



# Understanding the Genetic Susceptibility and Epidemiologic Risk Factors of Intracranial Aneurysms

## Citation

Lai, Pui Man Rosalind. 2015. Understanding the Genetic Susceptibility and Epidemiologic Risk Factors of Intracranial Aneurysms. Doctoral dissertation, Harvard Medical School.

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## ABSTRACT

### Background and Objectives

Intracranial aneurysms affect up to 3% of the population and carry a high mortality and morbidity prognosis when presented with aneurysm rupture and spontaneous subarachnoid hemorrhage (SAH). Despite its severity on patient prognosis and cost to society, the pathologic mechanism of cerebral aneurysm formation and rupture remains unclear. The roles of genetics and epidemiology have been implicated to play major roles in the pathogenesis of aneurysm and patient outcome after SAH. Our studies serve to investigate both the genetic and epidemiologic factors associated with cerebral aneurysms through studying genome-wide association study (GWAS) of mitochondrial genes and the Nationwide Inpatient Sample (NIS) database.

### Methods

For our genetic study of cerebral aneurysms, we analyzed data from two existing GWAS databases targeting the nuclear-encoded mitochondrial gene loci. We identified single nucleotide polymorphisms (SNPs) within 500kb of 794 candidate nuclear-encoded mitochondrial proteins using the human mitochondrial protein and MitoProteome databases. Plink was used to identify SNPs associated with cerebral aneurysms and a meta-analysis approach was used to calculate the pooled odds ratio (OR) and 95% confidence interval (CI) of the two combined studies. In addition, gene expression analysis using three gene omnibus (GEO) databases (GSE15629, GSE26969, GSE46337) was used to identify differential expression of the genes associated with the significant SNPs.

For our epidemiologic study of cerebral aneurysms, we analyzed patients using the NIS database from 2001 to 2010. Multivariate linear and logistic models were used to analyze the association between 1) cerebral aneurysm rupture and climatic factors, 2) cerebral aneurysm outcome and hospital teaching status, and 3) cerebral aneurysm outcome and patient insurance status.

### Results

#### Genetic studies:

A new genome-wide significant SNP on chromosome 19 (rs7937, OR=2.71, 95%CI 1.81-4.05,  $p=3.46 \times 10^{-5}$ ) was found to be associated with the formation of cerebral aneurysms. The expression of the gene associated with this SNP, *RAB4B*, was also found to be elevated in our subsequent differential gene expression analysis (*RAB4B*, OR=1.74, 95%CI 1.23-2.47,  $p=0.02$ ).

#### Epidemiologic studies:

There were 38,843 hospitalizations for the treatment of unruptured and ruptured aneurysms. In the analysis of SAH rupture with meteorological pattern, decreased sunlight and lower relative humidity were associated with increased rate of admission ( $p<0.001$ ). In ruptured cerebral aneurysms, the odds ratio of in-hospital death and non-routine discharges were 0.69 (95% CI 0.54-0.88) and 0.77 (95% CI 0.60-0.99) in teaching hospitals, independent of hospital aneurysm procedure volume. This difference was accentuated in patients who underwent microsurgical clipping. In the analysis of patient outcome with insurance status, the adjusted odds of in-hospital mortality were higher for Medicare (OR 1.23,  $p<0.001$ ), Medicaid (OR 1.23,  $p<0.001$ ), and uninsured patients (OR 1.49,  $p<0.001$ ) compared with those with private insurance.

### Conclusion

In our genetics analysis of cerebral aneurysms, we demonstrated that mitochondrial genes may play an important role in the pathogenesis of cerebral aneurysm formation, and further research is necessary to confirm and validate the relationship between *RAB4B* and cerebral aneurysm formation. Our nationwide study was the first to suggest the association between decreased sunlight and lower relative humidity with admission of ruptured cerebral aneurysms. Furthermore, the studies also showed that both the hospital teaching status and patient insurance status have significant associations with the outcome cerebral aneurysm rupture.

