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Is Early Clinical Evidence of Autonomic Shift Predictive of Infection Following Aneurysmal Subarachnoid Hemorrhage?

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Abstract

Background—Autonomic shift (AS), characterized by increased sympathetic nervous system activation, has been implicated in neurologically mediated cardiopulmonary dysfunction and immunodepression following stroke. We investigated the prevalence of AS defined by readily available clinical parameters and determined the association of AS with subsequent infection in a cohort of patients with aneurysmal SAH (aSAH).

Methods—Data were obtained from a single center cohort study of aSAH patients admitted January 1, 2007 through April 1, 2012. AS was defined as at least one early (<72 hours) routine clinical marker of neurologically mediated cardiopulmonary dysfunction based on electrocardiogram, echocardiogram, cardiac enzymes, or neurogenic pulmonary edema. Multivariable logistic regression models were developed to evaluate the association between AS and subsequent infection after adjusting for other covariates.

Results—A total 167 patients were included in the analysis (mean age 56, 27% male). AS was seen in 66/167 (40%; 95% CI, 32%–47%), and infection was seen in 80/167 (48%; 95% CI, 40%–55%). AS was associated with subsequent infection on unadjusted analysis (OR=2.11; 95% CI, 1.12–3.97); however, this association was no longer significant when adjusting for other predictors of infection (OR 1.36; 95% CI, 0.67–2.76). Age, clinical grade, and aneurysm location were all independent predictors of infection following aSAH.

Conclusions—We identified AS based on readily available clinical markers in 40% of patients with aSAH, though AS defined by these clinical criteria was not an independent predictor of infection. Additional studies may be warranted to determine the optimal definition of AS and the clinical significance of this finding.

Keywords

Aneurysmal subarachnoid hemorrhage; autonomic shift; infection; immunosuppression

Introduction

Acute brain injury is associated with increased susceptibility to bacterial infections.¹⁻³ These post-stroke infections have been shown to be independent predictors of poor outcome.³ The pathophysiological mechanisms underlying this susceptibility are incompletely understood. Though impaired corticobulbar dysfunction, depressed level of consciousness, and critical illness likely explain some increased susceptibility to infection following brain injury, recent evidence suggests that neurologically mediated immunodepression may also play a major role.^{1, 2, 4-6} Neurologically mediated immunodepression is hypothesized to occur via autonomic shift (AS), resulting in increased sympathetic nervous system activation mediated by disrupted cholinergic and adrenergic neural pathways. Elevated catecholamine levels in serum and lymphoid tissue are presumed to be associated with suppressed neutrophil respiratory burst and other mechanisms of cellular immune response following stroke.⁵⁻¹³ Similarly, elevated catecholamine levels in tissues of the heart and lung are associated with cardiac arrhythmias, electrocardiographic (ECG) changes, increased permeability and hydrostatic pulmonary edema, and heart failure secondary to neurogenic stunned myocardium.¹⁴

There is no consensus in diagnostic criteria for AS following stroke. Some have demonstrated baroreceptor reflex sensitivity to be associated with infection after intracerebral hemorrhage (ICH); however, this assessment requires specialized equipment and protocols to assess the autonomic nervous system.² A more simplified assessment of autonomic nervous system dysfunction after brain hemorrhage may be more generalizable to centers without specialized equipment.

If AS is shown to have a causal relationship with immunodepression following stroke, then interventions to lower the risk of infection could be tested in patients at highest risk. Animal models have suggested that beta blockers or prophylactic antibiotics can protect against post-stroke infection.^{9, 13} While beta-blockers have not been definitively tested in humans to protect against infection, three randomized clinical trials have investigated prophylactic antibiotics in humans following stroke with inconclusive results.^{13, 15, 16} Importantly, other than excluding patients with minor stroke, none of these studies risk-stratified patients as to the presence of AS or other predictors of infection.

The goals of our analysis were to use readily available clinical data in a cohort of aneurysmal subarachnoid hemorrhage (aSAH) patients to 1) determine the prevalence of AS, 2) evaluate the strength and temporality of the association between AS and infection, and 3) determine if an independent association between AS and subsequent infection exists. If AS is found to predict infection, this would be a novel finding that would help risk-stratify patients for infection who may then be candidates for future testing of more aggressive infection control measures.

