD measurements meeting the criteria for moderate to severe vasospasm. Angiographic vasospasm was a potential cause of neurological decline only if the resulting area of reduced perfusion corresponded to a neural territory that normally mediates that function. For example, vasospasm in the left middle cerebral artery could explain right-sided face and arm weakness due to impaired cerebral blood flow to the left pre-central gyrus known to mediate right-sided motor movements. A list of alternative etiologies for altered neurological status in aneurysmal SAH patients can be found in *table 4*. Based on this definition, and what is accepted clinically, symptomatic vasospasm was a diagnosis of exclusion.

2.5.2 Determination of Outcome

In accordance with the methodological standards for clinical decision rule derivation, outcome assessment was divided amongst 3 other investigators blinded to the identity of the predictor variables^{64,65}. This approach was used as the status of these variables could not be concealed since knowledge of their presence or absence was often necessary to establish the diagnosis of

symptomatic vasospasm. If there was uncertainty about the outcome, adjudication was mediated by a fifth investigator with stroke neurology expertise.

2.5.3 Inter-rater Reliability

Inter-rater reliability was assessed 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 effect⁹⁴.

The results from this initial evaluation period were included in subsequent analysis.

2.6 Data Analysis

Proportions and means with standard deviations were determined for all categorical and continuous variables respectively. Missing and outlying data points were identified through frequency tables and boxplots. These were then verified with the original data.

2.6.1 Logistic Regression

The covariates to achieve the most parsimonious model for predicting symptomatic vasospasm were chosen using purposeful selection as described by Hosmer and Lemeshow⁹⁵. Univariate analysis was conducted using the chi-square or Fisher exact test for categorical variables and two-sided t-test for continuous variables to identify predictors with significant associations to the outcome. Only those available at the time of presentation up to day 3 post-SAH were considered. Candidate variables for the preliminary multivariate model were selected and fit based on a conservative p-value of less than 0.2. Those that remained significant with a Wald-statistic p-value less than 0.05 formed a new, smaller model. The likelihood ratio test was used to confirm the eliminated variables did not contribute meaningfully to outcome prediction. Values of the estimated coefficients between the smaller and larger models were compared to determine if a

magnitude of change greater than 20% existed for any variable suggesting a necessary adjustment by a confounding variable amongst those removed. If this was found, the key variable was identified and refit into the model. Covariates eliminated earlier due to lack of significant association to the outcome were subsequently added back to the model individually to test whether they play an important role in the presence of other covariates based on a Wald-statistic p-value less than 0.05. The resulting main effects model was tested for clinically plausible interactions, which were included if they reached a likelihood ratio test p-value of less than 0.05.

The fit of the preliminary final model was assessed using the Hosmer and Lemeshow test. Receiver operating characteristic (ROC) curve analysis was performed including calculation of the area under the ROC curve and its corresponding 95% CI to determine the model's discrimination. Poor fitting covariate patterns were identified using the regression diagnostic statistics of leverage and change in chi-square, deviance, and beta-coefficients. The decision to retain or remove these covariate patterns weighed their effect on the estimated coefficients when removed from the multivariate model and whether they were clinically reasonable. All of the above analyses were performed using SAS software (Version 9.4 by SAS Institute Inc.)

2.6.2 Score Derivation

Using accepted methods, a risk score was developed using the estimated beta coefficients from the final multivariate logistic regression model^{96,97}. 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 associated with each point total was calculated using the equation below (B = point system constant):

$$\hat{p} = \frac{1}{1 + \exp(-\sum_{i=0}^p \beta_i X_i)} \text{ where } \sum_{i=0}^p \beta_i X_i = \beta_{intercept} + B(\text{Point Total})$$

A cut-off for the derived risk score was determined using the ROC curve illustrating the sensitivity and specificities for each point total.

2.6.3 Recursive Partitioning

Recursive partitioning is a non-parametric process of classifying subjects into sub-populations dichotomized about selected variables that allows maximizing of sensitivity or specificity without required calculations, thus improving clinical feasibility⁶³. Construction of decision trees through recursive partitioning to predict symptomatic vasospasm was performed using KnowledgeSEEKER (Version 9.0 by Angoss Software Corporation). Patients were divided into subsets based on a predictor variable with the goal of reducing population impurity as measured by entropy. This process was repeated using variables with the largest information gain (minimum ratio of 1%) until a subset where all patients had the same outcome status (ie. no symptomatic vasospasm) was achieved. Cut-offs for non-binary variables were assigned prior to analysis. Age was investigated in decades as well as dichotomized about age 60 and age 70. Neurological grade was classified as a WFNS Grade of 1 (GCS 15) or WFNS Grade of 2 to 5 (GCS 14 or less) and thickness of SAH on initial CT head split between Modified Fisher Grade 0 to 2 (thin or absent) and Grade 3-4 (thick).

All possible trees were grown with one third of the trees from each initial splitting variable selected for review by a panel of clinical experts. This consisted of neurosurgeons, a neurologist, a neurointensivist, and an emergency physician. Each reviewer then submitted an ordered list of

their top 5 models with consideration of sensitivity, specificity, ease of use, and the variables included. These rankings were then assigned weighted frequencies to establish the overall top 5 models. A final recursive partitioning model was then selected by the study investigators using the same criteria as the clinical experts. Pruning of the decision trees was not performed as the entire study population was used as a derivation cohort.

2.7 Ethical Concerns

Prior to data collection or analysis, approval from the Ottawa Health Science Network Research Ethics Board was obtained. Identifying information was stored separately from predictor and outcome data in an encrypted electronic database on the Ottawa Hospital server. Specifically, medical record numbers were only used to select charts for review and each patient assigned a unique study identification number. These identification numbers were necessary to link predictor and outcome data, which were assessed by separate investigators.

3.0 Results

3.1 Descriptive Statistics

From the cohort of 632 primary SAH patients suspected to be due to aneurysm or AVM rupture identified by the text miner, 463 were entered into this study. The most common criteria met for exclusion was death prior to day four post-SAH totalling 75 (44.38%) patients. Other reasons included presence of AVM (19.53%), non-aneurysmal SAH (15.38%), presentation past day 14 post-SAH (8.88%), symptomatic vasospasm on presentation (2.96%), normal CT head with absent or negative lumbar puncture results (2.96%), early transfer to another hospital (1.78%), and missing medical records (4.14%). Two unruptured aneurysms undergoing endovascular coiling complicated by intraoperative rupture were enrolled and analyzed in this study as they met our predefined inclusion criteria and were more likely similar rather than different than spontaneously ruptured aneurysms. It is recognized that their physiology is probably not identical due to wall compromise by mechanical forces rather than inflammation and the ability for the endovascular surgeons to limit extravasation from the aneurysm fundus. However, it was not possible to perform a meaningful sensitivity analysis to investigate this due to small numbers.

The clinical and radiological characteristics of all patients included in this study are summarized in *table 6*. Mean age at presentation was 56.0 ± 13.2 years (mean \pm standard deviation (SD)) with a majority in the sixth decade of life and female (70.2%). Almost half the patients had a history of hypertension and were actively cigarette smokers at 46.0% and 48.0% respectively. Previous SAH was uncommon only present in 2.2% patients and 10.4% had a family history of aneurysms and/or SAH. Home medications included statins for 14.0% of patients. Neurological grade at

presentation was generally good with 50.5% of patients WFNS grade 1 and only 13.2% WFNS grade 5. Thick subarachnoid blood with IVH was observed on CT head in 41.7% of patients corresponding to a modified Fisher grade 4, 14.5% were modified Fisher grade 3, 17.9% were modified Fisher grade 2, and 25.9% were modified Fisher grade 1 or 0. Anterior circulation aneurysms predominated at 82.5%. TCD's were only performed in 34.6% of patients with 3.9% meeting the criteria for angiographic vasospasm. A greater proportion of aneurysms underwent endovascular coiling (57.0%) than surgical clipping (43.0%) where the mean date of treatment was 3.4 ± 4.9 days post-SAH. CSF diversion by external ventricular drainage was required by 145 (31.3%) patients.

Radiological vasospasm was detected by CTA, MRA, catheter angiography, or TCD in 57.7% of patients in which, just over one third exhibited attributable neurological symptoms. The resulting overall incidence of symptomatic vasospasm in this cohort was 21.0% (*see table 7*). The distribution of demographics, clinical features, radiological findings, treatments, and complications between those who developed symptomatic vasospasm and those who did not are detailed in *table 9*. While just under 50% of patients were discharged home from hospital, the case fatality rate from aneurysmal SAH was 14.3%. Those who acquired symptomatic vasospasm had a marginally higher mortality rate at 16.5% (no vasospasm: 13.7%) and substantially reduced discharge to home, 38.1% (no vasospasm: 52.5%).

3.2 Inter-rater Reliability

The concordance between the three outcome assessors was evaluated for a pilot cohort of 25 aneurysmal SAH patients. Overall, the percentage agreement was 85.3% with identical diagnosis

by all assessors for 20 of 25 cases (*see table 8*). A Shrout-Fleiss intraclass correlation coefficient of 0.84 [95% CI: 0.71-0.92] was found indicating good inter-rater reliability in identifying symptomatic vasospasm.

3.3 Logistic Regression

3.3.1 Univariate Analysis

A total of 14 variables had a significant association with symptomatic vasospasm based on a p-value of less than 0.2 (*see table 9*). This included age by decades, history of connective tissue disorder, statin use at home, WFNS grade, ICU admission, modified Fisher grade, aneurysm location, aneurysm diameter, elevated velocities on TCD prior to day four post-SAH, modality of aneurysm treatment, prophylactic statin use, EVD placement, seizure prior to or on presentation to hospital, and intubation prior to day four post-SAH. While prophylactic hypervolemia had a substantial relationship to the outcome ($p=0.006$), it was not considered as the variable contained data collected up to 21 days post-SAH resulting in diminishing predictive utility. Similarly, TCD results prior to day four post-SAH did not undergo further analysis as there was a high number of missing information with 303 patients not having this exam performed, which would limit the modelling process.

3.3.2 Multivariate Analysis

After fitting the 13 predictors of symptomatic vasospasm into an initial multivariable model, only age by decades, modified Fisher grade, and aneurysm location remained significantly associated with clinical vasospasm. For age, being less than 40 years and 60 to 69 years did not reach significance when compared to age 70 or greater. modified Fisher grade 2 in relation to

modified Fisher grade 1 also had a p-value greater than 0.05. The likelihood ratio tests for both variables, age by decades and modified Fisher grade, were significant confirming their importance to the model.

EVD placement was determined to be a substantial confounder of modified Fisher grade as it was responsible for 65.8% of the 23.2% change in estimated beta coefficient for modified Fisher grade 4 when non-significant predictors were removed from the initial multivariate model. The associated p-value with EVD placement was 0.09 and its inclusion rendered the coefficient for modified Fisher grade 4 to be almost equivalent to that of grade 3 (1.49 and 1.46 respectively). Despite statistical evidence to support its inclusion into the model, the decision for it to remain removed was clinically-based. With the other significant predictors being available at the time of patient presentation to hospital, it was felt there would be greater utility of the model to predict symptomatic vasospasm risk prior to interventions such as EVD placement to guide further management.

Sequential addition of previously discarded predictor variables individually to the model did not reveal any that exhibited substantial contribution based on the Wald Chi-square p-value. No significant interactions were identified by the likelihood ratio test as shown in *table 10*. The resulting preliminary final model contained age by decades, modified Fisher grade and anterior vs. posterior circulation aneurysm location.

3.3.3 Model Assessment

The preliminary final model did not show evidence of poor fit based on the Hosmer and Lemeshow test, which had an associated p-value of 0.82. Discrimination was acceptable with an

area under the ROC curve of 0.73 [95% CI: 0.67-0.78]. In comparison, the area under the ROC curve with modified Fisher grade as the only predictor was 0.66 [95% CI: 0.60-0.71]. Regression diagnostics were calculated revealing several outlying covariate patterns with an associated large change in Pearson chi-square (ΔX^2) and deviance (ΔD) when removed. Specifically, there were four points (four covariate patterns, seven patients) with ΔX^2 greater than 10 with one as high as 26.19 and an equally elevated ΔD of 6.87 (*see figures 2 and 3*). One additional covariate pattern exhibited a Cook's distance greater than 0.25, which was overall low in magnitude but larger in comparison to others (*see figure 4*). No points with high leverage were identified as seen in *figure 5*. Each observation corresponding to the five poorly fitting or influential covariate points are outlined in *table 11* and their impact on the model after removal from the dataset is shown in *table 12*. While significant changes in beta coefficients are observed, particularly for modified Fisher grade and aneurysm location, these covariate patterns were retained in the dataset as they were biologically plausible. They involved seven patients who all developed symptomatic vasospasm but harbouring one high risk features such as age 50 to 69 years, modified Fisher grade 4, or an anterior circulation. The final model with its covariates is detailed in *table 13*.

3.3.4 Score Derivation

The smallest estimated coefficient, 0.23 from the relationship between modified Fisher grade 2 to grade 1, was assigned a point equivalence of 1 and used as the constant from which the point values for the remaining covariate categories were designated (*table 14*). This resulted in a score containing three clinicroadiographic variables totalling 0 to 17 points and associated with an estimated risk of symptomatic vasospasm from 0.01 to 0.38 (*table 15*). The symptomatic vasospasm score was retrospectively calculated for all 448 patients in the derivation cohort and was associated with an area under the ROC curve of 0.73. The prevalence of symptomatic

vasospasm for each point total are shown in *figure 6*. *Table 16* and *figure 7* illustrate the sensitivities and specificities for all possible score cut-offs.

3.4 Recursive Partitioning

A total of 89 decision trees were grown using recursive partitioning with modified Fisher grade, anterior compared to posterior aneurysm location, or WFNS grade as the initial splitting variable for the root node. From these, 25 were chosen for further assessment based on a high sensitivity or high specificity while maintaining a sensitivity of 97% or greater. The included variables, sensitivity, and specificity associated with each of the 25 decision trees are detailed in *table 17*. Clinical experts consisting of cerebrovascular neurosurgeons, neurointensivists, and an emergency physician, reviewed these trees independently agreeing on six candidates (three-way tie for fourth place) for the final recursive partitioning model based on statistical properties, clinical relevance, and perceived ease of use (see *appendix D*). Amongst these, the final model was chosen with the variables WFNS grade, modified Fisher grade, aneurysm treatment modality, aneurysm location, and age, having a sensitivity of 100% [95% CI: 96.2-100%] and specificity of 9.6% [95% CI: 7.0-13.1%] (see *figure 8*).

4.0 Discussion

4.1 SAH Cohort

Considering patients within the non-traumatic SAH cohort that were aneurysmal in origin, the annual rate of ruptured aneurysms was 60 per year. For comparison, the Canadian Collaborative Study Group of Stroke Hospitalizations identified 23140 discharges for SAH, both living and deceased, across Canada over a 10 year period from 1982 to 1991⁴. Assuming a majority were treated at the 14 Canadian cities with academic neurosurgical centres with aneurysmal rupture responsible for 85% of cases, this corresponds to 140 SAH patients annually per city. The difference in volume may be due to the declining rate of SAH, inclusion of ruptured aneurysms related to arteriovenous malformations by Ostbye's *et al.*, having multiple neurosurgical referral centres within a given city (e.g. Toronto), and varying catchment area population sizes^{3,4}.

