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Clinical Risk Factors for Acute Ischemic and Hemorrhagic Stroke in Patients with Infective Endocarditis

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Abstract

Background—Stroke as a complication of infective endocarditis portends a poor prognosis, yet risk factors for stroke subtype have not been well defined.

Aim—To identify risk factors associated with ischemic and hemorrhagic strokes.

Methods—A retrospective patient chart review was performed at a single U.S. academic center to identify risk factors and imaging for patients 18 years or older with infectious endocarditis and stroke diagnoses. Differences in patient characteristics by stroke status were assessed with univariate analysis, Chi squared or student T-test as well as logistic regression models for multivariable analyses and correlation matrices to identify possible collinearity between variables and to obtain odd ratios (OR) and their 95% confidence intervals.

Results—A final sample of 1157 was used for this analysis. The total number of non-surgical strokes was 178 with a prevalence of 15.4% (78% ischemic, 10% parenchymal hemorrhages, 8% subarachnoid hemorrhages, and 4% mixed ischemic/hemorrhagic). Multivariate risk factors for ischemic stroke included prior stroke (OR 2.0, 1.3-3.1), *Staphylococcus* infection (OR 2.0, 1.3-3.0), mitral vegetations (OR 2.2, 1.4-3.3) and valvular abscess (OR 2.7, 1.7-4.3). Risk factors for hemorrhagic stroke included fungal infection (OR 6.4, 1.2-34.0), male sex (OR 3.5, 1.4-8.3) and rheumatic heart disease (OR 3.3, 1.1-10.4).

Conclusions—Among patients with infectious endocarditis, there exist characteristics that relate differentially to ischemic and hemorrhagic stroke risk.

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ACRONYMS: IE infective endocarditis, OR odds ratio, MCA middle cerebral artery

Keywords

stroke; endocarditis; intracranial hemorrhage; rheumatic heart disease; subarachnoid hemorrhage

INTRODUCTION

Infectious endocarditis (IE) is a life-threatening disease with an annual incidence of up to 16 per 100,000 people in the United States (1-5). Strokes from septic emboli are a feared complication of IE, affecting 16% to 25% of patients, and are associated with increased rates of peri-operative and long-term morbidity and mortality (6-9). Differentiating hemorrhagic and ischemic stroke has consequences for clinical management to reduce stroke burden; hemorrhagic conversion may complicate decision-making for surgical intervention (10-12). Prior studies have been limited by sample size or combined stroke with other neurologic complications instead of assessing specific characteristics such as type, severity, or location; as such, risk factors for stroke subtypes are not well known.

The objective of this study was to identify patient-specific risk factors for ischemic and hemorrhagic stroke in a large sample of patients with IE treated at a tertiary care center with emphasis on identifying subgroups at high risk for stroke during their hospital stay. We hypothesized that these risk factors would vary by stroke subtype, namely ischemic and hemorrhagic stroke.

METHODS

We performed a retrospective study of risk factors and imaging for patients with IE and stroke diagnoses using patient chart review from Columbia University Medical Center/New York Presbyterian Hospital (CUMC/NYP). Subjects 18 years and older were identified using previously validated ICD-9 codes for IE as the primary discharge diagnosis: 036.42 (meningococcal endocarditis), 093.2x (syphilitic endocarditis), 98.84 (gonococcal endocarditis), 391.1 (acute rheumatic endocarditis), 397.9 (rheumatic diseases of endocardium, valve unspecified), 421.x (acute and subacute bacterial endocarditis), 422.92 (septic myocarditis) (1, 13-15). The data collection period ranged from January 1, 1996 to December 31, 2014. Diagnosis of definite, possible, and rejected endocarditis was made during review using modified Duke's criteria. This study was approved by and informed consent waiver obtained from the institutional review board of Columbia University (protocol number AAAP1003).

Manual data extraction from the CUMC/NYP electronic medical record was carried out by study team members. Demographic data, comorbidities, symptom type and onset, physical findings including NIHSS, disease-specific data including infectious etiology, echocardiographic data, and operative data were collected.