Material and Methods

The University of Michigan Institutional Review Board approved a waiver of consent for this observational study.

Study Design

A series of consecutive patients admitted to the University of Michigan Health System from January 1, 2007 through April 1, 2012 were screened for eligibility. Patients admitted prior to September 1, 2010 were screened using ICD-9-CM discharge diagnosis codes 430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), 437.3 (cerebral aneurysm, nonruptured), and 747.81 (anomalies of cerebrovascular system) through the first 5 positions. A study investigator then verified aSAH by confirming aneurysmal etiology for SAH or cerebrospinal fluid xanthochromia. All subsequent patients (September 2, 2010–April 1, 2012) were identified through the ongoing prospective University of Michigan Subarachnoid Hemorrhage Outcomes Registry by active surveillance on admission to the Neurological Intensive Care Unit. Data were obtained by chart review assisted by the Electronic Medical Record Search Engine (EMERSE) employed at the University of Michigan Health System. EMERSE is a web-based tool that uses natural language processing to search free-text medical records as well as coded data elements in the medical record. Study data were managed using REDCap electronic data capture tools hosted at the University of Michigan Health System.¹⁷ Patients were excluded from analysis for the following reasons: 1) non-aneurysmal causes of SAH; 2) death or withdrawal of care prior to day 3; 3) absence of a preoperative head computed tomography (CT) image within 24 hours of ictus (in order to assess severity of bleed and location of initial intracranial blood); 4) modified Fisher grades 0 and 1 (patients with minimal blood on head CT are unlikely to develop medical complications following ictus); 5) history of myocardial infarction; 6) history of immune system suppression; 7) no ECGs within 72 hours of ictus; 8) abnormal baseline ECG; 9) beta-adrenergic blockade; 10) any suspected or documented history of autonomic neuropathy including patients with end-stage renal disease or diabetes mellitus for > 15 years. Additionally, patients were excluded if clinical or laboratory signs of infection were present prior to ictus or the development of AS. This was done to eliminate confounding by an ongoing infection in the development of AS, or increase disease severity, need for invasive catheters, or mechanical ventilation due to ongoing infection, which may then predispose to further infection.

Outcome Variable

The outcome variable was the development of any infection up to 21 days from ictus. All patients from the prospective registry were evaluated for signs and symptoms of infection by daily chart review or physical examination. The EMERSE search engine was used to identify infectious complications in the remaining patients enrolled retrospectively. Clinical signs of infection were supported by radiographic and microbiology results. The definitions used for infections are listed in Appendix 1. Pneumonia was defined according to the American Thoracic Society criteria, urinary tract infection (UTI) according to the Centers for Disease Control and Prevention criteria, and severe sepsis according to the International Sepsis Forum criteria.^{18–20}

Explanatory Variables

The main variable of interest was AS (yes/no), defined as at least one sign or symptom of neurologically mediated cardiopulmonary dysfunction within 72 hours of ictus based on

ECG, echocardiogram, cardiac enzyme testing, or clinical diagnosis of neurogenic pulmonary edema. Cardiology consultations were reviewed when available. ECGs were reviewed independently by 2 fellowship-trained, board-certified neurointensivists (JF, VR), and disagreement resolved by consensus. Appendix 2 describes the specific criteria used to diagnose AS.

Potential Confounding Variables

Baseline demographics and measures of disease severity were recorded. Male gender, statin medication, current smoker, aneurysm location (posterior versus anterior circulation and posterior communicating artery), and presence of ICH were coded as dichotomous (yes/no) variables. Hunt-Hess grade and modified Fisher scale score were treated as categorical variables dichotomized at 4. Ethnicity and aneurysm treatment modality were treated as categorical variables. Age, length of stay, aneurysm diameter, and the Hijdra Sum Score (HSS; calculated as the composite of subarachnoid and intraventricular blood) were treated as continuous variables.