Death prior to day four post-SAH was the predominant exclusion criterion met. The percentage of eligible patients not enrolled as a result of this matches the 2-day mortality rate from aneurysmal SAH of 27.5% when considering 11-14% of all cases result in death prior to hospital arrival^{98,99}. The rate of non-aneurysmal SAH we encountered was consistent with reports describing 10% of spontaneous SAH being due to non-aneurysmal perimesencephalic hemorrhage (bleeding in the subarachnoid space near the midbrain thought to arise from a neighbouring vein or perforating artery rupture) and 5% from rare causes such as other vascular lesions, vessel wall dissection, inflammation, tumours, and recreational drugs¹⁰⁰. Of the patients enrolled, the severity of SAH is comparable to other studies when measured by good neurological grade (WFNS Grade 1)^{56,69} and thick SAH on initial CT^{25,49}.

4.2 Incidence of Vasospasm

Symptomatic vasospasm occurred in 21.0% of aneurysmal SAH patients in our study. This observed rate is slightly lower than the range (26.5% to 43.2%) from previously published prediction models whose outcome definitions varied⁵⁴⁻⁵⁹. One possible reason for reduced diagnosis of symptomatic vasospasm may be the requirement for angiographic narrowing of cerebral arteries in a vascular territory attributable to the observed neurological decline.

However, Dumont *et al.*'s artificial neural network used an identical primary outcome definition as ours resulting in 39 cases (35%)⁵⁸. There is also considerable distance in time, up to 30 years, between our study and others during which management of SAH has changed considerably subsequently affecting complication rates and outcome. The incidence of symptomatic vasospasm has decreased over time from 32.5% in studies published prior to 1994 to 28.5% in studies published between 1994 to 2009¹⁰¹. With calcium channel blocker prophylaxis (nimodipine or nicardipine) in 32 publications, this proportion declined to 22%. Nimodipine administration was fairly universal in this study with all but 3 patients adhering to this regiment explaining the lower incidence as well as suggesting efficacy of this prophylactic agent. Dumont *et al.* did not document the use of nimodipine in their derivation population⁵⁸. A recent study from 2014 investigating the role of aneurysm location on SAH and its related outcomes similarly found neurological deterioration with angiographic vasospasm in 22% of patients all of whom received nimodipine treatment¹⁰².

Our definition of symptomatic vasospasm was chosen to ensure reproducibility through primarily objective measures. Despite this, neurological deterioration secondary to ischemia precipitated by processes other than narrowing of cerebral arteries would be missed by our

criteria thus reducing the overall observed incidence. It is recognized that delayed, clinically-relevant cerebral infarcts can occur after aneurysm rupture in areas absent of angiographic vasospasm typically located at the perimeter of brain parenchyma territories perfused by the major cerebral artery branches, referred to as watershed areas¹⁰³. Several alternate mechanisms to proximal arterial stenosis have been proposed. Propagating waves of electrical activity in the cortex of the brain stimulated by alterations in the electrolyte environment secondary to blood breakdown products in the CSF have been recorded in humans¹⁰⁴. This depolarization of neurons impairs normal signalling resulting in reduced cerebral blood flow, inability to meet the energy demands of the brain, and spreading ischemia. Vasospasm in the distal, smaller calibre cerebral arteries (microvascular vasospasm) is thought to also occur supported by impaired cerebral blood flow with prolonged cerebral circulation time when angiographic vasospasm was minimal to absent¹⁰⁵. Inflammation and microthromboembolism, the formation and migration of blood clots that occlude circulation, have also been implicated⁹³.

4.3 Logistic Regression Modelling

4.3.1 Age, Modified Fisher Grade, and Aneurysm Location

Our study is the first logistic regression-derived clinical decision rule to include age as an independent predictor of symptomatic vasospasm. While present in Dumont *et al.*'s artificial neural network, age is entered with presumed importance and its individual contribution difficult to interpret⁵⁸. Its role in the development of vasospasm is uncertain with a systematic review from 2013 concluding “inconsistent evidence” from studies supporting greater risk in younger patients^{69,70}, with increasing age¹⁰⁶, or no difference with age^{47,48,53,56}. Macdonald *et al.*'s description of vasospasm risk peaking for aneurysmal SAH patients aged 40 to 59 years mirrors

the findings in our study⁴⁹. Senescent intracranial arteries have been shown to become increasingly stiff with reduced elasticity from vessel wall thickening, increased thickness-to-radius ratio, and the formation of collagen fibers^{107,108}. This, along with atherosclerosis may render elder patients more resistant to vasospasm and the ability to maintain luminal patency in the setting of restricted cerebral blood flow. Notably, cerebral blood flow has been shown to reduce with increasing age particularly in the posterior cortical areas¹⁰⁹. Why younger patients experienced lower rates of symptomatic vasospasm is uncertain but perhaps reflects an increased resilience to ischemia and preservation of autoregulation.

Thickness of SAH on CT head at the time of presentation has a robust association to symptomatic vasospasm regardless of how the clot thickness and distribution was classified^{25,54-57}. The Modified Fisher Grade, demonstrated in our study to independently increase susceptibility of vasospasm with higher grade, has not been included in prior rules despite improved prognostication over the original Fisher Grade⁵⁰. In a multivariate analysis of 218 SAH patients, Yin *et al.* described similar significance of this enhanced grading scale with an odds ratio of 2.99 [95% CI: 2.05-4.35]¹⁰⁶. The predictive value of IVH, particularly in both lateral ventricles, has been previously established and a crucial factor prompting revision of the Fisher grading scale^{48,55,56}. Interestingly, we did not find a meaningful difference between Modified Fisher Grade 1 and 2 representing the absence or presence of IVH accompanying thin SAH. Only eight cases of Grade 2 SAH experienced symptomatic vasospasm proving to be insufficient power. Confounding is unlikely to play a role as the relationship between Grade 1 and 2 was non-significant even in univariate analysis. EVD placement SAH day three or prior did not statistically alter the influence of Grade 3 and 4 such that their odds ratios were practically

equivalent, negating the importance of IVH. If true, the deleterious effects of hemorrhagic products in the CSF can be minimized by enhanced clearance through external ventricular drainage. Its omission from the final prediction rule stems from the possibility Modified Fisher Grade influenced placement of an EVD, the ability to change a patient's risk score in real time if included, and adhering to the rule's purpose of aiding management decision at the time of presentation.

Rupture of posterior circulation aneurysms, which includes those arising from the posterior cerebral, basilar, superior cerebellar, anterior inferior cerebellar, posterior inferior cerebellar, and vertebral arteries, were less likely to develop symptomatic vasospasm than anterior circulation aneurysms. Qureshi *et al*'s risk index also identified aneurysms of the anterior cerebral and internal carotid artery as high risk features⁵⁶. When other posterior circulation aneurysms failed to show correlation to vasospasm, those of posterior cerebral artery origin were protective having an odds ratio of 0.05 [95% CI: 0.01-0.41]⁷⁹. The relationship between aneurysm location and symptomatic vasospasm is unclear. Alba *et al*'s determined that rupture of vertebral and basilar artery aneurysms resulted in the second and third lowest mean SAH maximum thickness with pericallosal artery aneurysms (a branch of the anterior cerebral artery) having the lowest value but the highest rate of symptomatic vasospasm¹⁰². While this could explain our observed difference in vasospasm incidence given its association to SAH thickness, it is doubtful as the proportion of patients classified as Modified Fisher Grades 3 and 4 (thick SAH) were comparable between locations (anterior = 56.5%, posterior = 54.3%). However, IVH was present (Modified Fisher Grades 2 and 4) in substantially more SAH patients with posterior circulation aneurysms (anterior = 56.0%, posterior = 76.6%, chi-square p-value = 0.0006). This is

paradoxical, as IVH is adversely correlated with symptomatic vasospasm. Posteriorly-situated aneurysms have been reported to predict the occurrence of IVH but the severity of IVH is greater for anteriorly circulation aneurysms¹¹⁰. The clinical importance of IVH severity with respect to delayed cerebral ischemia remains to be determined however Jabbarli *et al.* did find a higher frequency of angiographic vasospasm by TCD in cases with severe IVH as opposed to minor or absent IVH.

4.3.2 Other Risk Factors

We used a p-value threshold of 0.2 to identify candidate risk factors with WFNS grade, ICU admission, EVD placement, intubation on presentation or prior to SAH day three, and statin prophylaxis reaching traditional significance ($p < 0.05$) but excluded in multivariate analysis. This indicates their relationships with symptomatic vasospasm were confounded by other variables providing no improvement in the predictive value of the model by their presence. Neurological grade has previously failed to predict symptomatic vasospasm when categorized by the WFNS grading scale except in the study by Charpentier *et al.* where grades 3 to 5 were considered severe^{47,48,55,69,80}. Replication of this finding in the current study illustrates the strong association between modified Fisher grade and WFNS grade. Greater SAH burden is likely to reduce level of consciousness (GCS) or induce focal motor deficits by mass effect. This association extends to the need for ICU admission, EVD placement, and early intubation. Reduced neurological status impairs airway protection increasing the risk for aspiration (fluids or food content inhaled into the respiratory system) necessitating intubation and ICU admission for mechanical ventilator support. EVD placement is likely a surrogate for IVH, a known predictor of acute hydrocephalus in aneurysmal SAH¹¹¹. Prophylactic statin administration was a promising vasospasm prevention

agent as an anti-inflammatory and augments cerebral blood flow, however the latest multicentre randomized controlled trial (simvastatin in aneurysmal subarachnoid hemorrhage (STASH)) in 2014 showed no between-group difference in suspected delayed ischemia or radiologically-evident infarcts¹¹². It is possible that prior to this publication, clinicians preferentially prescribed statins to high-grade patients given its safe profile.

4.3.3 Symptomatic Vasospasm Score

The Symptomatic Vasospasm Score derived by multivariate logistic regression estimates the risk to be 1.2% in a 70 years or older patient with thin to absent SAH, no IVH, and a posterior circulation aneurysm. A patient aged 40 to 59 years with thick SAH, presence of IVH, and an anterior circulation aneurysm is at highest risk estimated at 38.4%. This range differs from Qureshi *et al.*'s risk index, the only previously published rule to propose a simplified point system, due to differing incidence, 33% (Qureshi) compared to 21% (current study)⁵⁶. When all risk factors are present in both scores, the probability of developing symptomatic vasospasm almost doubles. Choosing a score cut-off is contingent on whether the purpose of the rule is to identify patients at low or high likelihood of developing the outcome of interest and if the consequences of an incorrect diagnosis or a missed diagnosis are more severe. In symptomatic vasospasm, the current practice is to monitor SAH patients as high risk for a minimum of 14 days post SAH. Clinicians are therefore more likely to accept over diagnosing vasospasm as missed cases can lead to serious morbidity or even mortality. The Symptomatic Vasospasm Score has high sensitivity near or at 100% for scores below 7 making this an ideal margin for low risk SAH patients. Sensitivity approaches specificity at a score of 14 where the estimated risk exceeds the population incidence initiating the high-risk group. With a maximum specificity

of 89%, this prediction rule has greater capability of correctly identifying low-likelihood patients.

4.4 Recursive Partitioning Model

4.4.1 Low Risk Patients

Having a sensitivity of 100% [95% CI: 96.2-100%] makes the recursive partitioning model best calibrated to identify SAH patients who have a low probability of symptomatic vasospasm.

Clinical variables that were associated with reduced risk were similar to those in the logistic regression model including WFNS grade 1, modified Fisher grades 0 to 2, endovascular coiling, posterior circulation aneurysms, and age 60 years or older. Patients without neurological deficit on presentation (WFNS grade 1 = GCS 15 and absent motor deficit) who undergo endovascular coiling for aneurysm treatment, have thin to absent SAH on initial CT regardless of IVH, and 60 years of age or older are predicted to not develop symptomatic vasospasm (*see figure 9*). Even amongst those arriving to hospital with reduced level of consciousness or motor deficit (WFNS grades 2 to 5), considered a high-risk feature, a similar low risk profile is predicted if their modified Fisher grade is 0 to 2 and the ruptured aneurysm is of posterior location. Seizures or syncope from a transient spike in intracranial pressure at the time of aneurysmal rupture could precipitate this scenario, neither of which have been implicated in the occurrence of vasospasm^{47,53}. Aneurysm treatment modality was a superior classifier of neurologically intact patients explaining its earlier position in the decision algorithm. While this represents a management characteristic, the decision to pursue surgical clipping or endovascular coiling is only directly influenced by vasospasm if it is evident at the time of presentation or treatment is performed during the period it is known to occur⁵. Endovascular coiling is preferred in these

scenarios and recommended in the elderly, poor neurological grade, basilar termination aneurysms, and when the technical difficulty of the surgical approach is equivalent^{5,113-115}. The increased risk of symptomatic vasospasm following surgical clipping might arise from brain retraction and vessel manipulation during the craniotomy¹¹⁶.

4.4.2 High Risk Patients

Poor neurological grade is a logical marker of elevated risk as it is positively correlated with the amount of SAH from aneurysmal rupture. Even when the grade was favourable, surgical clipping, thick SAH, and younger age were indicative of symptomatic vasospasm. The specificity of this model was low at 9.6% [95% CI: 7.0-13.1%] having classified a proportion of SAH patients who did not develop this complication as high risk (false positive) ensuring no positive cases were missed. Using this rule, a fraction of high risk patients would be expected to acquire neurological deterioration from vasospasm but be absent in all low risk patients.

4.4.3 Comparison to Logistic Regression

The clinical decision rule derived using recursive partitioning has the advantage of mirroring the process of clinical reasoning rather than relying on calculations and memorization of specific probabilities. Its construct is simpler despite containing two additional but relevant variables, increasing the likelihood of adoption by clinicians managing SAH patients. Recursive partitioning was able to utilize information from WFNS grade and aneurysm treatment, which was otherwise lost following multivariate logistic regression analysis in this, and other studies^{47,69,80,117}. On the contrary, the estimated beta coefficients and corresponding point scale established in the logistic regression model quantifies the risk difference between categorical

levels within and between predictor variables. Having thick SAH with IVH (modified Fisher grade 4) counts towards 7 points implying its contribution to the probability of symptomatic vasospasm is greater than individual lower grades as well as anterior circulation aneurysms and the highest risk age group (40-59 years). This allows translation to a graduated change in estimated risk contingent on the constellation of predictor variable identities rather than simply a binary classification which recursive partitioning is limited to. These features and the ability to achieve high sensitivity with improved specificity over the recursive partitioning model renders the logistic regression model the more favourable derived clinical decision rule.

4.5 Study Strengths

This study used a large, consecutive cohort of aneurysmal SAH patients to derive a clinical decision rule for symptomatic vasospasm during a period when endovascular therapy was available, but overall is second to the analysis by Adams *et al.* where 934 patients were enrolled⁵⁴. It offers strong evidence to support the use of clinical and radiographic characteristics to reliably predict the occurrence of symptomatic vasospasm with greater accuracy than the amount and distribution of SAH alone. Our logistic regression model out-performed the modified Fisher grade, which in itself, is an improvement over the original Fisher grade used widely in clinical settings as the primary tool to predict complications and outcome in SAH. Both rules established in this study achieve good prediction value while maintaining face validity and remaining easy to use with 5 or less variables.

We adhered to the methodological standards of clinical decision rule creation ensuring the predictor-outcome relationships to vasospasm determined in this study were robust⁶⁵. All

clinically-relevant predictors, as determined by literature review and expert opinion, were included for univariate analysis. We clearly defined symptomatic vasospasm based on objective angiographic findings of cerebral arterial narrowing and the description of accepted forms of neurological deterioration were adapted from criteria published by expert cerebrovascular neurologist and neurosurgeons⁹³. Despite conceptual difficulties blinding assessors to predictor or outcome information with both present in the same documentation and predictor information required to establish the diagnosis of vasospasm, we feel this was successfully achieved. The identity of the predictors of interest was hidden from outcome assessors while predictors were collected at presentation or prior to day 3 post-SAH falling outside the expected outcome period. The number of outcome events observed, 97, is sizeable just surpassing that of Qureshi *et al.*'s derivation population for their risk index but does not meet the large, multinational breadth of Adams *et al.*'s study^{54,56}. Both the logistic regression and recursive partitioning models were constructed using clinically relevant and simple variables to maximize internal and external validity. This is also the first time symptomatic vasospasm has been modelled using recursive partitioning offering an intuitive, feasible, clinical decision aid.