## Table of Contents

<b>ACKNOWLEDGMENTS</b>	<b>4</b>
<b>GLOSSARY OF ABBREVIATIONS</b>	<b>5</b>
<b>PART I: POLYMORPHISMS IN NUCLEAR-ENCODED MITOCHONDRIAL GENES AND CEREBRAL ANEURYSMS</b>	<b>6</b>
<b>INTRODUCTION</b>	<b>7</b>
I. INTRACRANIAL ANEURYSMS AND SUBARACHNOID HEMORRHAGE	7
II. GENOME-WIDE ASSOCIATION STUDIES AND ANEURYSMS	8
III. MECHANISM OF ANEURYSM FORMATION	9
IV. THE MITOCHONDRIA AND VASCULAR DYSFUNCTION	10
V. RESEARCH QUESTIONS AND HYPOTHESES	11
<b>METHODS</b>	<b>11</b>
<b>RESULTS</b>	<b>13</b>
<b>DISCUSSION</b>	<b>14</b>
<b>CONCLUSION</b>	<b>16</b>
<b>PART II: EPIDEMIOLOGIC RISK FACTORS OF THE DEVELOPMENT AND OUTCOME OF ANEURYSMAL SUBARACHNOID HEMORRHAGE</b>	<b>17</b>
<b>I. INTRODUCTION</b>	<b>18</b>
<b>II. THE NIS DATABASE AND RESEARCH QUESTIONS</b>	<b>18</b>
<b>III. ENVIRONMENTAL AND CLIMATIC ASSOCIATION WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE</b>	<b>19</b>
INTRODUCTION	19
METHODS	19
RESULTS	21
DISCUSSION	22
CONCLUSIONS	26
<b>IV. TEACHING HOSPITAL STATUS ON THE OUTCOME OF CEREBRAL ANEURYSMS</b>	<b>27</b>
INTRODUCTION	27
METHODS	28
RESULTS	30
DISCUSSION	32
CONCLUSIONS	35
<b>V. INSURANCE STATUS ON THE OUTCOME OF ANEURYSMAL SUBARACHNOID HEMORRHAGE</b>	<b>36</b>
INTRODUCTION	36
METHODS	37
RESULTS	38
DISCUSSION	41
<b>REFERENCES</b>	<b>46</b>
<b>TABLES</b>	<b>55</b>

## ACKNOWLEDGMENTS

This thesis would not have been possible without the guidance and support of my supervisor, Dr. Rose Du. Dr. Du has been my inspiration in neurosurgery and has been monumental in my growth, both as a medical student and as a scientist.

I am grateful to Dr. Ning Lin, Dr. Brad Gross, and Dr. Hormuz Dasenbrock, for their guidance and input in the project.

I would also like to thank our colleagues, Akiyama *et al.* for providing us with their GWAS database.

## **GLOSSARY OF ABBREVIATIONS**

AAA: Abdominal aortic aneurysm

GWAS: Genome-wide association study

IVH: Intraventricular hemorrhage

MMP: Matrix metalloproteinase

MtDNA: Mitochondrial DNA

NIS: Nationwide Inpatient Sample database

ROS: Reactive oxidative species

SAH: Subarachnoid hemorrhage

SNP: Single nucleotide polymorphism

**Part I: Polymorphisms in nuclear-encoded mitochondrial genes and cerebral aneurysms**

## **Introduction**

### *I. Intracranial aneurysms and subarachnoid hemorrhage*

An intracranial aneurysm, also known as a cerebral aneurysm, is the dilatation and ballooning of a region of an arterial vessel as a result of an abnormal weakening of the vessel wall. The earliest description of the disease dated to the late 1800s from incidental case reports during craniotomy for suspected brain tumors. Intracranial aneurysms have been estimated to affect up to 1-3% of the population(1), with higher prevalence among women and older age. Other known risk factors for developing aneurysms include patients with autosomal dominant polycystic kidney disease, familial predisposition, hypertension, and atherosclerosis (2).

The spontaneous rupture of an intracranial aneurysm leads to extravasation of blood into the subarachnoid and ventricular spaces, resulting in subarachnoid (SAH) and intraventricular hemorrhage (IVH). Aneurysm rupture carries a significant mortality and morbidity prognosis. The mortality rate of aneurysmal SAH has been estimated up to 40%, with up to half of patients die from the initial insult before reaching a medical facility, and the subsequent deaths as a result of cerebral vasospasm and infarction. Of those who survive, up to 66% can suffer permanent neurologic deficit(3).

Intracranial aneurysms were first reported to be treated by wrapping of a ruptured aneurysm in 1933 by Norman Dott, and by clipping of an aneurysm in 1938 by Walter Dandy(4). Surgical clipping has been regarded as the definitive mode of treatment for ruptured and unruptured aneurysms, which involves an operative procedure that clips the neck of the aneurysm to prevent blood flow, and thus, reducing the pressure and risk of rupture. Recent advancement in interventional neuroradiology has allowed for the development of a new approach in the treatment of intracranial aneurysms. Endovascular coiling, the insertion of coils with or without stents into the aneurysm through a catheter-based approach, was introduced in the early 1990s, and has

become a highly used prophylactic and therapeutic treatment. Both surgical clipping and endovascular coiling approaches are widely used in academic centers.

## *II. Genome-wide association studies and aneurysms*

The familial predisposition of intracranial aneurysm is a strong risk factor for the disease. There has been no known inherited pattern for the development of aneurysms. It is believed that the aneurysmal formation is a complex process and may be associated with multiple genetic alterations. To understand this familial predisposition, there have been many efforts into understanding the role of genetics, and in finding these associated genetic loci.