Clinical Management

Treatment of patients with aSAH at our institution is consistent with published guidelines and did not change during the study period.^{21, 22} Orotracheal intubation was performed in all patients with a Glasgow Coma Scale score ≤ 8 , when concern existed over airway protection or if indicated due to respiratory failure. Continuous aspiration of subglottic secretion tubes was not used. Routine glucocorticoids were not used. Antibiotic-coated external ventricular drains (Bactiseal; Codman and Shurtleff, Raynham, MA) and antibiotic prophylaxis were used during dwell time of all external ventricular drains. Urinary catheters were initially placed in all patients and removed once the aneurysm was secured and concern over inadvertent removal of other invasive catheters was minimal. Continuous dihydropyridine (L-type) calcium channel blocker was the preferred agent for blood pressure control, with intermittent beta-1-2/alpha-1 blockers, if needed.

Statistical Analysis

Continuous variables were screened for normality using normality plots and histograms. Parametric data are expressed as mean $\pm$ standard deviation (SD) and non-parametric data as median (interquartile range). Continuous variables were compared by infection status and AS with 2-sample *t*-tests or the Wilcoxon rank-sum test, as appropriate. Categorical variables were compared by infection status and AS using chi-square or Fisher exact test.

Logistic regression was used to assess the unadjusted association between AS and infection (infection=1; no infection=0). Multivariate logistic regression was then used to adjust for potential confounders of this relationship. Candidate variables for inclusion in the multivariable model were selected based on an unadjusted association with infection at a significance level of $p \leq 0.2$. Manual forward selection was used, retaining variables if they altered the association of other variables with outcome or if they improved model fit, although AS was forced into the model. The final model included age (continuous, per year), ICH (reference: no ICH), posterior circulation aneurysm (reference: anterior circulation and posterior communicating artery), and Hunt-Hess score of 4–5 (reference: 1 to 3). The Hunt-

Hess score was dichotomized as ≥ 4 , as this form provided the best model fit based on the Akaike Information Criterion compared with multiple dummy variables or other cut-points. Due to a potential concern for accuracy in the diagnosis of UTI based on chart review, we planned *a priori* to perform a sensitivity analysis repeating the logistic regression analysis and excluding isolated UTI from the definition of infection.²³ We did not adjust for use of invasive catheters or endotracheal tubes, as all patients received central venous catheters and urinary catheters during their stay, and the use of external ventricular drains and endotracheal tubes was expected to be collinear with disease severity and amount of blood on initial head CT scan. Statistical analysis was performed using SAS software, version 9.2 (SAS Institute, Cary, NC)

Results

During the study period, 217 patients with aSAH were identified. Of these, 34 patients did not have ECGs within 72 hours of ictus, 11 patients had known baseline ECG abnormalities, and 5 additional patients were taking a beta-blocker on admission and were thus excluded from analysis. Subsequently, 167 patients were included in the final analysis, of which 84/167 (50.3%) were enrolled prospectively. There was no difference in the proportion of AS ($p = 0.23$) or infection ($p = 0.94$) between patients identified retrospectively versus prospectively and, therefore, they were combined for analysis. Mean patient age was 56 years (± 13 years), 122/167 (73%) were female, and 137/167 (82%) were Caucasian. In patients diagnosed with AS, 62/66 (94%) had evidence on admission ECG or cardiac enzyme testing from within 24 hours of ictus. All others were diagnosed within 48 hours of ictus. Patient characteristics by AS and by infection are shown in Table 1. AS was seen in 66/167 patients (40%; 95% CI, 32%–47%), infection was seen in 80/167 patients (48%; 95% CI, 40%–55%), and infection excluding isolated UTI in 59/167 patients (35%; 95% CI, 28%–43%). Older age and higher Hunt-Hess grade were associated with both AS and infection. Increased volume of intracranial blood measured by HSS was associated with AS but not infection, as shown in Table 1. The most common infection was pneumonia (41/167 [25%]) followed by UTI (37/167 [22%]) and clostridium difficile (9/167 [5%]). AS was most often diagnosed by elevated cardiac enzymes (31/167 [19%]) followed by T-wave inversions on ECG (42/167 [25%]).

AS was associated with infection on unadjusted analysis (odds ratio [OR] 2.11; 95% CI, 1.12–3.97). However, when adjusted for potential confounders of age, Hunt-Hess grade ≥ 4 , posterior aneurysm location, and presence of ICH, AS was no longer associated with infection (OR 1.36; 95% CI, 0.67–2.76). ORs from the logistic regression model are shown in Table 2. Sensitivity analysis repeating the model-building strategy where isolated UTI was removed from the definition of infection similarly found no association between AS and infection (OR 1.85; 95% CI, 0.89–3.83) when adjusted for age, Hunt-Hess grade ≥ 4 , posterior location, ICH, and HSS (HSS was added in the sensitivity analysis model as it was associated with infection after excluding isolated UTI and it improved model fit).