4.6 Study Limitations

The major limitation of this study is its retrospective nature restricting variable information to what was historically recorded at the time of hospitalization. This study methodology potentiated diagnosis misclassification of symptomatic vasospasm, particularly if poor charting led to incomplete documentation of the observed neurological deficit and other clinically relevant features necessary to exclude alternative causes. The inability to standardize cerebral blood flow monitoring throughout the study period may also have contributed given the requirement of

angiographic vasospasm in our outcome definition. These discrepancies between patient charts were highlighted by the occasional need for adjudication during the outcome assessment process.

While it is conceivable that the lower incidence of symptomatic vasospasm we observed might be influenced by the reliance on retrospective diagnosis, it remains within the expected range when considering newer studies implementing routine nimodipine administration¹⁰¹. This could also have affected identification of pertinent pre-existing comorbidities that have previously been associated with the occurrence of symptomatic vasospasm, such as hypertension and diabetes mellitus^{49,53,75}. For these specific cardiovascular diseases though, their proportions (hypertension: 46%, diabetes mellitus: 8.42%) match those from previous publications (hypertension: 25-44%⁴⁹, diabetes mellitus: 3-9%⁵³).

Prior to clinical use, our proposed rule requires prospective evaluation in multiple institutions to capture variability in practice and SAH patient populations. Without validation, the clinical decision rule derived achieves only level 4 on the hierarchy of evidence⁶⁵. In designing the methods of this study, consideration was given to divide the sample into a derivation and validation cohort to establish internal validity of the resulting rules. This was decided against and the entire sample devoted to model analysis to ensure adequate statistical power to detect meaningful associations to vasospasm. In addition, validation using a split sample does not improve the level of evidence as the rule's external validity cannot be demonstrated⁶⁵.

Overestimating the incidence of symptomatic vasospasm as 35% led to the perceived required sample size being less than what was necessary. Despite the large number of patients enrolled, we did not accumulate the required number of outcomes, 124, to achieve our target precision as

reflected by the 95% CI for sensitivity at 96.19-100%. This may limit its acceptance for clinical testing or use if physicians or other health care providers deem its accuracy inadequate.

Lastly, the literature review performed primarily focused on previously published prediction rules for symptomatic vasospasm in aneurysmal SAH to identify attempts to clarify this diagnostic dilemma. The findings from this process were subsequently used to select candidate predictors to be used in logistic regression and recursive partitioning modelling. While established factors associated with the disease were included, it is possible that those not previously considered may have been neglected. This could restrict the overall prediction ability of the models from the current study by excluding important variables with good predictive value. A formal systematic review of associated predictors of symptomatic vasospasm can address this deficit in a prospective validation study of these derived clinical prediction rules.

4.7 Clinical Relevance and Future Research

With a logistic regression-based score and a recursive partitioning model to predict the development of symptomatic vasospasm, the risk for a given patient with aneurysmal SAH can be determined within the first 72 hours of admission allowing individualization of monitoring and preventative management. Low risk patients unlikely to develop this complication may prove safe to triage outside an acute care unit offering opportunities for significant cost-savings. High risk patients may benefit from increased frequency of neurological examination or bedside cerebral blood flow studies in addition to being ideal candidates for experimental therapies to reverse vasospasm or improve tolerance of the brain to ischemia^{36,85}. Prior to these changes in clinical practice, these rules require validation in a prospective, multicentre trial.

Such a trial would be possible with recruitment at Canadian neurosurgical centres from Ontario, Quebec, Alberta, and British Columbia through ongoing research initiatives by Dr. Dowlatshahi and Dr. Perry in stroke, intracerebral hemorrhage, and subarachnoid hemorrhage in these respective provinces. The importance of implementing such a trial in multiple neurosurgical centres is to capture inherent differences in aneurysmal SAH populations as well as practice protocols. It will ensure an adequate cohort of SAH patients is accrued in a reasonable timeframe to achieve narrow confidence intervals for sensitivity or specificity as the incidence of symptomatic vasospasm and rate of aneurysm rupture is low. Consecutively presenting aneurysmal SAH patients would be enrolled to prevent selection bias.

Implementation of the clinical decision rule will require prior physician training to ensure it is applied accurately and consistently. Additional training tools in the form of posters, pocket cards, or a smartphone application should also be available as references. Given that feasibility is a major criterion in successful development of a clinical decision rule, the rule's face validity and ease of use would be evaluated through physician-completed surveys. The prospective nature of this proposed trial will allow robust blinding of predictor assessment to the outcome as the variables would be collected prior to when the outcome is expected to occur. This methodology will also allow increased accuracy of outcome classification through standardization of examination and investigations pursued when an episode of symptomatic vasospasm is suspected. Follow up is expected to be excellent as the outcome typically occurs within 14-21 days of the initial hemorrhage corresponding to the typical hospital admission length for such patients. As part of the protocol development, a formal systematic review would be completed to

identify all biologically-plausible predictors of symptomatic vasospasm, which can be concurrently collected and used to further refine the clinical decision rule.

5.0 Conclusions

Clinical and radiographic features available early in the presentation of aneurysmal SAH can be used to reliably predict the onset of symptomatic vasospasm. These risk factors include amount and distribution of SAH on initial CT, age, and location of the ruptured aneurysm. Their combined contributions 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. SAH is thought to influence abnormal cerebral arterial narrowing and subsequent ischemia through induced inflammatory changes in the vessel wall structure and disrupted hemostasis of signalling agents that alter vascular diameter. The remaining factors are associated with increased vulnerability of the brain to reduced blood flow, stiffening of cerebral vessels, and increased severity of IVH. While recursive partitioning is able to utilize variables often eliminated achieving high sensitivity, logistic regression is favoured with the advantage of quantifying the risk associated with each predictor translating to a range of probabilities for the development of symptomatic vasospasm. Patients deemed at high risk by our proposed clinical decision rule should be considered for more aggressive monitoring in an intensive care setting with frequent cerebrovascular imaging. Identification of this profile of patients is likely accurate however prospective validation of this rule in other neurosurgical centers is required to classify SAH patients unlikely to develop symptomatic vasospasm as truly low risk.

Tables

Table 1. Subarachnoid Hemorrhage Grading Scales

Grade	Hunt and Hess* ¹⁴	WFNS ¹⁵	
		GCS	Motor Deficit**
1	Asymptomatic, or minimal headache and slight nuchal rigidity	15	Absent
2	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy	14-13	Absent
3	Drowsiness, confusion, or mild focal deficit		Present
4	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances	12-7	Absent or Present
5	Deep coma, decerebrate rigidity, moribund appearance	6-3	Absent or Present

* The overall Hunt and Hess grade is increased by 1 in the presence of serious systemic disease (hypertension, diabetes, severe atherosclerosis, chronic pulmonary disease, and severe angiographic vasospasm)

** Motor deficit includes aphasia, hemiparesis, or hemiplegia

WFNS = World Federation of Neurological Surgeons, GCS = Glasgow Coma Scale (*see table 2*)

Table 2. Glasgow Coma Scale (GCS)¹¹⁸

Eyes	Verbal	Motor
4 – Spontaneous eye opening	5 – Oriented	6 – Obeys commands
3 – Eyes open to voice	4 – Disoriented	5 – Localizes to painful stimuli
2 – Eyes open to pain	3 – Incomprehensible words	4 – Withdraws to painful stimuli
1 – No eye opening	2 – Incomprehensible sounds	3 – Decorticate posturing (abnormal flexion to painful stimuli)
	1 – Non-verbal	2 – Decerebrate posturing (abnormal extension to painful stimuli)
		1 – No motor response

The sum of the eyes, verbal and motor score gives the GCS ranging from 3 to 15. If the patient is intubated, the verbal score is not computed and instead replaced by the letter “T”.

Table 3. Alternative Etiologies to Cerebral Vasospasm for Altered Neurological Status in Aneurysmal Subarachnoid Hemorrhage

Neurological	<ul style="list-style-type: none">• Hemorrhage (aneurysm re-bleeding; epidural, subdural, intracerebral, or intraventricular hemorrhage)• Hydrocephalus• Seizures• Cerebral edema• Meningitis/Ventriculitis
Electrolyte Abnormality	<ul style="list-style-type: none">• Hyponatremia• Hyponatremia
Blood Gas Abnormality	<ul style="list-style-type: none">• Hypoxia• Hypercarbia
Cardiac	<ul style="list-style-type: none">• Arrhythmia• Hypotension• Hypovolemia• Hemodilution• Reduced cardiac output
Infection	<ul style="list-style-type: none">• Pneumonia• Urinary tract infection• Bacteremia
Medication	e.g. opioids, benzodiazepines, barbiturates

* adapted from “Management of Cerebral Vasospasm” by *Macdonald et al.*⁴⁰

Table 4. The Original Fisher Grade and Modified Fisher Grade^{46,50}

Grade	Fisher Grade	Modified Fisher Grade	
		SAH Classification	IVH
0		No SAH	Absent
1	No SAH		Absent
2	Diffuse thin layer of SAH (vertical layers <1 mm thick)	Localized or Diffuse Thin SAH	Present
3	Localized subarachnoid clot or thick SAH (vertical layers ≥1 mm thick)		Absent
4	ICH or IVH with absent or non-significant supratentorial SAH	Localized or Diffuse Thick SAH	Present

* SAH = subarachnoid hemorrhage, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage

Table 5. Previously Published Clinical Prediction Models and Decision Rules for Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Author	Derivation Population	Model/Rule Type	Predictors	SVS (%)	Validation	Limitations
Adams <i>et al.</i> , 1987 ⁵⁴	934 (International Cooperative Study on Timing of Aneurysm Surgery)	Logistic regression	<ul style="list-style-type: none"> Amount of SAH on presenting CT head Neurological grade (consciousness, orientation) Antifibrinolytic use 	31.9	No	<ul style="list-style-type: none"> Surgery 7-14 days post SAH No endovascular therapy CT obtained up to 5 days post-SAH Antifibrinolytics included in rule
Hijdra <i>et al.</i> , 1988 ⁵⁵	176 (Randomized controlled trial of tranexamic acid)	Logistic regression	<ul style="list-style-type: none"> Amount of SAH on presenting CT head (0-30 scale) Intraventricular blood (0-12 scale) Antifibrinolytic use* 	32	No	<ul style="list-style-type: none"> No endovascular therapy Study-specific grading of SAH thickness
Qureshi <i>et al.</i> , 2000 ⁵⁶	283 (Placebo group from North American centers in randomized controlled trial of tirilazad mesylate)	Logistic regression (Symptomatic vasospasm risk index)	<ul style="list-style-type: none"> Amount of SAH on presenting CT head Neurological grade (GCS) Anterior circulation aneurysms Early increased TCD velocities in MCA 	33	No	<ul style="list-style-type: none"> No endovascular therapy Non-standardized assessment of SAH thickness TCD criteria in rule does not include Lindegaard ratio
Gonzalez <i>et al.</i> , 2007 ⁵⁷	68 (Retrospective, single center)	Logistic regression (Vasospasm probability index)	<ul style="list-style-type: none"> Amount of SAH on presenting CT head (Fisher grade) Neurological grade (Hunt and Hess grade)** Spasm index (TCD velocity/hemispheric CBF) 	26.5	Jackknifed	<ul style="list-style-type: none"> Bedside xenon CBF units not widely available (required to calculate spasm index) Amount of SAH referenced to Grade 4
Dumont <i>et al.</i> , 2011 ⁵⁸	91 (Retrospective, single center)	Artificial neural network	<ul style="list-style-type: none"> Amount of SAH on presenting CT head (Modified Fisher grade) Neurological grade (GCS) Anterior circulation aneurysms Early increased TCD velocities in MCA Age Gender Placement of EVD Modality of aneurysm treatment 	35	Yes (22, same center as derivation population)	<ul style="list-style-type: none"> Ease of use in clinical setting untested Despite validation, only reaches level 3 evidence for clinical decision rules
Roederer <i>et al.</i> , 2014 ⁵⁹	81 (Retrospective, single centre)	Naive Bayes classifier, logistic regression	<ul style="list-style-type: none"> CSF drainage volume Mean arterial pressure Heart rate Intracranial pressure Blood glucose level Blood sodium level 	43.2	No	<ul style="list-style-type: none"> Includes only Fisher Grade 3 and 4 Vasospasm defined as angiographic vasospasm requiring intra-arterial vasodilator therapy

SVS = symptomatic vasospasm, SAH = subarachnoid hemorrhage, TCD = transcranial doppler, MCA = middle cerebral artery, CBF = cerebral blood flow, EVD = external ventricular drain, CSF = cerebrospinal fluid

* Hijdra *et al.* include antifibrinolytic use as this was significantly associated with delayed cerebral ischemia in a larger study that included the model derivation subjects

** Gonzalez *et al.* include Hunt and Hess grading in their model for clinical vasospasm despite a p-value of 0.1 in multivariate analysis likely due to clinical relevance

Table 6. Clinical and Radiological Characteristics of 463 Patients Presenting with Aneurysmal Subarachnoid Hemorrhage

Characteristic	Aneurysmal SAH Patients (n = 463)
Demographics	
Age (years), mean ± SD	55.99 ± 13.19
<40, n (%)	46 (9.9)
40-49, n (%)	106 (22.9)
50-59, n (%)	141 (30.5)
60-69, n (%)	87 (18.8)
≥70, n (%)	83 (17.9)
Female, n (%)	325 (70.2)
Comorbidities, n (%)	
Hypertension	213 (46.0)
Hypercholesterolemia	64 (13.8)
Diabetes	39 (8.4)
Coronary Artery Disease	45 (9.7)
Stroke	18 (3.9)
Connective Tissue Disorder	4 (0.9)
Sickle Cell Disease	1 (0.2)
Current Smoker	222 (48.0)
Cocaine/Amphetamine Use	9 (1.9)
Previous Hemorrhage (SAH/ICH/IVH)	10 (2.2)
Family History of Aneurysms or SAH	48 (10.4)
Home Medications, n (%)	
Statin	65 (14.0)
Antiplatelet	71 (15.3)
Anticoagulant	11 (2.4)
Clinical Features at Presentation	
WFNS Grade, n (%)	
1	234 (50.5)
2	62 (13.4)
3	23 (5.0)
4	83 (17.9)
5	61 (13.2)
Systolic Blood Pressure (mmHg), mean ± SD	158.26 ± 31.16
Temperature (°C), mean ± SD	36.23 ± 0.95
ICU Admission, n (%)	165 (35.6)
Radiological Findings	
Modified Fisher Grade, n (%)	
0/1	120 (25.9)
2	83 (17.9)
3	67 (14.5)
4	193 (41.7)
Location, n (%)	
Internal Carotid Artery	43 (9.3)
Posterior Communicating Artery	80 (17.3)
Anterior Cerebral Artery	17 (3.7)
Anterior Communicating Artery	145 (31.3)
Middle Cerebral Artery	97 (21.0)
Posterior Circulation	81 (17.5)
Diameter of Ruptured Aneurysm (mm),	7.13 ± 3.99

mean ± SD	
Multiple, n (%)	153 (33.1)
Total Number of Aneurysms, mean ± SD	1.49 ± 0.89
Hydrocephalus, n (%)	227 (49.0)
TCD (SAH Day 3 or prior), n (%)	
	Elevated
	18 (3.9)
	Normal
	142 (30.7)
	Not Performed
	303 (65.4)
Treatments	
SAH Day of Aneurysm Occlusion, mean ± SD	3.39 ± 4.86
Surgical Clipping, n (%)*	194 (43.0)
Endovascular Coiling, n (%)*	257 (57.0)
Nimodipine, n (%)	458 (98.9)
Statin, n (%)	190 (41.0)
Antiepileptic Drug, n (%)	437 (94.4)
Prophylactic Hypertension, n (%)	92 (19.9)
Prophylactic Hypervolemia, n (%)	285 (61.6)
Nicotine Replacement Therapy, n (%)	20 (4.3)
Complications (SAH Day 3 or prior)	
EVD Placement, n (%)	145 (31.3)
Seizures, n (%)	72 (15.6)
Intubation, n (%)	154 (33.3)
Pulmonary Edema, n (%)	60 (13.0)
Cardiac, n (%)	43 (9.3)
Hyponatremia (<135 mmol/L), n (%)	70 (15.1)
Anemia (≤100 g/L), n (%)	97 (21.0)
Disposition, n (%)	
Mortality	66 (14.3)
Home	229 (49.5)
Other Health Care Facility	168 (36.3)