Genome-wide association analysis (GWAS), also known as whole genome association study, was first introduced in 2005 as a global approach to study genetic variants of diseases (5). The method involves extracting genetic information from individuals with and without the disease, and studying whether there are single-nucleotide polymorphisms (SNPs), changes in single bases of the DNA, between the two groups. GWAS has revolutionized genetic epidemiology as this approach allows for testing of millions of genetic variants of complex, multifactorial disorders.

The first large-scale GWAS study on the genetic polymorphisms of intracranial aneurysms was published in 2008 by Bilguvar *et al.* to identify SNPs associated with sporadic and familial cerebral aneurysms(6). The study involved cohorts from European and Japanese populations of over 2100 aneurysm cases, and found common SNPs on chromosomes 2q, 8q and 9q to be associated with cerebral aneurysm. Specifically, *SOX17* on 8q and *CDKN2A* on 9p were suggested to play a role in the development of aneurysm through their involvement in the maintenance of endothelial cells. Subsequent GWAS studies have replicated the data and identified new risk loci associated with cell-cycle progression, vascular formation and repair, and systolic blood pressure (7-9). Currently, the most common SNPs that have been associated with intracranial aneurysms



have been associated with the following genes: *EDNRA*, *SOX17*, *CDKN2A/CDKN2B*, *CNNM2*, and *RBBP8* (10).

### *III. Mechanism of aneurysm formation*

Despite significant efforts and large-scale genetic studies into understanding this disease, the pathogenesis remains elusive and complex. Different pathways have been proposed to lead to the formation and rupture of cerebral aneurysms. The current model, through the study of human specimens and animal models of aneurysms, suggests that the formation of aneurysms may be a result of chronic inflammation at the vessel wall from hemodynamic stress. As blood travels in cerebral vessels and creates turbulence, specifically at branch point sites, the endothelium is damaged, resulting in the degeneration of the elastic lamina and the recruitment and infiltration of inflammatory cells. The upregulation of proinflammatory genes and activation of the immune response leads to the weakening of the arterial wall and subsequent dilation and remodeling of the vessel site(11). Processes such as hypertension, hypoxia, and smoking, can alter the balance of remodeling proteins, such as matrix metalloproteinases (MMPs), resulting in the susceptibility of aneurysmal formation (12).

Oxidative stress is toxic and damages biomolecules, including DNA and proteins, and has been associated with many vascular diseases like hypertension and atherosclerosis. The formation of reactive oxidative species (ROS), such as  $H_2O_2$ , has been found to play a significant role in the pathogenesis of cerebral aneurysms. ROS are involved in multiple steps of the pathogenesis, including the predisposition to initial endothelial damage and the recruitment and invasion of inflammatory cells. Animal models of aneurysmal formation have been demonstrated to support these postulations. There has been a number of studies that suggest alteration in genes that regulate ROS in the rodent model results in a reduction in the incidence of aneurysmal formation (13). Furthermore, this connection with ROS and its role in the regulation of MMPs, apoptosis and

inflammation, have been well established in the pathogenesis of abdominal aortic aneurysms (AAA) (14).

#### *IV. The mitochondria and vascular dysfunction*

The mitochondria play a key role in many cellular processes, including the regulation of apoptosis through calcium and the formation of adenosine triphosphate and ROS through the electron transport chain(15). There is a direct association between mitochondria and many vascular diseases, including familial hypertension, atherosclerosis, cancer tumorigenesis, and the vascular abnormalities in mitochondrial-associated genetic syndromes like MELAS.

Mitochondria contain their own DNA, mitochondrial DNA (mtDNA), which carries a maternal inheritance. MtDNA is organized in a circular, double-stranded plasmid, with a total of 37 genes encoding 13 proteins. While there are over 1500 proteins that function in the mitochondria, majority are encoded within the nucleus(16).

The mitochondrion is well regarded as the key source for the generation of ROS. The mitochondrial electron transport chain generates ROS as by-products, including superoxides (17). There are at least 10 known sites in the mitochondria that are capable of producing ROS(18).

While there has been no clinical study that demonstrated the relationship between mitochondrial dysfunction and aneurysmal formation, this association has been demonstrated in the animal model. Similar to Guo *et al.*, the expression of caspases have been shown in elastase-induced aneurysms in rabbit and rodent models(19). Furthermore, the intrinsic, mitochondrial-dependent mechanism of apoptosis is well recognized in the development of AAA in the rodent model through the upregulation of caspase-3 and caspase-9(20).

## *V. Research questions and hypotheses*

Given the existing associations between aneurysmal formation and oxidative stress, we hypothesize that mitochondrial genetic polymorphisms play an important role in the formation of intracranial aneurysms through changes in its regulatory pathways such as apoptosis and the generation of ROS. Specifically, we propose that changes in SNPs in nuclear-encoded mitochondrial genes result in changes in the regulation and expression of genes associated with susceptibility of aneurysmal formation. In the first part of our analysis, we examined two existing GWAS databases, concentrating on nuclear-encoded mitochondrial gene polymorphisms, to find associated SNPs with the formation of intracranial aneurysms. In the second part of our analysis, we used the gene omnibus database of patients with cerebral aneurysms to study gene expression changes of the nuclear-encoded mitochondrial genes.