Discussion

We demonstrated a moderately strong temporal relationship between AS and subsequent infection, which is consistent with the existing literature^{2, 4}. The vast majority of patients who presented with AS on clinical testing did so within 24 hours from ictus and had twice the odds of developing a subsequent infection compared to those without AS. However, AS did not appear to be an independent predictor of infection when adjusting for other confounders. The unadjusted association between AS and infection in our cohort was explained by older age, increased disease severity, and aneurysm location. Based on our data, it seems unlikely that early signs of neurologically mediated cardiopulmonary dysfunction, as defined in this analysis, will be able to serve as independent markers for immunodepression after aSAH. This has implications for future clinical trials that may employ more sophisticated measurements of the autonomic nervous system or serum markers of immunodepression to investigate neurologically mediated immunodepression.

The absence of an independent association between AS and infection after adjusting for confounders has many potential explanations. Importantly, we measured the presence of AS by routine clinical studies defined by signs of neurologically mediated cardiopulmonary dysfunction. The validity of AS measured in this way may be too low to be of clinical use in predicting infection. It remains possible that more valid measurements of the autonomic nervous system may identify components of AS in predicting subsequent infection. Indeed, loss of baroreceptor reflex sensitivity has been shown to correlate to an increased risk of infection following ICH.² However, even if baroreceptor reflex sensitivity provides a more valid measurement of AS in predicting infection, it is difficult to assess in critically ill patients. A specialized device is required, such as the Finometer device (Finapres Medical Systems BV, Amsterdam), and many medical conditions and medications can influence sensitivity of the device, making it difficult to use in many patients.²

Another possible explanation of our findings is that there is not a causal relationship between AS and immunodepression following aSAH. Immunodepression may be either mediated by mechanisms other than AS, or doesn't exist following aSAH. Indeed, while a small prospective pilot trial of 16 aSAH patients using detailed immune monitoring of serum markers for cellular immune status demonstrated changes in cellular immune function, evidence for immunodepression following aSAH has not been extensively studied.²⁴ Additionally, activation of the hypothalamic-pituitary-adrenal axis has also been implicated in immunodepression following stroke, and this may play a larger role in increased susceptibility to infection than simply shifting to sympathetic over-activity with increased tissue catecholamine levels.^{8-10, 12, 13} Also possible is that the increased risk of infection reported following brain injury is related entirely to corticobulbar dysfunction or depressed level of consciousness, which predisposes to aspiration, critical illness, and infection in general. However, due to our small sample size, we cannot exclude the possibility of a type II error in our failure to identify an adjusted association between AS and infection.

We did observe older age, increased disease severity (determined by Hunt-Hess grade), and posterior circulation aneurysm location as factors independently associated with infection in our cohort. These factors may play a much larger explanatory role in subsequent infection

than the presence of AS. Certainly higher Hunt-Hess grade and posterior circulation aneurysm location may be associated with depressed level of consciousness and/or cranial nerve dysfunction, predisposing to aspiration or dysphagia and, hence, pneumonia. Interestingly, others have linked markers of stroke severity, such as higher National Institutes of Health Stroke Scale scores or larger infarct or hemorrhage volumes, to immunodepression and infection following stroke.^{2, 25, 26}

The early prevalence of AS and incidence of subsequent infection were high in our cohort, but consistent with previous literature.^{13, 14, 24, 27–29} The unadjusted association between AS and infection seemed to be primarily due to pneumonia. Due to small sample size we did not perform multivariable analysis predicting specific individual types of infection, though an association between immunodepression following stroke and pneumonia has been reported previously.^{2, 24} If the risk of pneumonia is uniquely elevated following brain injury, it remains unclear whether this is due to specific mechanisms of neurologically mediated immunodepression or due to increased aspiration risks.