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

SD = standard deviation, SAH = subarachnoid hemorrhage, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage, WFNS = World Federation of Neurological Surgeons, TCD = transcranial doppler, EVD = external ventricular drain

Table 7. Occurrence of Vasospasm in 463 Patients Presenting with Aneurysmal Subarachnoid Hemorrhage

Vasospasm	Aneurysmal SAH Patients (n = 463)
Radiological, n (%)	267 (57.7)
Imaging Modality for First Detection	
TCD	127 (47.6)
CTA	82 (30.7)
MRA	10 (3.8)
Catheter Angiography	48 (18.0)
Symptomatic, n (%)	97 (21.0)
Absent, n (%)	196 (42.3)

SAH = subarachnoid hemorrhage, TCD = transcranial doppler, CTA = computed tomography angiography, MRA = magnetic resonance angiography

Table 8. Concordance in Diagnosing Symptomatic Vasospasm Between Three Study Investigators for the Pilot Cohort

	25 Aneurysmal SAH Patients
Overall Percentage Agreement (%)	85.3
Complete Agreement, n (%)	20 (80)
Partial Agreement, n (%)	4 (16)
No Agreement, n (%)	1 (4)
Shrout-Fleiss Intraclass Correlation Coefficient (2,1)	0.84 [95% CI: 0.71-0.92]

Table 9. Association of Proposed Clinical and Radiological Predictors to Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Characteristic	Patients with Symptomatic Vasospasm (n = 97)	Patients without Symptomatic Vasospasm (n = 366)	p-value
Demographics			
Age (years), mean ± SD	54.62 ± 11.56	56.35 ± 13.58	0.25
<40, n (%)	7 (7.2)	39 (10.7)	
40-49, n (%)	26 (26.8)	80 (21.9)	
50-59, n (%)	34 (35.1)	107 (29.2)	0.15
60-69, n (%)	20 (20.6)	67 (18.3)	
≥70, n (%)	10 (10.3)	73 (20.0)	
Female, n (%)	73 (75.3)	252 (68.9)	0.22
Comorbidities, n (%)			
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)	1.00
Current Smoker	51 (52.6)	171 (46.7)	0.30
Cocaine/Amphetamine Use	2 (2.1)	7 (1.9)	1.00
Previous Hemorrhage (SAH/ICH/IVH)	2 (2.1)	10 (2.7)	1.00
Family History of Aneurysms or SAH	9 (9.3)	39 (10.7)	0.85
Home Medications, n (%)			
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, n (%)			0.02
1	35 (36.1)	199 (54.4)	
2	18 (18.6)	44 (12.0)	
3	8 (8.3)	15 (4.1)	
4	20 (20.6)	63 (17.2)	
5	16 (16.5)	45 (12.3)	
Systolic Blood Pressure (mmHg), mean ± SD	161 ± 34.63	157.5 ± 30.18	0.33
Temperature (°C), mean ± SD	36.23 ± 0.92	36.22 ± 0.96	0.95
ICU Admission, n (%)	45 (46.4)	120 (32.8)	0.01
Radiological Findings			
Modified Fisher Grade, n (%)			<0.0001
0/1	11 (11.3)	109 (29.8)	
2	8 (8.3)	75 (20.5)	
3	21 (21.7)	46 (12.6)	
4	57 (58.8)	136 (37.2)	
Location, n (%)			
Posterior Circulation, n (%)	7 (7.2)	74 (20.2)	0.002
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)	

Diameter of Ruptured Aneurysm (mm), mean ± SD	6.61 ± 3.69	7.27 ± 4.06	0.15
Multiple, n (%)	29 (29.9)	124 (33.9)	0.46
Total Number of Aneurysms, mean ± SD	1.47 ± 0.91	1.49 ± 0.88	0.86
Hydrocephalus, n (%)	54 (55.7)	173 (47.3)	
TCD (SAH Day 3 or prior), n (%)			0.14
Elevated	7 (7.2)	11 (3.0)	
Normal	31 (32.0)	111 (30.3)	
Not Performed	59 (60.8)	244 (66.7)	
Treatments			
SAH Day of Aneurysm Occlusion, mean ± SD	2.89 ± 3.62	3.52 ± 5.14	0.26
Surgical Clipping, n (%)*	47 (49.5)	147 (41.3)	0.15
Endovascular Coiling, n (%)*	48 (50.5)	209 (58.7)	
Nimodipine, n (%)	97 (100.0)	361 (98.6)	0.59
Statin, n (%)	49 (50.5)	141 (38.5)	0.03
Antiepileptic Drug, n (%)	94 (96.9)	343 (93.7)	0.32
Prophylactic Hypertension, n (%)	18 (18.6)	74 (20.2)	0.72
Prophylactic Hypervolemia, n (%)	48 (49.5)	237 (64.8)	0.006
Nicotine Replacement Therapy, n (%)	4 (4.1)	16 (4.4)	1.00
Complications (SAH Day 3 or prior)			
EVD Placement, n (%)	39 (40.2)	106 (29.0)	0.03
Seizures, n (%)	20 (20.6)	52 (14.2)	0.12
Intubation, n (%)	41 (42.3)	113 (30.9)	0.03
Pulmonary Edema, n (%)	12 (12.4)	48 (13.1)	0.85
Cardiac, n (%)	10 (10.3)	33 (9.0)	0.70
Hyponatremia (<135 mmol/L), n (%)	16 (16.5)	54 (14.8)	0.67
Anemia (≤100 g/L), n (%)	21 (21.7)	76 (20.8)	0.85

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

SD = standard deviation, SAH = subarachnoid hemorrhage, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage, WFNS = World Federation of Neurological Surgeons, TCD = transcranial doppler, EVD = external ventricular drain

Table 10. Testing Interactions Between Covariates Within the Main Effects Model with Associated Likelihood Ratio Test and Wald Chi-Square Test Results

Interaction	Log-Likelihood	Degrees of Freedom	Likelihood Ratio Test p-value	Wald Chi-Square p-value
Main Effects Model	412.59			
Agecat1*modfisher2	398.47	12	0.29	0.97
Agecat1*modfisher3				0.95
Agecat1*modfisher4				0.95
Agecat2*modfisher2				0.99
Agecat2*modfisher3				0.96
Agecat2*modfisher4				0.95
Agecat3*modfisher2				0.99
Agecat3*modfisher3				0.95
Agecat3*modfisher4				0.96
Agecat4*modfisher2				0.99
Agecat4*modfisher3				0.95
Agecat4*modfisher4				0.95
Agecat1*antpost	411.03	4	0.81	0.93
Agecat2*antpost				0.30
Agecat3*antpost				0.61
Agecat4*antpost				0.85
Modfisher2*antpost	409.46	3	0.37	0.97
Modfisher3*antpost				0.99
Modfisher4*antpost				0.53

Agecat = age in decades where 1 is <40 years, 2 is 40-49 years, 3 is 50-59 years, 4 is 60-69 years (reference = ≥70 years); Modfisher = Modified Fisher grade from 1 to 4 (reference = grade 0/1); antpost = anterior versus posterior circulation aneurysm

Table 11. Covariate Values, Observed Outcome, Predicted Probability, Change in Pearson Chi-Square (ΔX^2), Change in Deviance (ΔD), Leverage, and Change in β -Coefficients (Cook's Distance (c)) For Patients with Poor Fitting or Influential Covariate Patterns

Subject	Age (Years)	Modified Fisher Grade	Aneurysm Location	Symptomatic Vasospasm	Predicted Probability	ΔX^2	ΔD	Leverage	c
42/104	60-69	0/1	Anterior	Present	0.08	11.98	5.26	0.01	0.16
96	50-59	0/1	Posterior	Present	0.04	26.19	6.87	0.01	0.29
133	<40	4	Posterior	Present	0.13	6.82	4.32	0.04	0.29
140	≥ 70	4	Posterior	Present	0.06	15.56	5.84	0.02	0.27
148/333/ 375	<40	0/1	Anterior	Present	0.09	10.30	5.03	0.02	0.22

Table 12. Effect of Poor Fitting and Influential Covariate Patterns on the Estimated β -Coefficients and Model Statistics of the Preliminary Final Model

Variable	All Data Coefficients	% Change in Coefficient With Covariate Pattern Deletion					All 5 Covariate Patterns
		42/104	96	133	140	148/333/375	
Age <40 years vs. \geq 70 years	0.8500	-6.15	-4.88	22.44	-16.58	75.12	90.19
Age 40-49 years vs. \geq 70 years	1.2031	-3.05	-2.40	0.52	-11.59	-2.08	-20.49
Age 50-59 years vs. \geq 70 years	1.1698	-2.26	1.90	0.17	-11.92	-1.54	-14.70
Age 60-69 years vs. \geq 70 years	0.6903	20.15	-0.28	1.07	-18.83	0.64	3.24
Modified Fisher Grade 2 vs. 0/1	0.2325	-90.84	-52.56	-1.08	-6.41	-136.69	-369.03
Modified Fisher Grade 3 vs. 0/1	1.4942	-15.49	-6.54	-0.09	0.01	-24.13	-59.54
Modified Fisher Grade 4 vs. 0/1	1.6962	-14.26	-7.46	1.98	-0.29	-16.64	-47.71
Anterior vs. Posterior Aneurysm Location	1.2635	-0.67	-14.76	-11.64	-13.79	3.48	-47.10
Intercept	-4.4241	-5.30	-6.58	-2.53	-6.79	-5.40	-33.65
Model Statistics							
Hosmer-Lemeshow	4.4283	1.5361	5.5269	4.3650	2.7111	1.6048	4.4371

Table 13. Final Logistic Regression Model Predicting Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Predictor	Estimated β -Coefficient	Standard Error	Estimated Odds Ratio	95% Confidence Limits	Wald Chi-Square p-value
Intercept	-4.42	0.6636			<0.0001
Age (ref. = ≥ 70 years)					
Age <40 years	0.85	0.59	2.34	0.74-7.36	0.15
Age 40-49 years	1.20	0.45	3.33	1.39-7.97	0.007
Age 50-59 years	1.18	0.43	3.22	1.40-7.42	0.006
Age 60-69 years	0.69	0.46	1.99	0.82-4.87	0.13
Modified Fisher Grade (ref. = 0/1)					
2	0.23	0.50	1.26	0.48-3.34	0.64
3	1.49	0.42	4.46	1.96-10.13	0.0004
4	1.70	0.37	5.45	2.62-11.33	<0.0001
Aneurysm Location (ref. = posterior)					
Anterior	1.26	0.43	3.54	1.51-8.29	0.004

ref. = reference

Table 14. Derivation of the Symptomatic Vasospasm Score

Risk Factor	Categories	β-Coefficient	Points = β-Coefficient/B
Age	<40	0.85	4
	40-49	1.20	5
	50-59	1.17	5
	60-69	0.69	3
	70+	<i>reference</i>	0
Modified Fisher Grade	0/1	<i>reference</i>	0
	2	0.23	1
	3	1.49	6
	4	1.70	7
Location of Aneurysm	Posterior	<i>reference</i>	0
	Anterior	1.26	5

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

Table 15. Estimated Risk of Symptomatic Vasospasm Based on the Point Total from the Symptomatic Vasospasm Score

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

Table 16. Sensitivity, Specificity, and 1-Specificity of the Symptomatic Vasospasm Score Stratified by Point Cutoff

Point Cutoff	Sensitivity (%)	Specificity (%)
0	100.0	0.0
1	100.0	0.6
3	100.0	1.4
4	100.0	2.0
5	100.0	4.0
6	99.0	9.4
7	99.0	15.6
8	97.9	17.6
9	95.8	20.7
10	91.6	26.1
11	85.3	45.6
12	75.8	56.1
14	65.3	69.7
15	60.0	72.8
16	47.4	83.3
17	32.6	89.2

Table 17. Top 25 of 89 Proposed Recursive Partitioning Models to Predict Symptomatic Vasospasm Risk in Aneurysmal Subarachnoid Hemorrhage Patients

Variables Included	Sensitivity (%)	Specificity (%)
modified Fisher grade, age <70 vs. ≥ 70 years, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement, prophylactic hypervolemia	100	12.8
modified Fisher grade, age <70 vs. ≥ 70 years, pre-existing hypertension, diabetes, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement	97.9	21.0
modified Fisher grade, age <70 vs. ≥ 70 years, anterior vs. posterior circulation aneurysm, positive TCD SAH day 3 or earlier, hydrocephalus requiring EVD placement*	100	12.8
modified Fisher grade, age <70 vs. ≥ 70 years, seizure prior to or during first 24 hours of presentation, surgical clipping vs. endovascular coiling*	100	13.4
modified Fisher grade, age <70 vs. ≥ 70 years, pre-existing hypertension, diabetes, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement*	96.9	23.2
modified Fisher grade, age <70 vs. ≥ 70 years, pre-existing hypertension, diabetes, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	97.9	18.0
modified Fisher grade, sex, age <70 vs. ≥ 70 years, pre-existing hypertension, diabetes, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	96.9	23.5
modified Fisher grade, sex, age <70 vs. ≥ 70 years, seizure prior to or during first 24 hours of presentation, surgical clipping vs. endovascular coiling	99.0	16.4
modified Fisher grade, age <70 vs. ≥ 70 years, pre-existing hypertension, diabetes, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement, anemia SAH day 3 or earlier	97.9	20.2
modified Fisher grade, age <70 vs. ≥ 70 years, seizure prior to or during first 24 hours of presentation, surgical clipping vs. endovascular coiling, anemia SAH day 3 or earlier	100	13.1
modified Fisher grade, age <70 vs. ≥ 70 years, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement*	99.0	19.4
modified Fisher grade, WFNS 1 vs. 2 to 5, age 40-60 vs. <40 or ≥60 years, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement*	99.0	21.0

modified Fisher grade, age <60 vs. ≥60 years, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement, intubation on presentation or prior to SAH day 4, prophylactic hypervolemia	99.0	18.6
modified Fisher grade, WFNS 1 vs. 2 to 5, age 40-60 vs. <40 or ≥60 years, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling, anemia SAH day 3 or earlier, hyponatremia SAH day 3 or earlier	97.9	22.1
WFNS 1 vs. 2 to 5, age <70 vs. ≥70 years, anterior vs. posterior circulation aneurysm, anemia SAH day 3 or earlier, hyponatremia SAH day 3 or earlier	96.9	21.3
modified Fisher grade, WFNS 1 vs. 2 to 5, age <60 vs. ≥60 years, anterior vs. posterior circulation aneurysm, surgical clipping vs. endovascular coiling **	100	9.6
modified Fisher grade, WFNS 1 vs. 2 to 5, age <60 vs. ≥60 years, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	99.0	13.9
modified Fisher grade, WFNS 1 vs. 2 to 5, sex, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	97.9	17.5
modified Fisher grade, WFNS 1 vs. 2 to 5, anterior vs. posterior circulation aneurysm, hydrocephalus requiring EVD placement	97.9	16.7
modified Fisher grade, WFNS 1 vs. 2 to 5, age <70 vs. ≥70 years, hydrocephalus requiring EVD placement	97.9	15.6
modified Fisher grade, WFNS 1 vs. 2 to 5, age <60 vs. ≥60 years, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	100	9.6
modified Fisher grade, WFNS 1 vs. 2 to 5, age <60 vs. ≥60 years, anterior vs. posterior circulation aneurysm, positive TCD SAH day 3 or earlier, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	100	10.9
WFNS 1 vs. 2 to 5, sex, anterior vs. posterior circulation aneurysm, positive TCD SAH day 3 or earlier, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	99.0	14.5
modified Fisher grade, WFNS 1 vs. 2 to 5, sex, positive TCD SAH day 3 or earlier, surgical clipping vs. endovascular coiling, hydrocephalus requiring EVD placement	97.9	17.2
modified Fisher grade, WFNS 1 vs. 2 to 5, anterior vs. posterior circulation aneurysm, positive TCD SAH day 3 or earlier, hydrocephalus requiring EVD placement	97.9	16.4