### **Methods**

#### Genome-wide association analysis:

We used two existing GWAS databases for our analysis. The first database (Akiyama *et al.*(21)) involved a Japanese cohort of 194 aneurysmal cases and 288 control cases. The second database was the Familial Intracranial Aneurysm Linkage Study (FIALS), with a total of 2507 individuals, and 434 with known cerebral aneurysms represented in the database. The FIALS database can be accessed at: ([http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000293.v1.p1#restricted-access](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000293.v1.p1#restricted-access)).

The human mitochondrial protein database (<http://bioinfo.nist.gov>) and MitoProteome database were used to identify a total of 794 candidate nuclear-encoded mitochondrial proteins and their associated genes. All SNPs within 500kb of the 794 candidate genes were identified, resulting in a total of 1,048,576 SNPs. BioMart Version 2.20.0, a web-based tool with centralized

database of the most up-to-date genetic information (<http://www.ensembl.org/biomart/>) was used to identify the SNPs.

Plink v1.9, an online whole genome association analysis toolset (<http://pngu.mgh.harvard.edu/~purcell/plink/>) was used for all association analyses in this study. For the Akiyama *et al.* database, a logistic regression model was used to perform the association between the selected SNPs and individuals with cerebral aneurysms. For the FIALS database, a family-based association (TDT) approach was used to test for disease trait to generate a list of significant SNPs. The resulting list of SNPs and odds ratio from both studies were combined by a meta-analysis approach using meta-regression in Stata 12.0. A random-effects model was used to calculate the pooled odds ratio (OR) and 95% confidence interval (CI), with  $p < 0.05$  indicating statistical significance after Bonferroni adjustment for multiple testing.

### Gene Expression

We analyzed gene expression of the 794 nuclear-encoded mitochondrial genes identified in our study using the Bioconductor packages in R version 3.1.2. Gene expression was obtained from three gene expression omnibus (GEO) databases at the National Center for Biotechnology Information (NCBI): GSE15629, GSE26969 and GSE46337. The GEO databases contain public repository for gene expression data (<http://www.ncbi.nlm.nih.gov/geo>).

The nuclear-encoded mitochondrial genes were isolated from the three databases. Expression data was log-transformed and quantile normalized using R. Differential expression analysis was performed using linear models with least squares regression and empirical Bayes moderated t-statistics (22). A meta-analysis using the random-effects model was used to combine the three studies, with Bonferroni adjustment for multiple testing. An adjusted p-value of less than 0.05 was considered statistically significant.

## RESULTS

### *GWAS meta-analysis*

We conducted a meta-analysis of the GWAS data from 482 patients by Akiyama *et al.* and 2507 subjects from FIALS. To selectively analyze nuclear-encoded mitochondrial genes, we identified 1,048,576 candidate SNPs from the mitochondrial database search, of which 6391 and 246 SNPs were present in the Akiyama *et al.* and FIALS databases respectively. The meta-analysis of the 246 SNPs present in both studies demonstrated 12 significant SNPs after adjustment for multiple testing. The pooled OR and 95% CI of all 12 SNPs are presented in **Table 1**.

### *Gene expression*

Given the possibility of association between mitochondrial genes and cerebral aneurysms, a subsequent meta-analysis of three gene expression (GEO) databases were performed. Subjects were classified into two categories: subjects with aneurysms (n=19) or controls (n=10). We analyzed genes associated with the 12 SNPs identified in our previous GWAS analysis. Among the 12 genes of interest, three genes (*PNKD*, *PPP2R2B* and *RAB4B*) had statistically significant changes in gene expression using the fixed-effects model. Only *RAB4B* was found to be significant under a random-effects model (**Table 1**).

## DISCUSSION

GWAS studies have been widely used to study the novel genetic foci contributing to the susceptibility of intracranial aneurysm development (7, 23). Previous GWAS studies have yielded significance for SNPs primarily on chromosome 9p (*CDKN2BAS*) and chromosome 8q (*SOX17*) (7, 24-27). A recent large meta-analysis of 134 studies has identified 19 SNPs, with the most robust SNPs from variants on chromosomes 4, 8 and 9(28). These genetic analyses, in combination with the studies of molecular markers, suggest that hemodynamic stress and inflammatory pathways play a critical role in the formation of aneurysms. However, none of the SNPs identified in the prior study was associated with oxidative stress or mitochondrial dysfunction.