Stroke Definitions

Stroke timing was defined as present at admission, during hospitalisation (i.e. inpatient stroke), or perioperative stroke. Non-surgical stroke was defined as any stroke not occurring in the perioperative period. Strokes were classified as ischemic, hemorrhagic, or mixed (i.e.,

co-existing non-contiguous ischemic and hemorrhagic strokes). Index stroke was defined as the initial event and excluded recurrent strokes. In-hospital stroke evolution was defined as the development of new stroke symptoms with imaging evidence of new infarct(s) or expansion of prior infarct(s) excluding ischemic lesion edematous change after admission.

Stroke Ascertainment

The study team members noted any mention of symptomatic stroke evaluated by the NIHSS during initial data extraction for secondary review. Two vascular neurologists evaluated each possible stroke and defined stroke-related variables including type, anatomical distribution and volume (using the ABC/2 formula), hemorrhagic conversion, mycotic aneurysms, and radiographic modalities (16, 17). In cases of mixed strokes, we used the event that led to initial neurological evaluation. Categories for stroke territories were not exclusive and one stroke may have involved several anatomic areas. Inter-reader reliability measures were obtained in 30 cases. The agreement rate in event type (ischemic versus hemorrhagic) was 94%, in arterial territory 86%, in location and extent (posterior versus anterior versus bilateral) 90%, and in exact anatomical location 71% (the agreement rate was 95% for at least one anatomical area).

Statistical Analysis

The main outcome of interest was any non-surgical ischemic or hemorrhagic stroke to identify risk factors. Perioperative stroke analyses have been previously reported and were excluded from our results (18). Descriptive statistics were reported as percentages or means $\pm$ standard deviation. Differences in patient characteristics by stroke status were assessed with univariate analysis, Pearson's chi-squared test, and student's t-test. The reference group for patients with stroke was patients without stroke. We fitted logistic regression models with variables that had a P value ≤ 0.20 to run multivariable analyses with the exception of age, sex and ethnicity, which we included in all models. We used the correlation matrix of the full model to identify possible co-linearity between the variables used. We tolerated a correlation of $R^2 \leq 0.25$ in the model in co-linear variables. If a variable was co-linear, we kept the most specific variable. We carried out subgroup analyses that we considered of clinical relevance. For ischemic stroke, we evaluated predictors of inpatient ischemic strokes and for ischemic stroke with volume $>1000 \text{ mm}^3$. The volume cutoff of $>1,000 \text{ mm}^3$ was chosen to differentiate punctuate infarcts from larger infarcts. For hemorrhagic strokes, we evaluated predictors of inpatient hemorrhagic stroke and performed separate analyses for intraparenchymal versus subarachnoid hemorrhage. A P value of ≤ 0.05 was considered statistically significant for these analyses.

RESULTS

Sample Characteristics

The electronic data search identified a final sample of 1157 patients for analysis. Figure 1 shows study enrollment of patients with IE including presence or absence of stroke. The characteristics of the sample are described in Tables 1-2.

The prevalence of non-surgical stroke in our sample was 15.4% (78% ischemic, 10% parenchymal hemorrhage, 8% subarachnoid hemorrhage, and 4% mixed ischemic and hemorrhagic strokes). The majority of cerebrovascular events (N=141, 79%) occurred before or at the time of admission; a third of the sample (36%) consisted of referrals from smaller local hospitals.

Ischemic Stroke

Ischemic strokes were often localised to the middle cerebral artery (MCA), were multifocal (with predominant bilateral frontal lobe involvement), and had a presumed embolic mechanism as demonstrated by the involvement of cortical and medullary arteries in all but 1.4 % of the cases (Table 3). Half of ischemic strokes consisted of sub-centimeter lesions, and among lesions $>1,000 \text{ mm}^3$ of volume, a fifth had a volume $>30,000 \text{ mm}^3$. Among ischemic strokes, 35.4% had hemorrhagic conversion.

Index Ischemic Stroke

We identified history of prior stroke of any kind (OR 1.96, 1.25-3.07), coagulase positive *Staphylococcal* infection (OR 1.98, 1.31-3.00), mitral vegetation (OR 2.15, 1.43-3.25), and valvular abscess (OR 2.71, 1.69-4.33) as independent variables associated with ischemic stroke risk (Table 4). Prior stroke (OR 2.20, 1.23-3.96) and mitral vegetations (OR 1.90, 1.09-3.31) were also associated with risk of ischemic stroke for volumes $>1,000 \text{ mm}^3$ with the addition of diabetes as another associated factor (OR 1.94, 1.13-3.34). Of note there were no differences in stroke rates by native versus prosthetic valves.