* = most clinically relevant, easy to use, and statistically robust models considered for the final model, ** = final model

Figures

Figure 1. PRISMA Flow Diagram of Study Identification and Selection

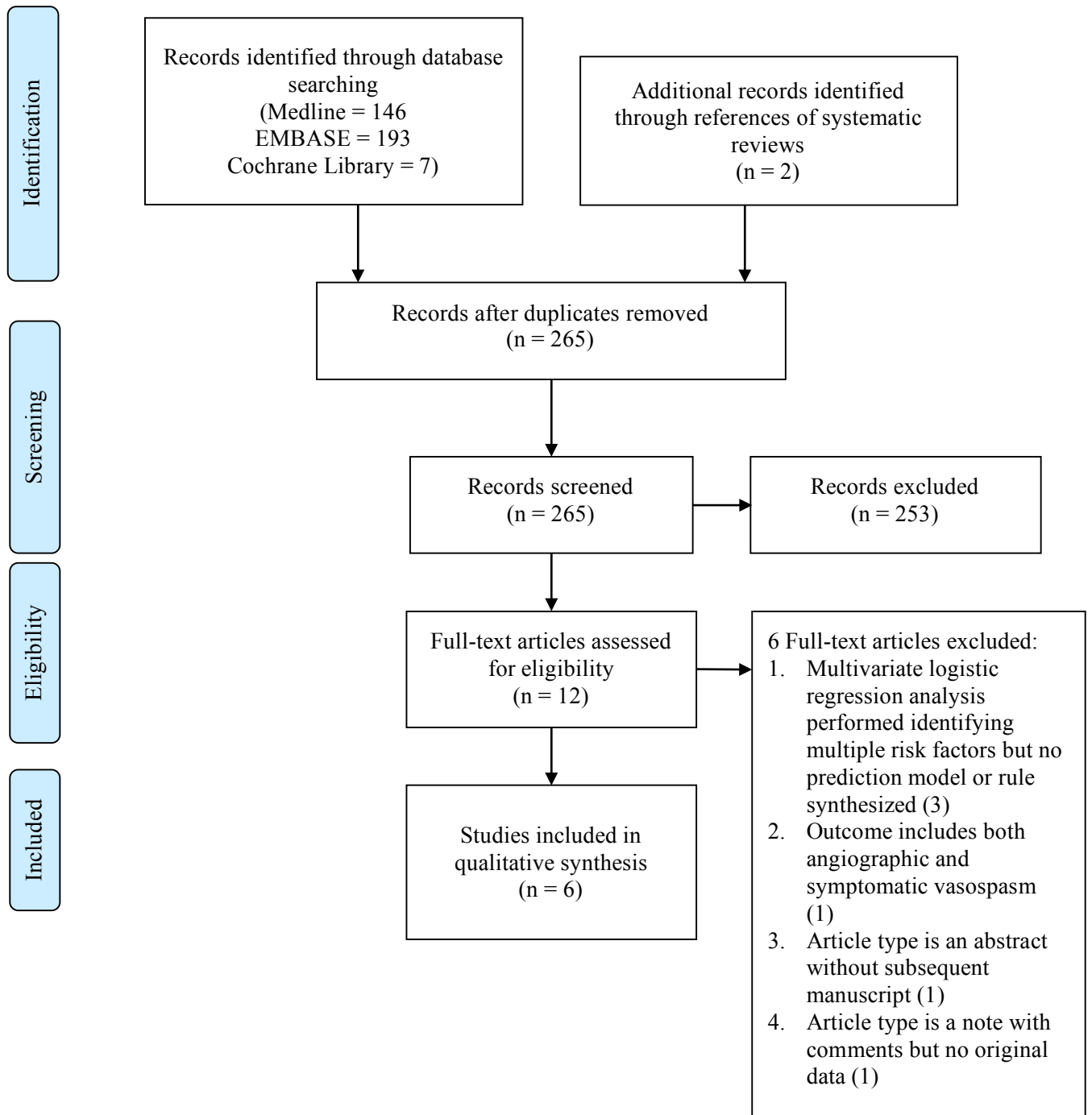


Figure 2. Plot of Change in Pearson Chi-Square Versus Estimated Probability For The Preliminary Final Model Predicting Symptomatic Vasospasm

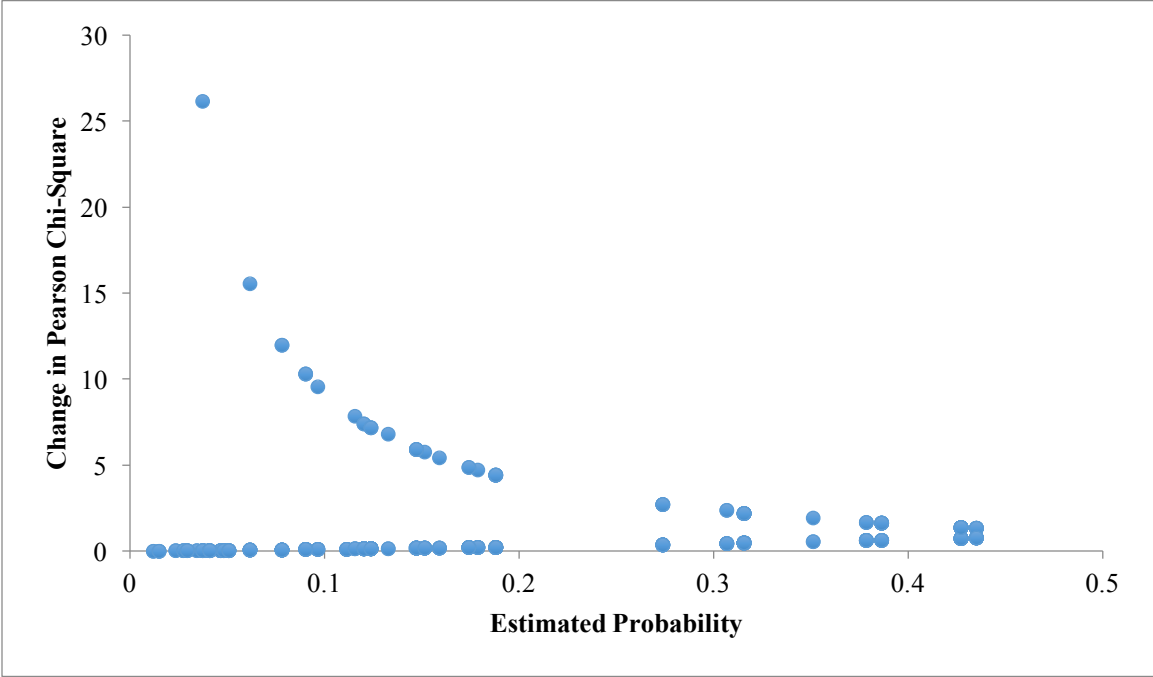


Figure 3. Plot of Change in Deviance Versus Estimated Probability For The Preliminary Final Model Predicting Symptomatic Vasospasm

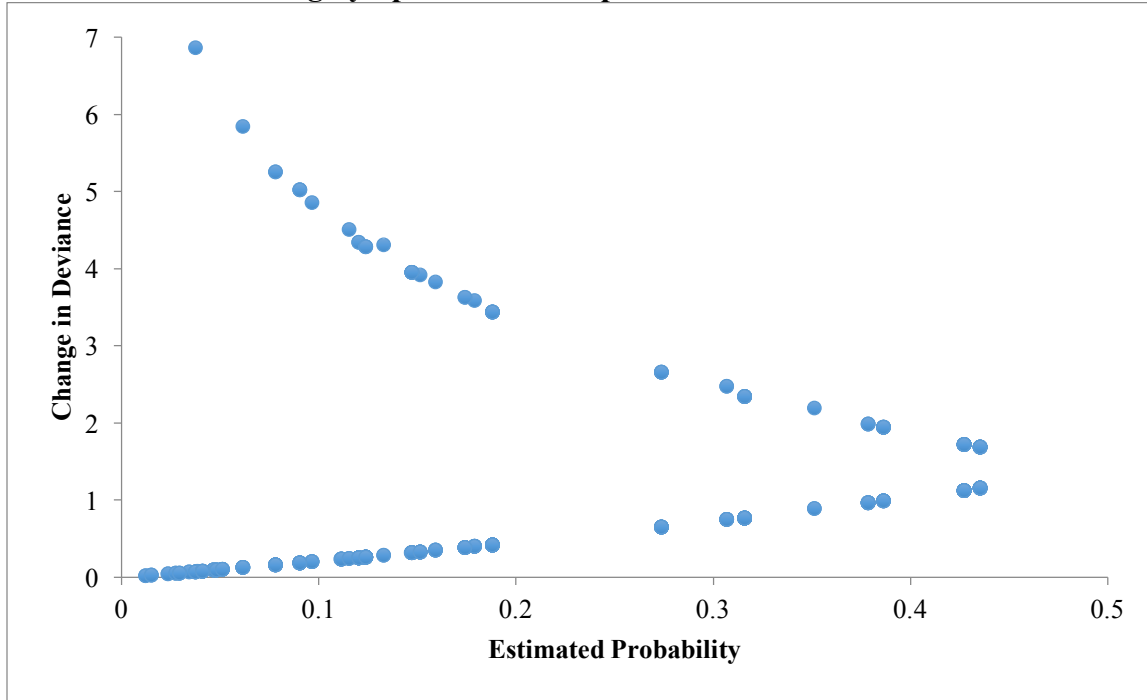


Figure 4. Plot of Cook's Distance Versus Estimated Probability For The Preliminary Final Model Predicting Symptomatic Vasospasm

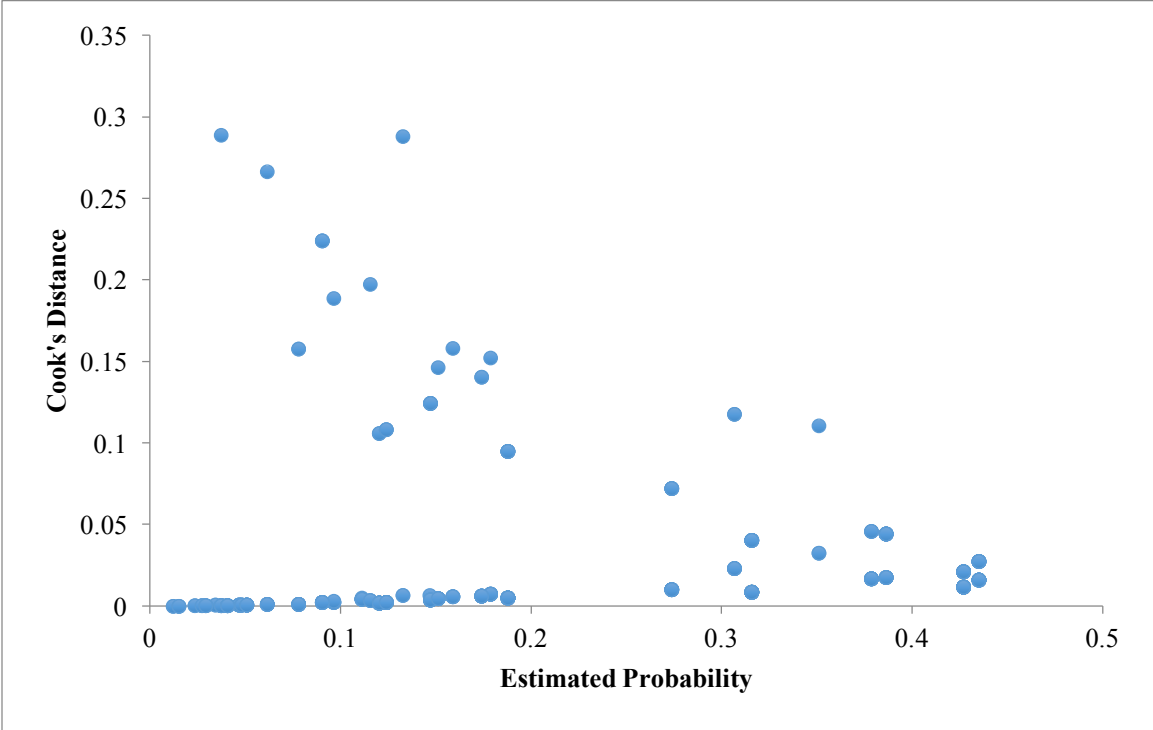


Figure 5. Plot of Leverage Versus Estimated Probability For The Preliminary Final Model Predicting Symptomatic Vasospasm

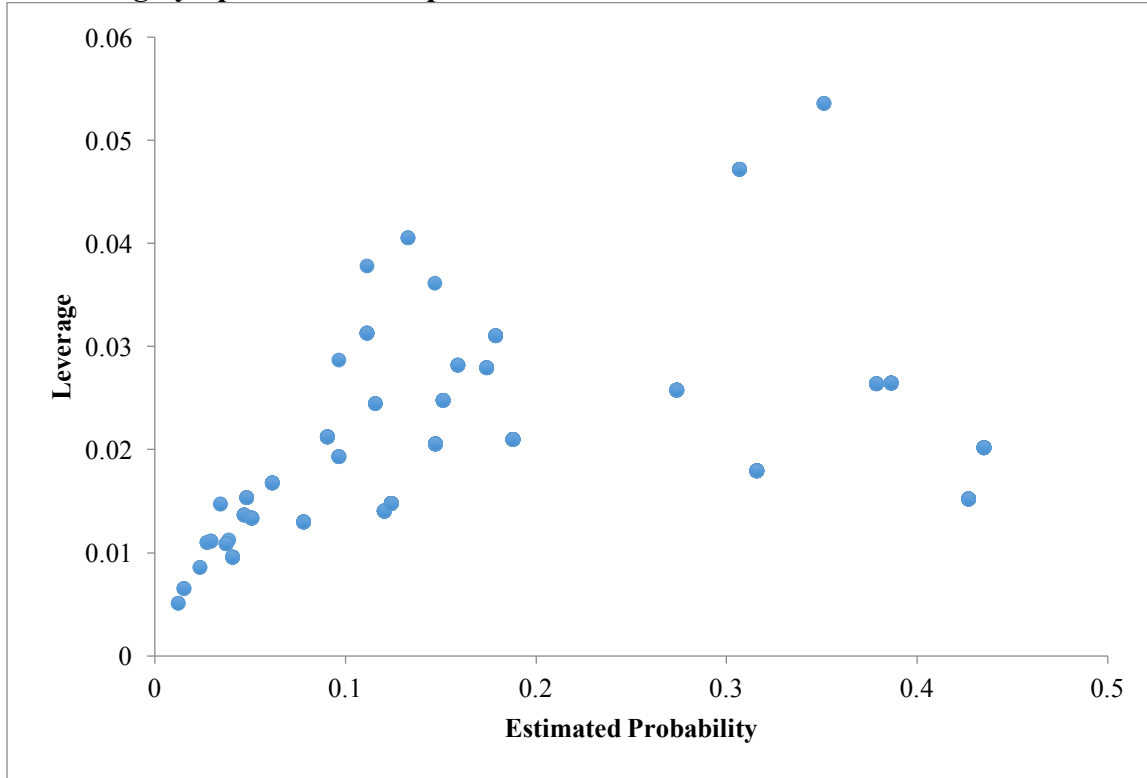


Figure 6. Prevalence of Symptomatic Vasospasm For Each Point Total According to the Symptomatic Vasospasm Score