Our study has several limitations. Because it is a retrospective analysis of a single tertiary academic center cohort, patients may not be representative of the general aSAH population; however, a large proportion of aSAH patients are treated at similar high-volume centers, as recommended by guidelines. Additionally, we did not have information on catecholamine levels to evaluate any association with our measures of AS or infection. Lastly, despite excluding patients with pre-existing ECG abnormalities or cardiac histories, without a baseline ECG it was not possible to definitively say that all ECG abnormalities were new.

Conclusions

We identified evidence suggestive of AS based on readily available clinical studies in 40% of patients with aSAH; however, AS defined by these clinical criteria was not an independent predictor of infection. Additional studies may be warranted to determine the optimal definition of AS and to determine any clinical significance of this finding.

Acknowledgments

Disclosure

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Appendix 1

Definitions of Infections

Pneumonia: New or progressive infiltrate on chest radiograph with at least 2 other features (leukocytosis or leukopenia, purulent secretions, new or worsening oxygenation deficit, temperature > 38.5°C).

Tracheobronchitis: Purulent secretions with either a new fever or leukocytosis (or leukopenia) in the absence of a new or progressive infiltrate on chest radiograph.

Urinary tract infection: Pyuria and a positive culture with > 10³ organisms/mL or any culture with > 10⁵ organisms/mL with or without pyuria.

Catheter-associated blood stream infection (CABSI): Positive blood cultures and one of the following: 1) a catheter tip showing > 15 cfu of the same organism by roll-plate technique or 10⁵ of the same organism by sonication technique; 2) differential time to positivity with the same organism growing 2 hours or sooner from the catheter than blood; 3) 10⁵ of the same organism growing on quantitative culture of the catheter.

Ventriculitis/meningitis: Positive CSF culture in the setting of either symptoms or worsening CSF pleocytosis.

Clostridium difficile-associated diarrhea: Positive *C. difficile* test in the setting of any symptoms of infection. Prior to January 2010 the enzyme immunoassay for *C. difficile* toxin

A/B was performed. Subsequently, the enzyme immunoassay for *C. difficile* antigen and *C. difficile* toxin A/B was performed with confirmation by polymerase chain reaction against the toxin.

Wound infection: Neurosurgeon documentation.

Severe sepsis: Two or more systemic inflammatory response syndrome criterion in the setting of a documented infection and with > 1 organ system dysfunction.

Appendix 2

Diagnosis of Neurologically Mediated Cardiopulmonary Dysfunction

Diffuse and non-coronary artery distribution, typical evolution and reversibility of changes, lack of or only minimal cardiac enzyme elevations, echocardiographic patterns and cardiology consultations (when available) were used in combination to differentiate neurogenic electrocardiogram (ECG) abnormalities from acute coronary syndrome and other etiologies. The following ECG abnormalities were documented: primary rhythm, ST segment depression (STD; > 0.1 mV, 80 ms post-J point), ST segment elevation (STE; > 0.1 mV), T-wave inversion (TWI), Large U-waves (> 1 mm), abnormal Q-wave or QS-wave (> 30 ms or pathological R-wave in V1 to V2), and corrected QTc prolongation (> 440 ms and confirmed using Bazett's Formula). We excluded isolated QTc prolongation or isolated U-waves from the definition of autonomic shift (AS) based on the fact that QTc prolongation may be due to many factors following aSAH, including electrolyte abnormalities and medications. Creatine phosphokinase-MB (CK-MB) and cardiac Troponin-I (cTn-I) were detected by using chemiluminescent immunoassay and immunometric chemiluminescence, respectively. The CK-MB isoenzyme was considered elevated only if 2 levels were above the reference range or if the MB index was above 1%. When available, ECGs, echocardiograms, and cardiology consults were used to rule out acute coronary syndrome and to diagnose neurogenic elevations in cardiac enzymes. Reports of echocardiograms were considered positive for neurogenic stunned myocardium if either mid-basal or apical hypokinesis was present as determined by a board-certified cardiologist who interpreted the study as part of routine care. The EMERSE search engine was used to identify a diagnosis of neurogenic pulmonary edema from attending neurointensivist notes. A secondary review of chest x-rays and the clinical history to rule out other etiologies was done by one author (JF). Both increased permeability and hydrostatic pulmonary edema were allowed.

Table 1

Patient characteristics dichotomized by presence of autonomic shift and infection.