Among patients with documented vegetations, the mean vegetation sizes were 14.6 ± 8.5 mm for mitral valves, 11.2 ± 5.5 mm for aortic valves, and 16.3 ± 7.7 mm for right sided vegetations ($P<0.001$ for the trend). There was a significant association between vegetation size $> 10\text{mm}$ with ischemic stroke (OR 2.2, 1.2-4.1); vegetations ≤ 10 mm showed no significant association.

Inpatient Ischemic Stroke

Of the 43 patients with ischemic stroke during admission, 29 were new and 14 were recurrent. The risk of inpatient ischemic stroke during admission was 3% for patients with no stroke on admission, 4% in patients admitted with hemorrhagic stroke, and 11% among patients admitted with ischemic stroke. The main variables associated with inpatient ischemic stroke were coagulase positive *Staphylococcus* infection (OR 3.54, 1.74-7.18) and valvular abscess (OR 3.09, 1.39-6.87) (Table 4). When looking at the sample with available vegetation size, we found associations between inpatient stroke and *Staphylococcus* infection (OR 4.3, 1.5-15.6) as well as inpatient stroke and valvular abscess (OR 5.7, 1.7-19.4). The single largest absolute risk of inpatient ischemic stroke was 8% among those with vegetation size > 10 mm.

Hemorrhagic Stroke

Compared to ischemic strokes, parenchymal hemorrhages were larger in volume and more commonly localised to the MCA (Table 3). Parenchymal hemorrhages were localised to the territory of penetrating arteries in 10.5% of cases compared with 1.4% for ischemic strokes.

Subarachnoid hemorrhages were more commonly localised to the frontal lobe, the MCA and cortical territories, and were isolated to a single anatomical location in 71% of cases. The prevalence of mycotic aneurysm was double in patients with parenchymal hemorrhages compared to those with ischemic stroke (15.0 vs. 6.9%). No patients with subarachnoid hemorrhages had mycotic aneurysms.

Index Hemorrhagic Stroke

Of the 39 (3.4%) non-recurrent hemorrhagic strokes, 20 were parenchymal (1.7%) and 19 (1.7%) were subarachnoid. We identified male sex (OR 3.45, 1.44-8.27), history of rheumatic heart disease (OR 3.31, 1.06-10.37), and fungal infection (OR 6.39, 1.20-33.97) as risk factors associated with hemorrhages of any kind (Table 5). Prior strokes showed association with subarachnoid hemorrhage (OR 3.62, 1.25-10.47). In the subsample with known vegetation size, there was no association between vegetation size > 10 mm with parenchymal hemorrhage (OR 0.8, 0.1-6.1) or subarachnoid hemorrhage (OR 1.7, 0.4-6.6).

Inpatient Hemorrhagic Stroke

The risk of inpatient hemorrhagic stroke for all patients was 1.7%. The risk was the lowest among patients with IE admitted without stroke at (0.3%), followed by those admitted with ischemic stroke (5.2%), and finally those admitted with hemorrhagic stroke (30.3%). The single largest absolute risk of inpatient hemorrhagic stroke was 5% among those with fungal endocarditis.

DISCUSSION

This retrospective study describes the prevalence and timing of stroke in patients with IE at a large tertiary care center to identify possible risk factors for non-surgical cerebrovascular events. We report a set of variables that may be helpful in identifying patients with IE at high risk of inpatient ischemic and hemorrhagic stroke.

Our overall incidence of non-surgical stroke was 15.4%, similar to prior rates ranging 18-22% (19, 20). Prior studies identified ischemic stroke as the most common subtype in IE at around 60-65% of total strokes; our result was higher possibly from distinguishing hemorrhagic conversion (20, 21). The MCA territory was most commonly affected and was multifocal with presumed embolic mechanism, replicating prior reports of over 90% of cerebral embolic events in IE occurring in the MCA territory (22). This finding may be a simple reflection of the embolic material tracking flow rather than a susceptibility of the MCA to IE-related emboli (23). The same explanation seems fit for the predominant involvement of the frontal lobe (the largest of all lobes) compared to other anatomic regions.