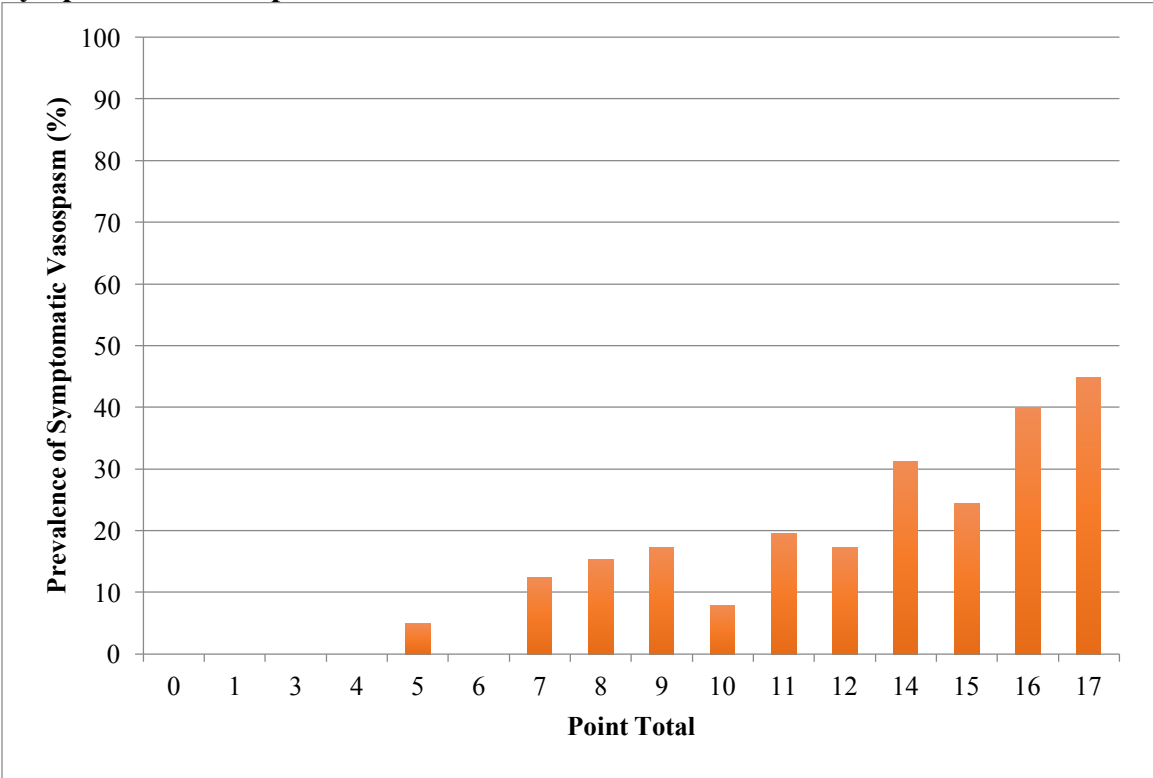


Figure 7. Sensitivity and Specificity of the Symptomatic Vasospasm Score For All Point Cutoffs

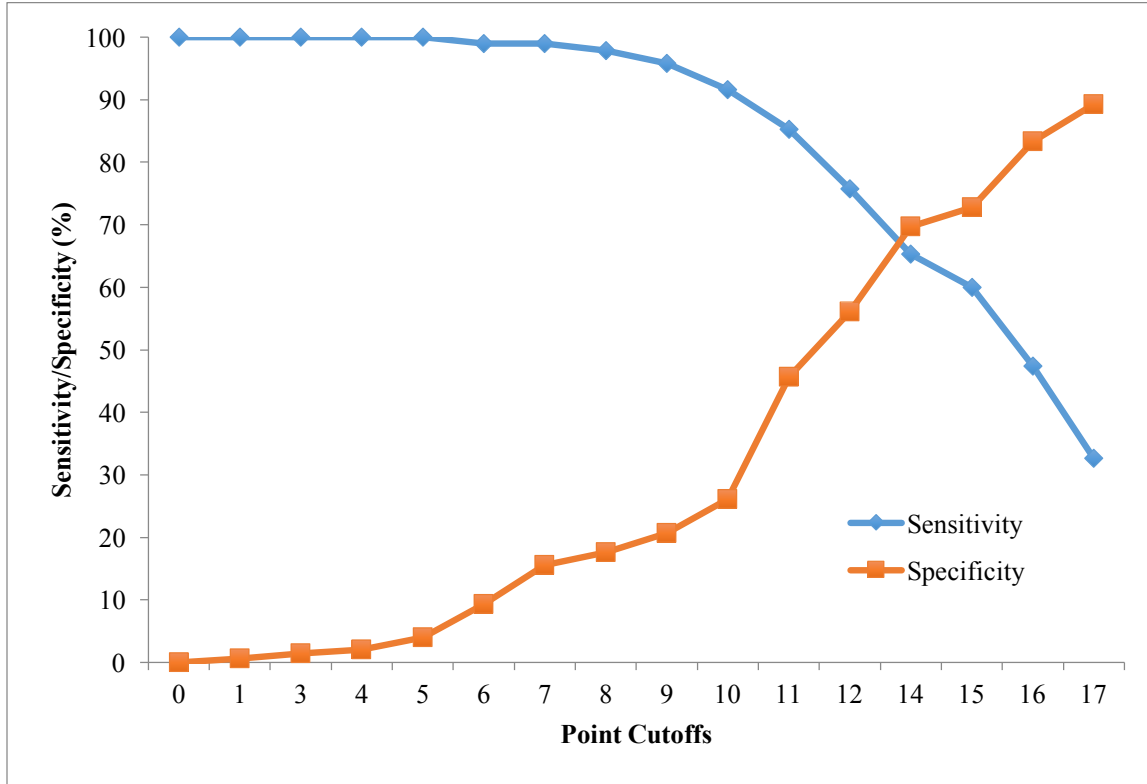


Figure 8. Final Recursive Partitioning Model to Predict Symptomatic Vasospasm Risk in Aneurysmal Subarachnoid Hemorrhage Patients

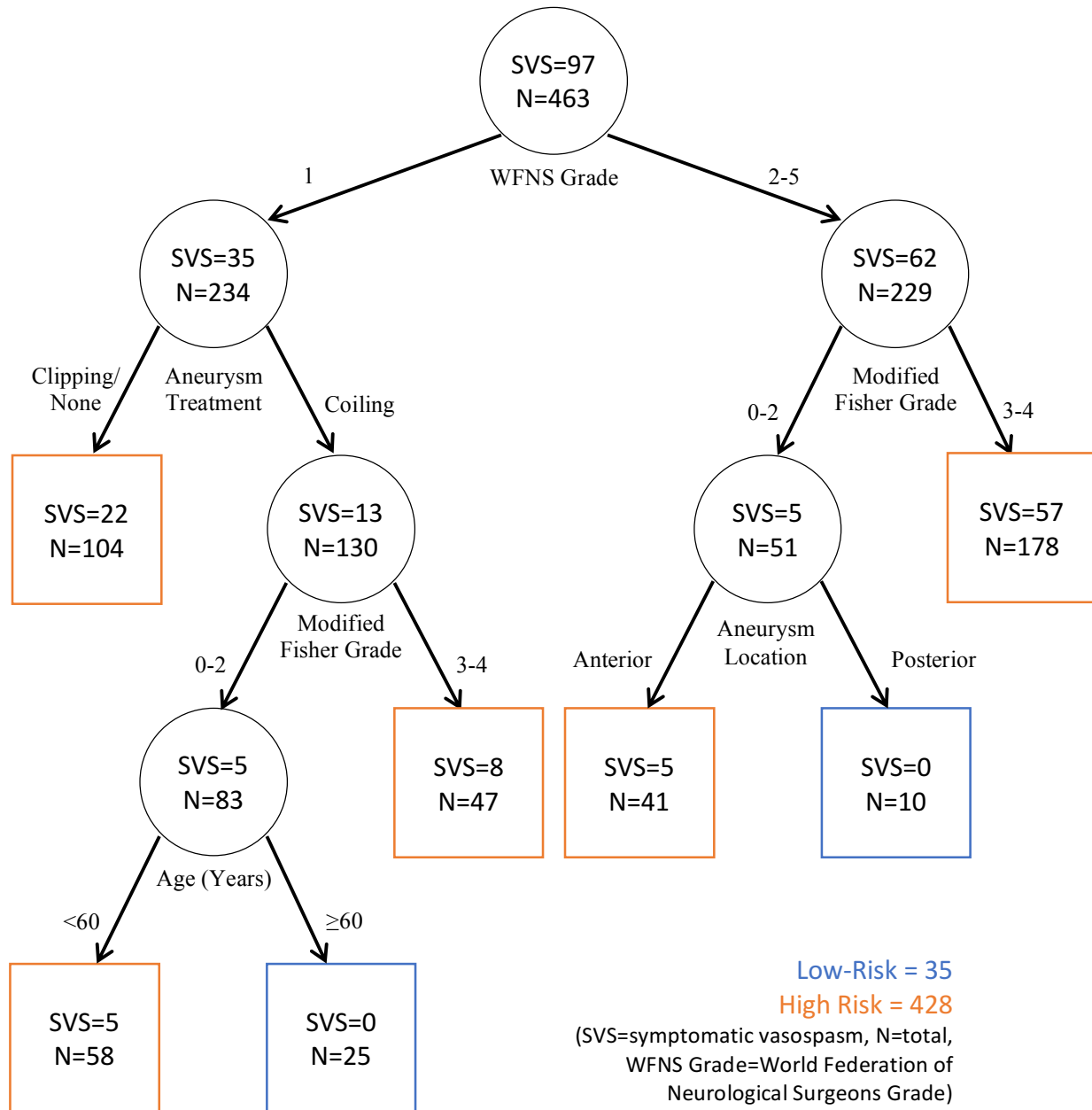
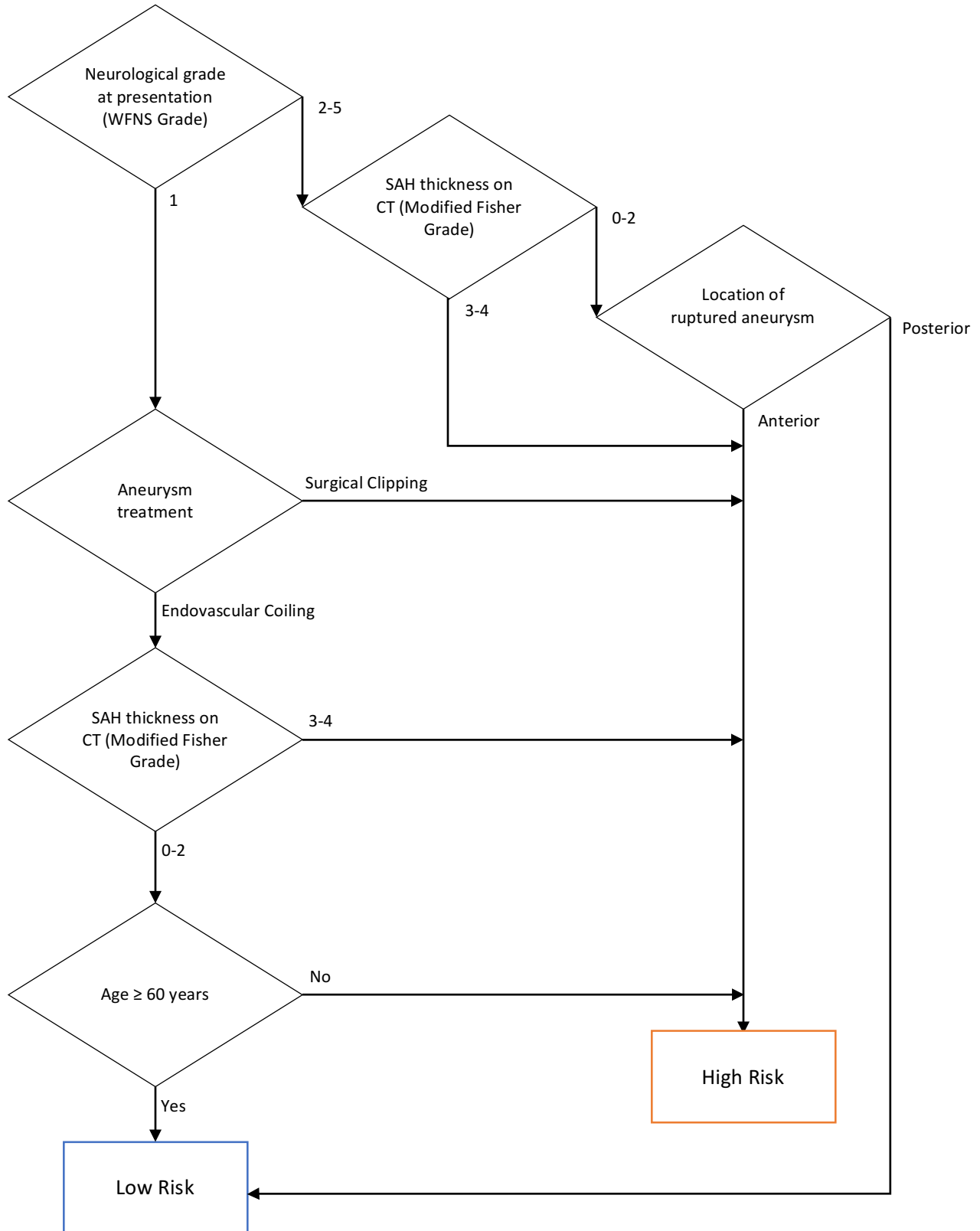


Figure 9. Proposed Algorithm To Predict Risk of Symptomatic Vasospasm in Patients Presenting with Aneurysmal Subarachnoid Hemorrhage



Appendix A: Literature Review

Major Concepts:

1. Clinical prediction rules
 - MeSH – Decision support techniques
 - Decision aids
 - Decision analyses
 - Decision modeling
 - Decision support models
 - Clinical prediction rules
 - Logistic models
 - Logistic regression
 - Neural networks
 - Regression analysis
 - Statistical regression
2. Intracranial Vasospasm (MeSH)
 - Intracranial angiospasm
 - Intracranial vascular spasm
 - Cerebral vasospasm
 - Cerebral artery spasm
 - Cerebrovascular spasm
 - Cerebral angiospasm
3. Subarachnoid Hemorrhage
 - Haemorrhage/haemorrhage