The proinflammatory pathway and its association with oxidative stress have been implicated to play a significant role in the formation of intracranial aneurysms. While there is no SNP identified to date that are associated with this pathway, studies have found biomarkers of oxidative stress and inflammation to be upregulated in aneurysmal SAH. Apoptosis has also been proposed as a mechanism for vessel wall weakening and subsequent dilatation(23). The mitochondria are the powerhouse for both the production of oxidative species and the key regulator of apoptosis. Furthermore, mitochondria-dependent apoptosis has been demonstrated in the formation of AAA in rodents (20).

There has been no study to date to our knowledge that has focused on finding genetic loci of mitochondria-associated genes. Given the evidence that mitochondrial proteins play an important role in the regulation of the inflammatory and apoptotic pathways, we performed an analysis on two existing GWAS databases to identify potential key genetic players in the formation of cerebral aneurysms, and combined the results with gene expression to validate the findings.

In this study, combining two GWAS datasets resulted in 12 SNPs associated with the formation of cerebral aneurysms. The genes associated with the three SNPs found in this meta-

analysis, Paroxysmal Nonkinesigenic Dyskinesia (*PNKD*), Protein Phosphatase 2 Regulatory Subunit B (*PPP2R2B*), and RAS-related Protein (*RAB4B*), were subsequently found to be differentially expressed. Specifically, *RAB4B* was found to be significant in both the fixed- and random-effects models. *RAB4B* on chromosome 19q13.2, is a member of the RAS oncogene family involved in vesicular trafficking and expressed in endothelial cells(29). The Rab-dependent endosome-to-plasma membrane has been reported to play a key role in the trafficking and signaling of vascular endothelial growth factor 2 (*VEGF2*), and has been hypothesized to be important for intracellular signaling and proliferation during angiogenesis(30). While *RAB4B* has not previously been reported to be associated with cerebral aneurysmal formation, it has been identified in prior GWAS analyses as a susceptibility locus for Kawasaki disease and the formation of coronary artery aneurysms (31).

The 19q13 loci has previously been associated with cardiovascular pathology (32, 33). Furthermore, 19q has also been suggested to be involved in the pathogenesis of aortic abdominal and intracranial aneurysms (34). There is strong association between smoking and 19q13 (35, 36). Among all SNPs on this chromosome, rs7937 was highly associated with the number of cigarettes smoked per day in one study (36). Perhaps the association between rs7937, *RAB4B* and other genes with the development of cerebral aneurysm can be explained through changes from environmental behavior. Despite these postulations, this is the first association found between *RAB4B* and the formation of cerebral aneurysms.

*PPP2R2B* has previously been implicated to play a role in the regulation of apoptosis(37). Specifically, *PPP2R2B* has also been associated with the formation of cerebral aneurysm and coronary artery diseases in prior analyses (37, 38).

The major limitation of a GWAS approach to this study is the identification of association and not causality. At the molecular level, a genetic variant may not result in changes in gene or

protein expression. To address this, we included a genetic expression analysis to provide further support for this possible association. However, a GWAS approach remains a powerful tool to identify significant novel candidate genes which can be subsequently further studied in biological models.

## **CONCLUSION**

In conclusion, using a GWAS approach with gene expression validation, this study demonstrated that there may be an association between mitochondrial genes and intracranial aneurysm. *RAB4B* was identified as the strongest association among all nuclear-encoded mitochondrial genes studied, and may serve as a good candidate for further studies to verify its role in the formation of cerebral aneurysms.



**Part II: Epidemiologic risk factors of the development and outcome of aneurysmal subarachnoid hemorrhage**

## **I. Introduction**

Aneurysmal SAH is believed to be a largely unpredictable, spontaneous event. While genetic susceptibility is a known risk factor for the formation of aneurysm, many epidemiologic variables have also been implicated in the development of the disease. Both the formation and rupture of cerebral aneurysms have been shown to be associated with multiple factors, including the characteristics of the aneurysm, the age of the patient, and changes in systolic blood pressure and body temperature (39, 40).

## **II. The NIS Database and research questions**

The Nationwide Inpatient Sample (NIS, Healthcare Cost and Utilization Project, Agency Healthcare Research and Quality) database is the largest all-payer longitudinal inpatient care database in the United States, consisting of approximately 8 million annual hospitalizations. All discharges from sampled hospitals (from across 41 states) are included in the NIS, which is an approximately 20% stratified sample of American non-federal hospitals. The NIS contains data about diagnoses, procedures, and hospital characteristics to allow for analysis of national trends in health care outcomes. We used the NIS database for a nationwide analysis to study the effects of environmental factors, teaching hospital status, and patient insurance status on the incidence and outcome of aneurysmal SAH.