Major risk factors for ischemic stroke in our study included prior stroke of any kind, *Staphylococcus* infection of any kind, and mitral valve vegetations and abscesses. We did not find previous studies reporting prior stroke as a risk for IE-related stroke and hypothesise that patients with established vascular disease may be more susceptible to brain injury as shown in related studies (24, 25). Previous studies demonstrated increased risk of stroke with certain species including *Staphylococcus*, HACEK organisms, and fungi (26, 27). We report here a differential risk for stroke subtype: *Staphylococcus* species in ischemic strokes

versus fungi for hemorrhages. Both *Staphylococcus* and fungal species have previously been found to be associated with increased embolic risk in patients with IE (11, 28). This differential association may be related to pathophysiology of stroke subtype, with ischemic stroke being the result of emboli and hemorrhage being the result of arterial rupture, possibly related to angioinvasive species. The reason for this higher embolic risk in cases of *Staphylococcus* endocarditis is not well understood, but could perhaps be a function of vegetation size or level of tissue destruction at the valve compared to other pathogens. These hypotheses require future research to further elucidate these findings.

We found that mitral but not aortic valve vegetations were associated with ischemic stroke. This finding was unexpected, and while previous studies have shown increased general embolic risk for mitral valve vegetations, we could not find a segregated analysis of stroke risk by vegetation location other than a smaller study reporting association of mitral valve infections with higher risk of cerebrovascular complications (11, 29, 30). In a post hoc analysis, we found an increased association between ischemic stroke and vegetation size, a finding that has been well reported in the literature (11, 31). We were unsure how these findings might relate to each other. One hypothesis is that lower systolic shear stress around the mitral valve may allow larger vegetations to form on that valve compared to the aortic valve (32, 33). Alternatively, left atrium stasis from mitral valve dysfunction may predispose to vegetation formation similar to clot formation in atrial fibrillation (34).

Our study found distinct risk factors for subarachnoid hemorrhages, possibly related to differences in pathophysiology. Multiple studies in non-IE populations have shown an association between subarachnoid hemorrhage and atrial fibrillation (35, 36). Consequently, subarachnoid hemorrhage could be related to possible emboligenic mechanism leading to a clot-like disruption in blood flow. In the case of intraparenchymal hemorrhage, septic emboli could lead to local inflammation, thereby increasing the risk of mycotic aneurysm formation and primary arterial rupture. This is reflected by the fact that none of the patients with subarachnoid hemorrhage had mycotic aneurysms, while the rate of mycotic aneurysm was highest in patients with intraparenchymal hemorrhage. If true, it would suggest that preventing IE-related emboli might decrease the rate of ischemic stroke and subarachnoid hemorrhage.

Nearly 80% of all stroke events in our study were present at admission. Several studies have shown the majority (60-74%) of strokes preceded diagnosis of IE (11, 37-39). For the remaining IE patients without stroke at presentation, this study may offer guidance to clinicians who are treating patients at risk for developing strokes during hospital admission. Additionally, 35.4% of the ischemic strokes in our study underwent hemorrhagic conversion. Combined with parenchymal and subarachnoid hemorrhages, almost half of all strokes featured some intracranial bleeding. This finding is important given the need for some patients to undergo urgent valve replacement or repair. The impact of these brain hemorrhages in surgical and non-surgical outcomes is a target for future analyses.

This study suffers from several limitations. Our institution serves as a referral center and may be influenced by referral bias. Secondly, neuroimaging was not performed systematically, which may underestimate cerebrovascular complications related to IE. Our

findings are closely aligned with prior studies assessing frequency of various cerebrovascular events such that these effects may be limited. Additionally, our data did not provide information about pre-admission medication regimens (e.g., anti-thrombotics), which could be a confounding factor for certain stroke subtypes. Lastly, not all modified Duke criteria could be used to classify cases of IE due limited chart information for some patients; however, we included cases that were likely endocarditis based on clinical suspicion even if formal criteria were not met (40, 41).

CONCLUSIONS

This retrospective study reaffirms prior findings of stroke incidence in patients with IE and identifies several distinct risk factors for ischemic and hemorrhagic stroke in this population. These factors may be useful to clinicians evaluating risk of stroke in patients with newly diagnosed IE and offer important information for differentiating stroke subtypes to improve clinical management.