MEDLINE Search Strategy

1. exp Decision Support Techniques/
2. (decision adj2 support adj2 techni*).tw.
3. (decision adj2 aid*).tw.
4. (decision adj2 analys*).tw.5. (decision adj2 model*).tw.6. (decision adj2 support adj2 model*).tw.7. (clinical adj2 prediction adj2 rule*).tw.8. exp Logistic Models/9. (logistic adj2 model*).tw.10. (logistic adj2 regression*).tw.
11. exp "Neural Networks (Computer)"/
12. (neural adj2 network*).tw.
13. exp Regression Analysis/
14. (regression adj2 analys*).tw.
15. (statistical adj2 regression*).tw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp Vasospasm, Intracranial/
18. (intracranial adj2 vasospasm*).tw.
19. (intracranial adj2 angiospasm*).tw.
20. (intracranial adj2 vascular adj2 spasm*).tw.
21. (cerebral adj2 vasospasm*).tw.
22. (cerebral adj2 artery adj2 spasm*).tw.
23. (cerebrovascular adj2 spasm*).tw.
24. (cerebral adj2 angiospasm*).tw.
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. exp Subarachnoid Hemorrhage/
27. (subarachnoid adj2 hemorrhage*).tw.
28. (subarachnoid adj2 haemorrhage*).tw.
29. 26 or 27 or 28
30. 16 and 25 and 29

EMBASE Search Strategy

1. exp decision support system/
2. (decision adj2 support adj2 techni*).tw.
3. exp medical decision making/
4. (decision adj2 aid*).tw.
5. (decision adj2 analys*).tw.
6. (decision adj2 model*).tw.
7. (decision adj2 support adj2 model*).tw.
8. (clinical adj2 prediction adj2 rule*).tw.
9. exp statistical model/
10. (logistic adj2 model*).tw.
11. (logistic adj2 regression*).tw.
12. exp artificial neural network/
13. (neural adj2 network*).tw.
14. exp regression analysis/
15. (regression adj2 analys*).tw.
16. (statistical adj2 regression*).tw.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp brain vasospasm/
19. (intracranial adj2 vasospasm*).tw.
20. (intracranial adj2 angiospasm*).tw.
21. (intracranial adj2 vascular adj2 spasm*).tw.
22. (cerebral adj2 vasospasm*).tw.
23. (cerebral adj2 artery adj2 spasm*).tw.
24. (cerebrovascular adj2 spasm*).tw.
25. (cerebral adj2 angiospasm*).tw.
26. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp subarachnoid hemorrhage/
28. (subarachnoid adj2 hemorrhage*).tw.
29. (subarachnoid adj2 haemorrhage*).tw.
30. 27 or 28 or 29
31. 17 and 26 and 30

Cochrane Library Search Strategy

1. (decision adj2 support adj2 techni*).tw.
2. (decision adj2 aid*).tw.
3. (decision adj2 analys*).tw.
4. (decision adj2 model*).tw.
5. (decision adj2 support adj2 model*).tw.
6. (clinical adj2 prediction adj2 rule*).tw.
7. (logistic adj2 model*).tw.
8. (logistic adj2 regression*).tw.
9. (neural adj2 network*).tw.
10. (regression adj2 analys*).tw.
11. (statistical adj2 regression*).tw.

12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. (intracranial adj2 vasospasm*).tw.
14. (intracranial adj2 angiospasm*).tw.
15. (intracranial adj2 vascular adj2 spasm*).tw.
16. (cerebral adj2 vasospasm*).tw.
17. (cerebral adj2 artery adj2 spasm*).tw.
18. (cerebrovascular adj2 spasm*).tw.
19. (cerebral adj2 angiospasm*).tw.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. (subarachnoid adj2 hemorrhage*).tw.
22. (subarachnoid adj2 haemorrhage*).tw.
23. 21 or 22
24. 12 and 20 and 23

Appendix B: Ethics Approval



Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
<http://www.ohri.ca/ohsn-reb>

June 4, 2015

Dr. Dariush Dowlatshahi
The Ottawa Hospital - Civic Campus
Department of Medicine
Division of Neurology, C2182b
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Dowlatshahi:

Re: Protocol # 20150367-01H Clinical Prediction of Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Protocol approval valid until - June 3, 2016

I am pleased to inform you that your Application for Chart Review underwent expedited review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB), and is approved. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

Approval is for the following:
- Protocol (version 1) dated May 1, 2015

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHSN-REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.



Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
<http://www.ohri.ca/ohsn-reb>

May 11, 2016

Dr. Dariush Dowlatshahi
The Ottawa Hospital - Civic Campus
Department of Medicine
Division of Neurology, C2182b
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Dowlatshahi:

RE: Protocol# - 20150367-01H Clinical Prediction of Symptomatic Vasospasm in Aneurysmal Subarachnoid Hemorrhage

Renewal Expiry Date - June 3, 2017

I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHSN-REB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the REB office.

The projected date of study completion has been extended to December 2016.

The OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.

Appendix C: Data Collection Forms

Predictor Collection Form

Study ID:

Admission date (Month/Day/Year): / /

Day Post-SAH: _____

Demographics

Age:

Sex: M F

Comorbidities

Cardiovascular Risk Factors	Intracranial Hemorrhage	Smoking Status
<input type="checkbox"/> Hypertension <input type="checkbox"/> Hyperlipidemia <input type="checkbox"/> Diabetes <input type="checkbox"/> Coronary Artery Disease / MI <input type="checkbox"/> Stroke (CVA) <input type="checkbox"/> TIA <input type="checkbox"/> Connective Tissue Disorder <input type="checkbox"/> Sickle Cell Disease	<input type="checkbox"/> No Previous <input type="checkbox"/> SAH <input type="checkbox"/> Intracerebral Hemorrhage / Intraventricular Hemorrhage	<input type="checkbox"/> Lifetime non-smoker <input type="checkbox"/> Current Smoker <input type="checkbox"/> Previous Smoker

Family History: Aneurysms SAH None / Unknown

Illicit Drug Use:

- Amphetamine
- Cocaine
- Non-use / Not available

Medications:

Statin (prior to admission) Name: _____ mg q _____ h

Antiplatelet

- ASA
- Plavix
- Aggrenox
- Other: _____

Anticoagulant

- Warfarin (last INR: _____)
- Heparin (last PTT: _____, last anti-Xa: _____)
- Dabigatran
- Rivaroxaban
- Apixaban
- Other: _____

Nicotine replacement therapy (during hospitalization)

Clinical Presentation

GCS (3-15): Eyes: ___ + Voice: ___ + Motor: ___ = ___

Motor Deficit: Yes

- Only one of face/arm/leg
- Hemiparesis
- Decorticate Posturing

No

- Severe Headache
- Meningismus
- Drowsy/Confused

- Decerebrate Posturing
- Stuporous
- Coma
- Cranial Nerve Palsy

systolicBP: ____ Temperature (°C): ____

Neuroimaging

CT Head

Modified Fisher Grade (0-4): ____

Aneurysm

Location: R L

- Internal Carotid
 - Paraophthalmic
 - Supraclinoid
 - Posterior Communicating
 - Anterior Choroidal
 - Terminus/Bifurcation
- Anterior Cerebral
 - Anterior Communicating
 - Pericallosal
 - Callosomarginal
- Middle Cerebral
- Posterior Cerebral
- Vertebrobasilar
 - Basilar Tip
 - SCA
 - AICA
 - PICA

Size (largest diameter in mm):

Multiple: Y N (number: ____)

TCD

Day Post-SAH		2		4		6		8		10		12		14	
		MFV	LR	MFV	LR	MFV	LR	MFV	LR	MFV	LR	MFV	LR	MFV	LR
ACA	R		-		-		-		-		-		-		-
	L		-		-		-		-		-		-		-
MCA	R														
	L														
PCA	R		-		-		-		-		-		-		-
	L		-		-		-		-		-		-		-

MFV = Mean flow velocity in cm/second, LR = Lindegaard Ratio, ACA = Anterior cerebral artery, MCA = Middle cerebral artery, PCA = Posterior cerebral artery

Management

Unit of Admission: ICU NOA/NACU

Aneurysm Therapy:

Date (Month/Day/Year): ____ / ____ / ____

Day Post-SAH: ____

- Surgical Clipping
- Endovascular Coiling
 - Balloon-assisted
 - Stent-assisted
- Nimodipine ____ mg q ____ h
- Statin
 - New since admission
 - Simvastatin ____ mg q ____ h
 - Pravastatin ____ mg q ____ h
 - Other: _____ mg q ____ h
- Anticonvulsant
 - New since admission Prior to admission
 Agent: _____

Non-Vasospasm Complications (SAH Day 3 or earlier):

- Hydrocephalus
 - Required EVD
- Seizures
 - Initial presentation
 - During hospitalization
 - Prior to aneurysm treatment
 - After aneurysm treatment
- Hyponatremia (Na<135mmol/L) – SAH Day#: _____ Serum Na SAH Day#3 (mmol/L):
- Anemia (Hb≤100g/L)

	Hb (g/L)	Date (Month/Day/Year)	SAH Day #
First Occurrence		/ /	
Lowest Value		/ /	
SAH Day #3		/ /	
Most recent to symptomatic vasospasm diagnosis		/ /	

- Pulmonary Edema
- Intubation
- Cardiac
 - Acute Coronary Syndrome
 - Arrhythmia (Ventricular Tachycardia, Supraventricular Tachycardia)
 - Heart Failure (EF≤ 40%)

Outcome Assessment Form

Study ID:

Assessor's Initials:

Date of presumed aneurysm rupture, SAH Day#0 (mm/dd/yyyy): / /

VASOSPASM

Radiological Vasospasm:

Modality:

- CT Angiogram (CT HEAD/CT NECK/CT PERFUSION)
- MRA
- Catheter Angiogram (ANGIO CEREBRAL, EMBOLIZATION)
- Transcranial Doppler US (US ND TCDOPLER – mean flow velocity > 120 cm/s)

Date (mm/dd/yyyy)

Yes No
SAH Day# (3-21)

/ /

/ /

/ /

/ /

Vessel(s) and laterality:

- Anterior Cerebral R L
- Middle Cerebral R L
- ICA R L
- Posterior Cerebral R L
- Basilar
- Vertebral R L

New Neurological Symptoms:

Date of Onset (mm/dd/yyyy): / /

SAH Day# (3-21):

Yes No

(Symptom should not be present immediately after surgical clipping or endovascular coiling)

- Hemiparesis
- Hemiparesthesia
- Aphasia
- Apraxia
- Neglect
- Hemianopia
- Decreased level of consciousness (≥ 2 GCS points)

Alternate Causes:

Neurological:

Yes No Unable to

Determine

NEW Hemorrhage

- Aneurysm rebleeding
- Epidural hemorrhage
- Subdural hemorrhage
- Intracerebral/intraventricular hemorrhage
- Worsening hydrocephalus
- Seizures (positive electroencephalography (EEG), clinical symptoms)
- Worsening cerebral edema

Electrolyte Abnormality:

Yes No Unable to

Determine

- Hyper/hyponatremia (sodium; > 155 mmol/L or < 135 mmol/L)
- Hyper/hypokalemia (potassium; > 5 mEq/L or < 3.5 mEq/L)

Blood Gas Abnormality:

Yes No Unable to

Determine

- Hypercarbia ($CO_2 > 45$ mmHg)
- Hypoxia ($O_2 < 92\%$, only interpret from arterial blood gas)

Infection:

Yes No Unable to

Determine

- Suspected source of infection AND
- Positive culture collected within 24 hours of symptoms OR
- Antibiotic treatment course of 7 days or more

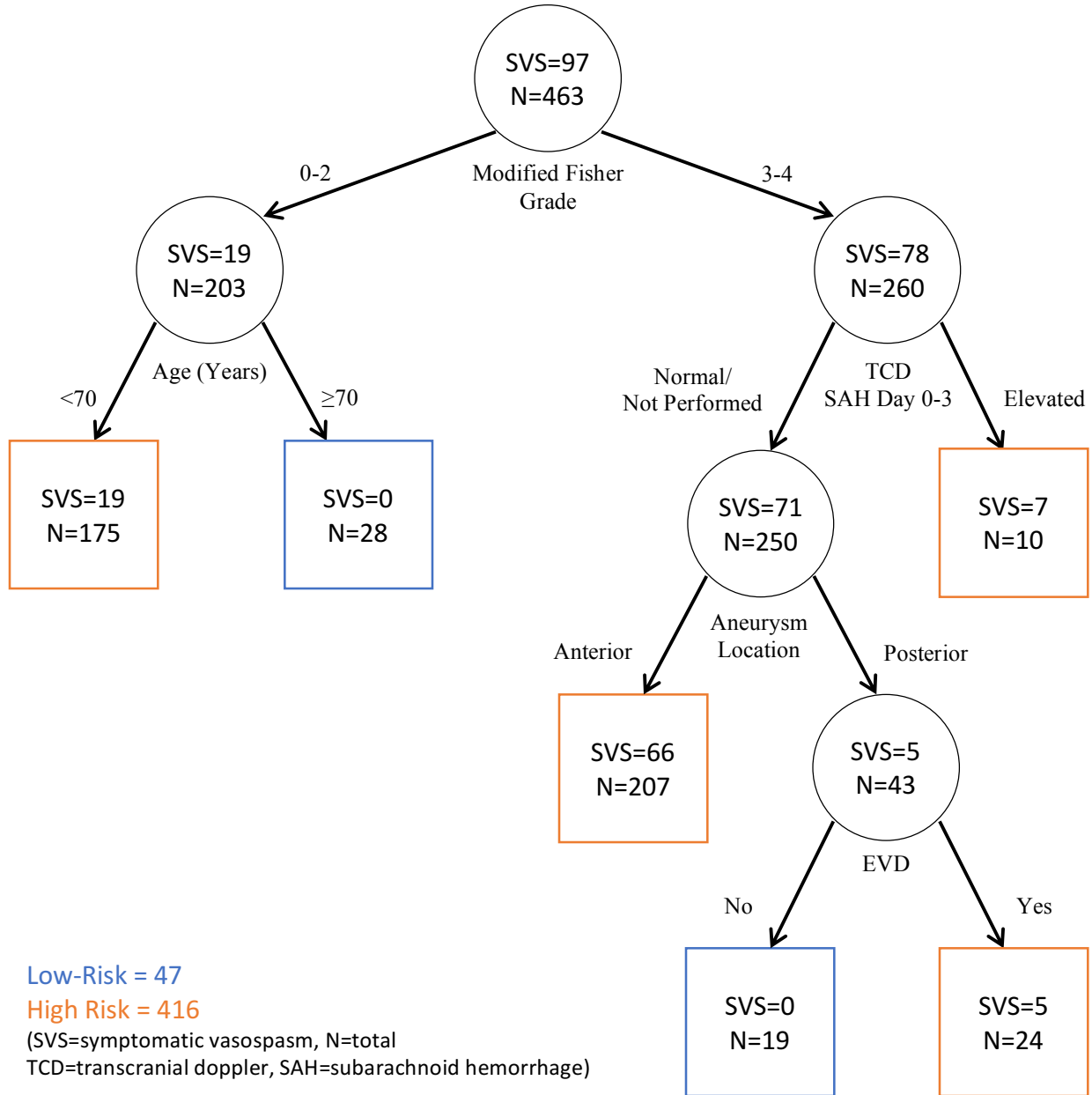
- Cardiac: Yes No Unable to Determine
- Hypotension (*sBP <90 mmHg or dBP <60 mmHg or MAP < 35*)
 - Arrhythmia (*ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia*)
- Medication Induced: Yes No Unable to Determine
- Opioids
 - Benzodiazepines
 - Antipsychotics (*e.g. Haldol*)
 - Antiepileptics (*if on Dilantin, can check dilantin level and correct for albumin, >80 umol/L*)