### **III. Environmental and climatic association with aneurysmal subarachnoid hemorrhage<sup>1</sup>**

#### *INTRODUCTION*

Regional weather patterns and seasonal changes have been hypothesized to have an impact on the risk of rupture of cerebral aneurysms. Several studies have suggested that hospital admission for aneurysmal SAH is associated with variations in temperature, atmospheric pressure, humidity, and the lunar cycle (42-44). Moreover, associations between meteorological parameters and cerebral aneurysm rupture have also been observed to vary by sex (45, 46). However, the findings in the literature have been inconsistent: other studies have suggested that SAH does not vary with season or temperature (47, 48).

Although prior retrospective studies have analyzed the association between weather patterns and the risk of cerebral aneurysm rupture in patients treated at a single hospital or a limited geographic area, few large-population or nationwide studies have found an association between meteorological factors and aneurysmal SAH. Furthermore, no study to date has analyzed the association between weather patterns and the post-procedural outcomes of patients treated for ruptured cerebral aneurysms. In this study, we used the NIS database to study the association of four weather parameters with the admission of aneurysmal SAH: average monthly temperature, precipitation, humidity and percent sunlight.

#### *Methods*

##### *Inclusion Criteria and Outcome Measures*

Diagnostic codes from the International Classification of Disease, 9<sup>th</sup> Revision, Clinical Modification (ICD-9-CM) were used to identify patients with ruptured cerebral aneurysms in the NIS database. Patients were included if they had a diagnosis code for SAH (ICD-9-CM 430) or

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<sup>1</sup> This work was previously published in Lai *et.al.* 2014 (41).

intracerebral hemorrhage (ICD-9-CM 431) and at least one procedural code for aneurysm repair, by “clipping of aneurysm” (ICD-9-CM 39.51), “endovascular repair or occlusion” (ICD-9-CM 39.72), or “other repair of aneurysm” (ICD-9-CM 39.79).

The endpoints evaluated were state-adjusted hospital admission rate and in-hospital mortality. State-adjusted hospital admission rate was determined by calculating the total number of patients identified by hospital state and admission month, divided by the state population in millions. Hospital state, admission month and in-hospital mortality are directly encoded in the NIS database. Annual state population was obtained from the 2000-2010 State Characteristics Intercensal Population Estimates File, US Census Bureau, Population Division (<http://www.census.gov/popest/data/intercensal/index.html>) and was used to adjust for state hospital admission.

Climate data was obtained from the State of the Climate Report 2010 released by the National Climatic Data Center (<http://www.ncdc.noaa.gov/>). The report outlines the climatic conditions at major weather observing stations in all 50 states, which includes data for monthly temperature (degree Fahrenheit), monthly precipitation (inches), percent possible sunlight, and relative morning humidity. Percent possible sunlight is defined as the total time for sunshine to reach the surface of the earth, expressed as a percentage of the maximum sunlight possible from sunrise to sunset with clear sky conditions. Average relative morning humidity is a percentage of the amount of moisture in the air compared to the maximum potential moisture the air can hold at the same temperature and pressure. The monthly values of all observing stations in each state were averaged across all years to generate averaged, independent monthly data across each state for all climate variables.

### *Statistical Analysis*

Statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, Texas), and probability values were considered statistically significant if  $p < 0.05$ . Multivariable linear regression analysis was performed to evaluate the association between annual average monthly state temperature, precipitation, percent possible sunlight, and relative morning humidity on annual state-adjusted hospital monthly admission rate and in-hospital mortality rate. Subsequent multivariate regression models were constructed after patients were also stratified by sex, to evaluate if sex modifies any potential associations between hospital admission or outcomes and weather.

### *Results*

#### Study Population

16,970 patients with SAH who underwent surgical clipping or endovascular coiling to repair a cerebral aneurysm were identified from 723 hospitals across 41 states. 67.8% ( $n=11,484$ ) of patients included were females. The median age for all patients [interquartile range (IQR)] was 53 (34-72), and for females and males were 54 (35-73) and 51 (33-69) respectively. 6933 (40.9%) and 7325 (43.2%) patients underwent endovascular coiling only and surgical clipping only respectively. The in-hospital mortality for the patient population was 13.6% (14.1% female only, 12.7% for male only). The median [IQR] hospital length of stay was 17 (3-31) days.

#### *Multivariate Analyses*

Multivariate regression was utilized to analyze the association between average monthly state temperature, precipitation, daily percent possible sunlight, and relative morning humidity on state-adjusted hospital admissions for and mortality during hospitalization for aneurysmal SAH, adjusted by sex (**Table 2**). Higher daily percent sunlight and greater average morning humidity

were associated with a decreased rate of state population adjusted hospital admission ( $p < 0.001$ ); however, no significant differences in mortality were seen. Greater precipitation was associated with reduced in-hospital mortality ( $p = 0.001$ ). Temperature was not found to be associated with significantly different rates of admission or in-hospital mortality. No changes in the statistical significance of parameters were found when multivariate analyses were constructed without sex as a covariate (data not shown).