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Figure 1.

Study Enrollment. 1411 patients with presumed IE were screened, resulting in 1157 confirmed first admissions. 935 cases did not involve any stroke. Of the 219 cases of IE with possible stroke, 178 were confirmed to involve non-surgical strokes: 145 ischemic strokes, 19 parenchymal hemorrhages, and 14 subarachnoid hemorrhages. The remaining cases were added back to the 935 to result in 979 cases of IE without non-surgical stroke. Co-existing stroke subtypes were summed across all groups for analysis, yielding a total of 148 ischemic strokes, 20 parenchymal hemorrhages, and 19 subarachnoid hemorrhages in Tables 4-5.

Table 1

Demographic/Clinical Characteristics of Non-Surgical Stroke

(in % unless otherwise specified)	All patients (N=1157)	By Stroke Subtype at Admission		
		No stroke (N=979)	Ischemic (N=145)	Hemorrhagic (N=33)
Age (mean $\pm$ SD, median, range)	60.5 $\pm$ 17.7, 62, 18-101	60.8 $\pm$ 17.9, 62, 18-101	60.0 $\pm$ 16.1, 62.5, 21-90	57.7 $\pm$ 16.2, 57.6, 25-88
Men	58.6	59.2	54.7	82.1 *
Ethnicity				
NH White	38.3	37.9	40.5	38.5
Black/AA	14.6	14.4	15.5	7.7
Hispanic	23.3	23.6	20.9	23.1
Other/mixed	23.9	24.0	23.0	30.8
Hypertension	58.7	58.2	62.2	59.0
Diabetes	30.0	28.8	37.8 *	30.8
Dyslipidemia	28.0	27.7	29.7	25.6
Smoking	12.1	12.5	9.5	10.3
History of MI, Stent, or CABG	21.8	22.1	19.6	10.3
Rheumatic Heart Disease	4.5	4.2	6.8	12.8 *
ESRD	12.0	12.1	17.6	10.3
COPD	9.0	9.3	6.8	7.7
CHF	29.1	28.9	30.4	17.9
Prior Stroke	15.3	13.5	27.0 *	22.0
History of Atrial Fibrillation	25.8	26.3	22.3	25.6

* p-value <0.05

Abbreviations: NH non-Hispanic; AA African-American; MI myocardial infarction; CABG coronary artery bypass graft; ESRD end-stage renal disease; COPD chronic obstructive pulmonary disease; CHF congestive heart failure

Table 2**Microbiological and Echocardiographic Findings of Non-Surgical Stroke**

(in % unless otherwise specified)	All patients (N=1157)	By Stroke Subtype at Admission		
		No stroke (N=979)	Ischemic (N=145)	Hemorrhagic (N=33)
MICROBIOLOGY				
Positive Cultures	87.6	87.3	89.2	94.9
Staph aureus or lugdunesis	33.4	31.7	44.6 [*]	35.9
MRSA	11.5	12.1	7.4	12.8
Coagulase (–) Staphylococcus	13.6	13.0	17.6	2.6
Streptococci (any)	23.2	24.3	15.5 [*]	25.6
Streptococcus viridans	6.7	7.4	2.7 [*]	10.3
Enterococcus	10.2	10.3	9.5	20.5 [*]
HACEK	1.7	1.8	0.7	2.6
Fungus	1.6	1.6	1.4	5.1
ECHOCARDIOGRAPHY				
Affected Valve				
Aortic	34.5	34.4	35.1	25.6
Mitral	35.0	31.3	59.5 [*]	51.3 [*]
Tricuspid	7.7	8.0	6.1	7.7
Pulmonary	1.1	1.2	0.0	0.0
Type of Valve Affected				
Native	77.4	77.5	76.4	84.6
Mechanical	5.3	5.4	4.7	7.7
Tissue	17.3	17.1	18.9	7.7
All Prosthetic	22.6	22.5	23.6	15.4
Any Vegetation	64.9	62.6	80.4 [*]	66.7
Aortic	17.7	17.5	18.9	12.8
Mitral	20.0	17.7	35.1 [*]	28.2
Vegetation Size (mm, median, IQR) ^{**}	11, 7-15	10, 7-15	14, 9-19	12, 6-20
Any Abscess	12.6	10.5	26.4 [*]	17.9

*
p-value <0.05

Abbreviations: MRSA methicillin-resistant Staphylococcus aureus; HACEK Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella; LVH left ventricular hypertrophy.