Did this patient experience symptomatic vasospasm?				
Extremely Unlikely	Unlikely	Neutral	Likely	Extremely Likely
1	2	3	4	5

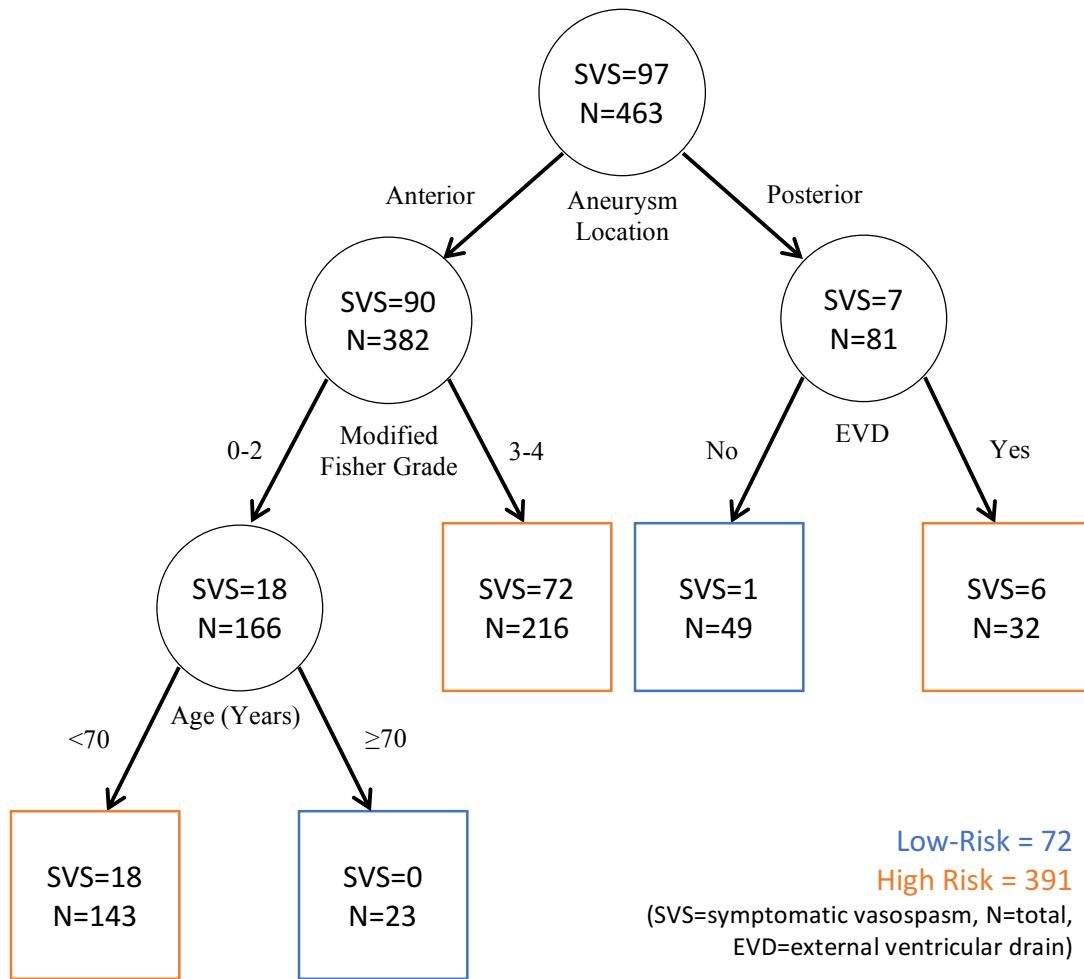
**If the conclusion is "Neutral" (3), this case will need further adjudication by a third investigator*

Appendix D: Recursive Partitioning Models Considered for Finalization as Recommended by Clinical Experts

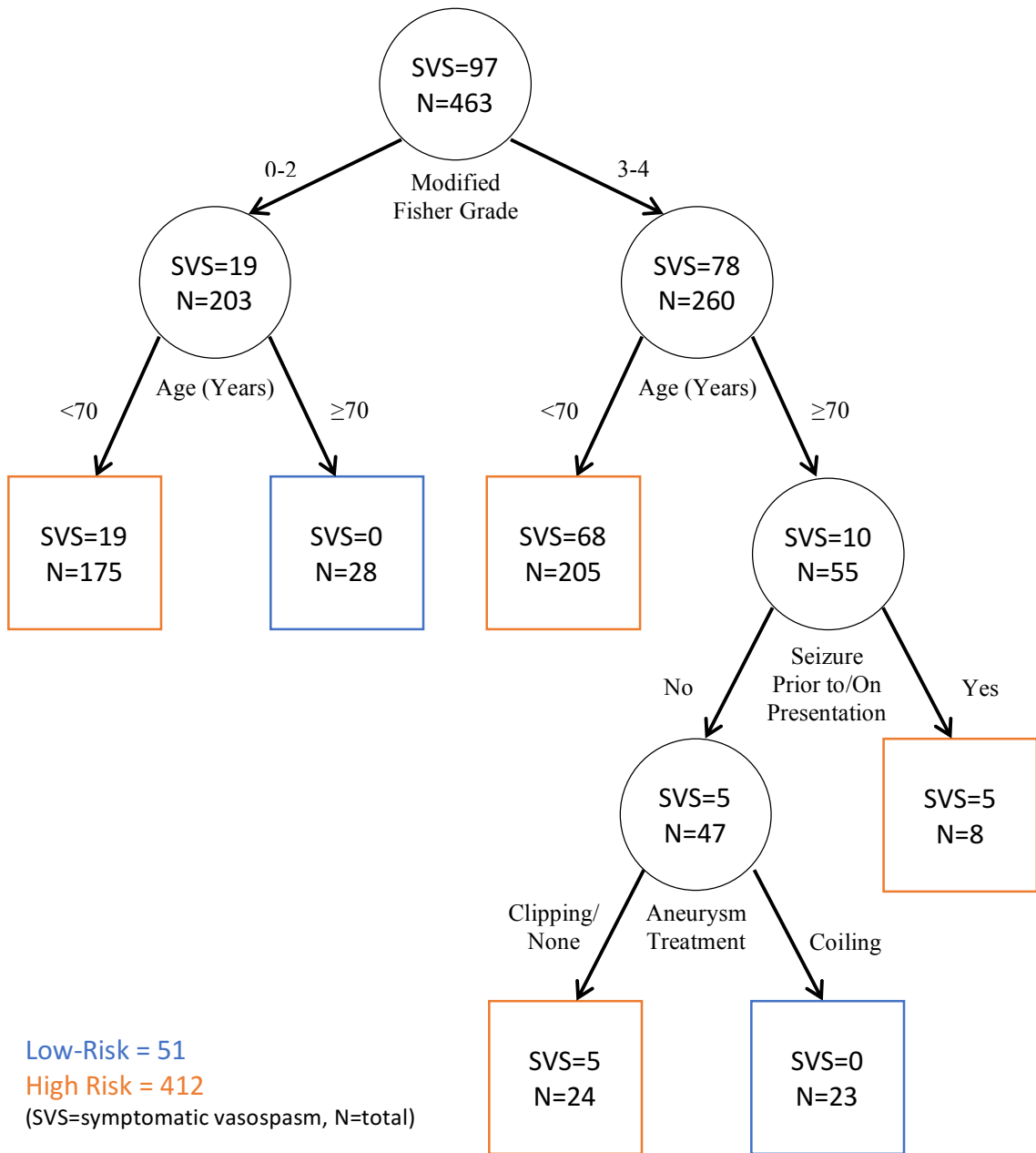
Model 1: (sensitivity = 100%, specificity = 12.84%)



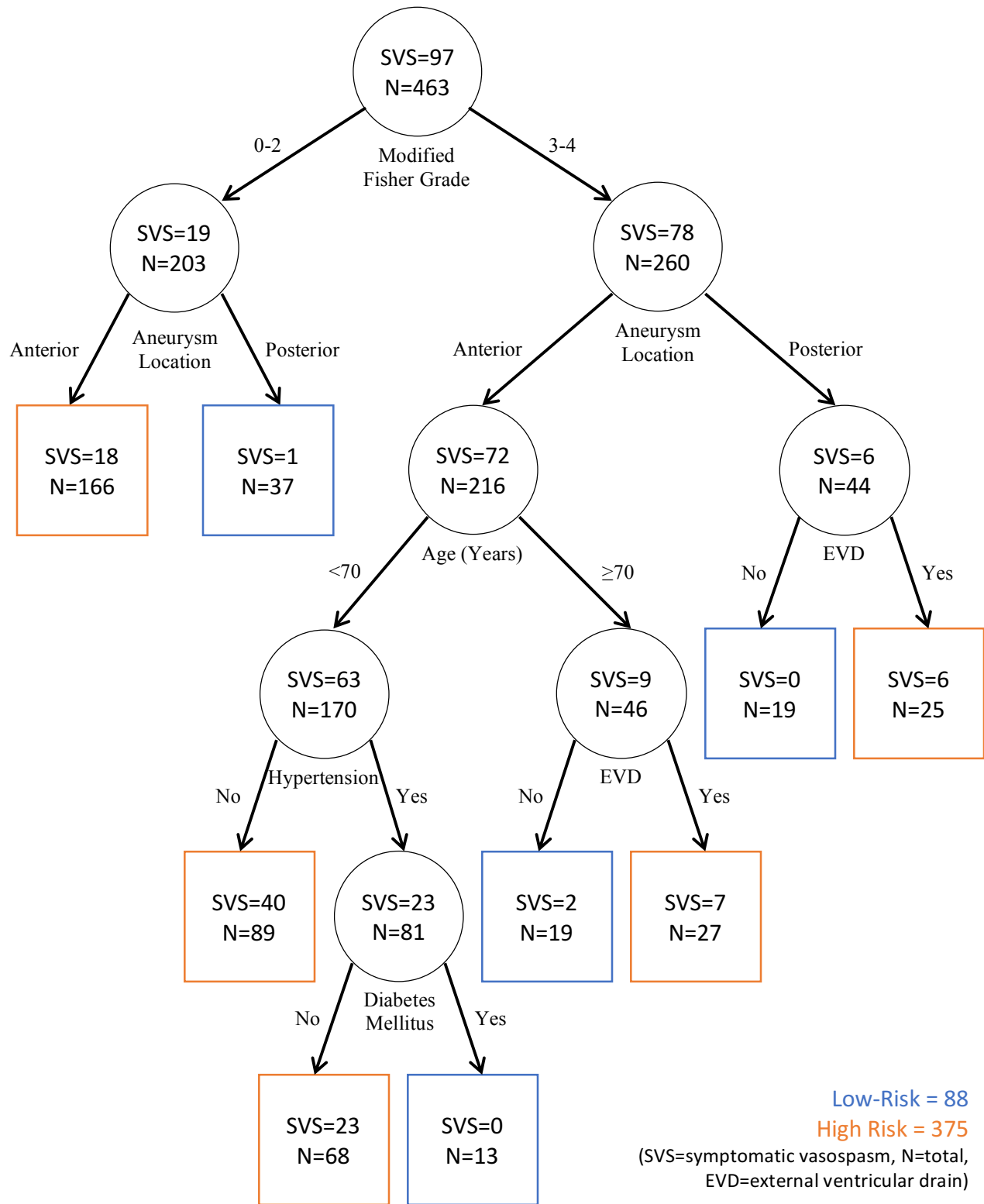
Model 2: (sensitivity: 98.97%, specificity 19.40%)



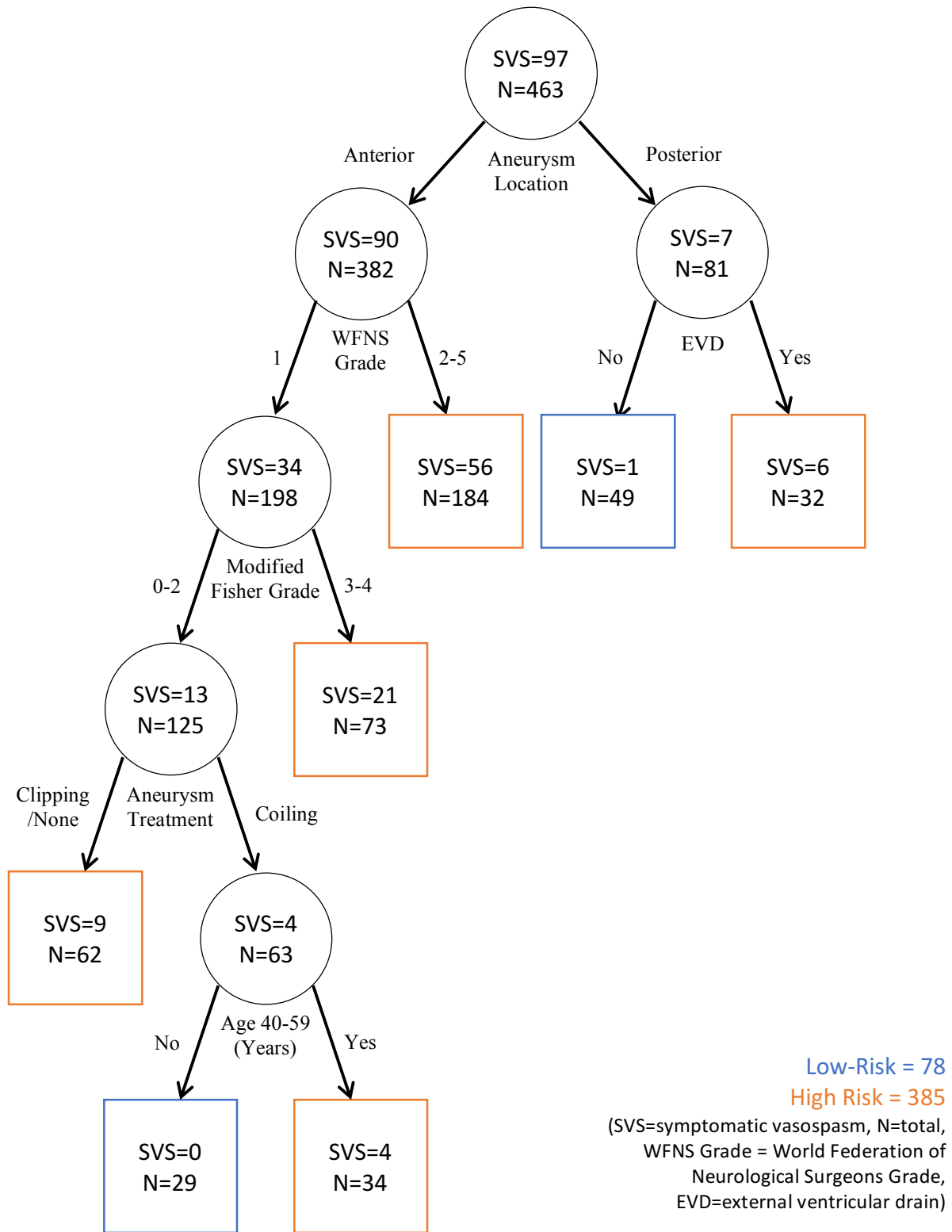
Model 3: (sensitivity = 100%, specificity = 13.39%)



Model 4: (sensitivity = 96.91%, specificity = 23.22%)



Model 5: (sensitivity: 98.97%, specificity 21.04%)



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