### *Discussion*

The degree to which the rupture of cerebral aneurysms is impacted by variations in season or weather has been widely debated. Many institutional or regional retrospective studies have examined the relationship between climate and aneurysmal SAH, but the findings in the literature have been inconsistent. Prior research has suggested that ambient temperature, precipitation, sunlight, average humidity, and the lunar cycle may all be associated with an increased risk of rupture of cerebral aneurysms (43, 44, 49-52). On the other hand, others have found no associations between weather patterns and SAH (42, 47, 48). One recent large meta-analysis review of the literature found SAH to be associated with the winter and January (53). In the analysis, multiple studies reported associations with temperature and humidity, although the directions of effects were conflicting due to the heterogeneity of the population pool. To date, the climatic effects on spontaneous SAH continue to be unclear and conflicting.

In this study, 16,970 patients from 723 hospitals across 41 US states over a 10-year period who presented with aneurysmal SAH were analyzed. Four specific meteorological parameters were examined—temperature, precipitation, sunlight, and humidity—to evaluate how these factors are associated with admission rates for and outcomes after aneurysmal SAH. After adjusting for state population, greater sunlight and higher average morning humidity were found to be associated with decreased rate of hospital admission for ruptured cerebral aneurysms. The

increased admission with decreased sunlight is consistent with prior studies demonstrating increased admission with winter and January.

There are few reports studying the correlation of aneurysmal SAH and sunlight exposure. Neidert *et al.* recently reported no association between hourly sunlight and incidence of aneurysmal SAH(54). However, there have been prior studies suggesting a distinct latitudinal pattern for SAH occurrence with progressively decreasing rates from north to south (55-57). Furthermore, multiple studies have associated summer months with lower rates of SAH (53, 58). These phenomena have previously been postulated to be associated with hours of sunshine(59). Sunlight exposure have also been correlated previously with cerebral infarction(60) as well as with the rupture of AAA(61).

It has been postulated that sunlight may impact blood pressure, which ultimately affects the risk of aneurysm rupture. There are new evidences suggesting seasonal blood pressure to be associated with daylight hours(62). Sunlight exposure has been shown to alter blood pressure through the effects of UV light on vitamin D and parathyroid hormone status, stimulating changes in vascular smooth muscle and intracellular calcium, adrenergic responsiveness, and endothelial function (63, 64). Vitamin D deficiency is associated with high blood pressure and the prevalence of the deficiency has seasonal as well as geographic variation based on sunlight exposure(65). Thus, it is biologically plausible that the association between decreased sunlight hours and greater hospital admissions of cerebral aneurysms may be at least partially attributable to the effects of Vitamin D on blood pressure. Moreover, blood pressure is a known independent risk factor associated with both formation and rupture of cerebral aneurysms (66, 67).

The association of sunlight exposure and SAH has also been attributed to the regulation of serotonin by the light/dark cycle. Serotonin in CSF has been reported to fluctuate with both daylight exposure and seasonal variations, with peaks in the spring and troughs in the fall (68, 69).

It has been postulated that the changes in serotonin level affect the sensitivity of cerebral vessels(55), and subsequently, influences the rupture of cerebral aneurysms. Furthermore, sunlight exposure may also affect patient behaviors, such as tobacco smoking and exercise, which may also impact the risk of aneurysm rupture (70).

Studies have previously reported no association between average humidity and spontaneous SAH (42, 50, 54, 71-73). One systematic review and meta-analysis found a total of 15 studies on the association of relative humidity and SAH incidence. Among the studies, a significant relationship between SAH and humidity was found in three studies (53, 74). In our analysis, lower relative morning humidity was found to be associated with increased rate of hospital admission for aneurysmal SAH. One study found that decreased relative humidity and air pressure increase insensible water loss and blood viscosity(75). Arterial wall shear stress is directly proportional to velocity of blood flow and blood viscosity, potentially increasing the risk of aneurysm rupture. Cigarette smoking has been proposed to have a similar mechanism of increasing the risk of cerebral aneurysm rupture: increasing wall shear stress through greater blood viscosity and volume (76). Thus, it is possible that low relative humidity may have a transient effect on blood viscosity.

While many previous studies have examined the relationship between ambient temperature and aneurysmal hemorrhage, the data has been conflicting. While some studies have reported no association between temperature and SAH (48, 54, 72-74), others have found a correlation of aneurysmal hemorrhage with low or extreme temperatures (40, 44, 46, 64, 71, 77). In this study, average monthly temperature was not found to be associated with a differential rate of hospital admission for ruptured cerebral aneurysms. Although temperature is influenced by many factors, it is correlated with sunlight. It can be postulated that the previously reported association between rupture of cerebral aneurysms and temperature may be at least partially attributable to differential



sunlight exposure. In this study, sunlight and temperature were analyzed separately and only sunlight, but not atmospheric temperature, was found to be associated with hospital admission rates.