**
Interquartile range only available in 388 patients.

Table 3

Radiographic Characteristics of Non-Surgical Strokes *

(in % unless otherwise specified)	Any ischemic stroke (N=148)	Any parenchymal hemorrhage (N=20)	Any subarachnoid hemorrhage (N=19)
Arterial Territory			
MCA	91.7	100	84.6
ACA	34.7	0.0	0.0
PCA	38.2	0.0	23.1
BA	44.4	16.7	0.0
VA	2.8	0.0	0.0
Anterior and Posterior Circulation	51.0	15.8	7.1
Bilateral Anterior	12.4	21.2	14.3
Left-sided Anterior Only	15.9	10.5	35.7
Right-sided Anterior Only	13.1	47.4	14.3
Posterior Only	6.9	0.0	21.4
Cortical	39	78.9	100.0
Subcortical (medullary artery territory only)	4.8	0.0	0.0
Subcortical (penetrating artery territory only)	1.4	10.5	0.0
Cortical and Medullary Artery	27.6	0.0	0.0
Mixed (penetrating and cortical or medullary)	26.2	5.3	0.0
Anatomical Location			
Frontal Lobe	85.4	72.2	69.2
Parietal Lobe	57.6	50.0	30.8
Temporal Lobe	29.2	22.2	25.4
Occipital Lobe	38.2	5.6	30.8
Basal Ganglia	20.1	5.6	0.0
Brain Stem	18.8	0.0	0.0
Cerebellum	43.1	16.7	0.0
Infarct Size			
> 1,000 mm ³ (1 cm ³)	51.7	75.0	–
1,000-10,000 mm ³ (1-10 cm ³)	58.1	46.2	–
10,001-30,000 mm ³ (11-30 cm ³)	20.3	23.1	–
>30,000 mm ³ (>30 cm ³)	21.6	30.3	–
Mycotic Aneurysm	6.9	15.0	–
Parenchymal Diagnostic Method Used			
Brain CT only	23.6	57.9	64.3
Brain MRI (+/- brain CT)	77.6	36.8	28.6
Intracranial Arterial Methods Used			

(in % unless otherwise specified)	Any ischemic stroke (N=148)	Any parenchymal hemorrhage (N=20)	Any subarachnoid hemorrhage (N=19)
Brain CTA	12.2	15.8	21.4
Brain MRA	39.2	10.5	14.3
DSA	20.9	47.4	28.6

* Components of mixed presentations were considered separately.

Abbreviations: MCA middle cerebral artery; ACA anterior cerebral artery; PCA posterior cerebral artery; BA basilar artery; VA vertebral artery; DSA digital subtraction angiography.

Table 4

Logistic Regression Models for Non-Surgical Ischemic Stroke

Stroke Subtype	Factor	p-value	OR	95% CI
Index Stroke (present on admission)				
	Prior Stroke	0.004	1.96	1.25-3.07
	Coagulase-positive Staphylococcus	0.001	1.98	1.31-3.00
	Mitral Vegetation(s)	<0.001	2.15	1.43-3.25
	Abscess	<0.001	2.71	1.69-4.33
Inpatient Stroke				
	Coagulase-positive Staphylococcus	<0.001	3.54	1.74-7.18
	Abscess	0.006	3.09	1.39-6.87
Large strokes (i.e. stroke Volume > 1,000 mm ³)				
	Diabetes	0.017	1.94	1.13-3.34
	Prior Stroke	0.008	2.20	1.23-3.96
	Mitral Vegetation(s)	0.023	1.90	1.09-3.31

Table 5

Logistic Regression Models for Non-Surgical Hemorrhagic Stroke

Stroke Subtype	Factor	p-value	OR	95% CI
Index Hemorrhage				
	Male Sex	0.006	3.45	1.44-8.27
	Rheumatic Heart Disease	0.040	3.31	1.06-10.37
	Fungal Infection	0.029	6.39	1.20-33.97
Subarachnoid Hemorrhage				
	Male Sex	0.011	5.25	1.47-18.71
	Prior Stroke	0.018	3.62	1.25-10.47