Variable	Overall N = 167	Autonomic Shift		Infection	
		No Autonomic Shift n = 101	Autonomic Shift n = 66	No Infection n = 87	Infection n = 80
Age (SD)	55.5 (13.1)	53.7 (12.7)	58.4 (13.2)	52.8 (11.8)	58.5 (13.8)
					<i>p</i> -Value
					0.005
Male	45 (27%)	29 (29%)	16 (24%)	25 (29%)	20 (25%)
					0.59
Race					
					0.80
Caucasian	137 (82%)	79 (78%)	58 (88%)	73 (84%)	64 (80%)
Black	16 (10%)	11 (11%)	5 (8%)	7 (8%)	9 (11%)
Asian	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Hispanic	4 (2%)	4 (4%)	0 (0%)	2 (2%)	2 (3%)
Other	9 (5%)	6 (6%)	3 (5%)	5 (6%)	4 (5%)
Non-white Race	30 (18%)	22 (22%)	8 (12%)	14 (16%)	16 (20%)
					0.51
Hunt-Hess Score					
					0.02
1	24 (14%)	17 (17%)	7 (11%)	12 (14%)	12 (15%)
2	51 (31%)	40 (40%)	11 (17%)	33 (38%)	18 (23%)
3	54 (32%)	32 (32%)	22 (33%)	31 (36%)	23 (29%)
4	29 (17%)	10 (10%)	19 (29%)	9 (10%)	20 (25%)
5	9 (5%)	2 (2%)	7 (11%)	2 (2%)	7 (9%)
Hunt-Hess Score of 4–5	38 (23%)	12 (12%)	26 (39%)	11 (13%)	27 (34%)
					0.001
Statin Use	19 (11%)	9 (9%)	10 (15%)	9 (10%)	10 (13%)
					0.66
Current Smoker	86 (51%)	54 (53%)	32 (48%)	49 (56%)	37 (46%)
					0.19
Hijdra Sum Score, median (IQR)	25.0 (19.0–30.0)	24.0 (17.0–28.0)	28.0 (23.0–31.0)	25.0 (19.0–29.0)	26.0 (18.5–30.0)
					0.46
Intracerebral Hemorrhage	42 (25%)	21 (21%)	21 (32%)	16 (18%)	26 (33%)
					0.04
Modified Fisher Score of 4	41 (25%)	22 (22%)	19 (29%)	19 (22%)	22 (28%)
					0.47

Variable	Autonomic Shift			Infection		
	Overall N = 167	No Autonomic Shift n = 101	Autonomic Shift n = 66	No Infection n = 87	Infection n = 80	p-Value
Aneurysm Size, median (IQR; mm)	6.0 (4.0–9.0)	6.0 (4.0–8.0)	6.0 (4.0–9.0)	6.0 (4.0–8.6)	6.0 (4.0–9.0)	0.78
Posterior Aneurysm Location	31 (19%)	17 (17%)	14 (21%)	10 (11%)	21 (26%)	0.01
Treatment Modality						0.27
Clip	77 (46%)	54 (53%)	23 (35%)	45 (52%)	32 (40%)	
Coil	82 (49%)	45 (45%)	37 (56%)	39 (45%)	43 (54%)	
Neither	8 (5%)	2 (2%)	6 (9%)	3 (3%)	5 (6%)	
Length of Stay, median (IQR; days)	19 (14–24)	18 (14–24)	20 (15–25)	15 (13–21)	21 (17–29)	<.001
Deceased at Discharge	13 (8%)	3 (3%)	10 (15%)	6 (7%)	7 (9%)	0.66

IQR = interquartile range; SD = standard deviation

Table 2

Unadjusted and adjusted odds ratio for autonomic shift predicting subsequent infection in study population with aneurysmal subarachnoid hemorrhage.

Parameter	Autonomic Shift Alone Odds Ratio (95% CI)	Adjusted Model Odds Ratio (95% CI)
Autonomic Shift	2.11 (1.12 – 3.97)	1.36 (0.67 – 2.76)
Age (per year)		1.03 (1.01 – 1.06)
Posterior Aneurysm Location		3.00 (1.23 – 7.32)
Intracerebral Hemorrhage		1.80 (0.80 – 4.02)
Hunt-Hess Grade 4–5		2.84 (1.17 – 6.88)

CI = confidence interval