In this study, greater precipitation was found to be associated with significantly reduced in-hospital mortality after, but not with different admission rates for SAH. This suggests that precipitation may be less important for the actual rupture of aneurysms. However, precipitation may affect individuals' behaviors related to health, potentially impacting outcomes.

Prior research has suggested that the association between weather patterns and cerebral aneurysm rupture may vary by sex. Some studies have reported an association between admission for SAH and seasonal variations in females, while others have only made this observation in males (42, 78). To evaluate whether there is any associations between meteorological parameters and cerebral aneurysm rupture differ based on sex, separate regression analysis were constructed with and without sex as a covariate. Sex was not found to change the observed associations between sunlight or humidity and hospital admission for aneurysmal SAH.

There are many important limitations of this study. Weather patterns were examined in this study by state, but there may be large variations in meteorological parameters within given states. Moreover, average monthly values were utilized for the individual meteorological factors, but likewise weather may change substantially within a specific month. Prior analyses have suggested that daily changes in weather may be associated with aneurysmal SAH (71, 77); however, daily variations could not be examined as the specific day of admission is not available in the NIS. Barometric pressure is an additional meteorological parameter that has been previously reported to be associated with the rupture of cerebral aneurysms (66), but this data was not available from the State of the Climate Report. Coding inaccuracies are a potential concern for any study based on ICM-9-CM identifiers. Furthermore, this study population was limited to those who underwent

procedural treatment for cerebral aneurysm repair, but did not include patients who died before intervention.

Nonetheless, the NIS is the largest all-payer database in the United States, and few large sample studies have found a relationship between weather patterns and cerebral aneurysm rupture. Moreover, the NIS provides a very large sample of patients from a large geographic area who presented across a decade, allowing for a comprehensive analysis of the association between meteorological parameters and SAH.

### *Conclusions*

This is the first nationwide retrospective study to associate sunlight exposure and humidity with the risk of cerebral aneurysm rupture. Greater precipitation was associated with reduced in-hospital mortality. The associations of external climatic factors with aneurysmal SAH may be explained by homeostatic regulation, hormonal fluctuations and changes in human behavior, although further investigation is needed to elucidate these connections. Further research is needed to confirm these findings and further understand the pathophysiology of these relationships between climate and cerebral aneurysms.

## IV. Teaching hospital status on the outcome of cerebral aneurysms<sup>2</sup>

### *INTRODUCTION*

While high volume hospitals and centralized care have been traditionally advocated for high-risk neurosurgical procedures (80, 81), there have been much controversies in the relationship between hospital teaching status and patient outcome. Although academic medical centers usually house highly qualified and sub-specialized physicians, patients sometimes express hesitations over the prospect of being treated by physicians in training. Some literature also suggests increased adverse outcome during the summer, which could coincide with an influx of novice residents(82), although this effect was not observed in patients with SAH(83). Patients with more severe illness or complex medical conditions may be preferentially directed to academic centers due to multiple specialty involvements, thus further complicating the effect on outcome by teaching status. Due to the complexity of managing complications associated with SAH and of treating ruptured aneurysms, it is critical to direct patients with ruptured aneurysms to hospitals with the best outcomes for this group of patients. Furthermore, directing patients with unruptured aneurysms to appropriate centers will avoid consequences of rupture and unnecessary complications. Moreover, teaching hospitals are often large, high volume centers, and favorable outcomes associated with teaching status could be in fact explained by the hospital volume status (84).

In this study, we examined the Nationwide Inpatient Sample (NIS) to determine whether hospital teaching status is an independent determinant for patient outcome after intracranial aneurysm treatment.

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<sup>2</sup> This work was previously published in Lai *et al.* 2014 (79).

## *METHODS*

### *Patient Selection and Endpoint Variables*

Diagnostic codes from ICD-9-CM were used to identify patients with ruptured and unruptured aneurysms from the NIS database. Patients were included in the study of ruptured aneurysms if they had diagnosis codes for SAH (ICD-9-CM 430) or intracerebral hemorrhage (ICH, ICD-9-CM 431) and at least one procedural code for aneurysm repair, by “clipping of aneurysm” (ICD-9-CM 39.51), “endovascular repair or occlusion” (ICD-9-CM 39.72) or “other repair of aneurysm” (ICD-9-CM 39.79).

Patients with both a procedural code for aneurysm repair and a diagnosis code for unruptured aneurysm (ICD-9-CM 437.3) were included in the study for unruptured aneurysms. Patients were excluded from the unruptured group if they had diagnosis codes for SAH or ICH.

Data was stratified by teaching status of the hospital in which patients were treated. A hospital is coded to be a teaching hospital if it has an AMA-approved residency program, is a member of the Council of Teaching Hospital (COH), or has a ratio of full-time equivalent interns and residents to beds of 0.25 or higher. The average number of aneurysm repair procedures each year was used as a measurement for volume of hospital and calculated for each hospital by counting the total number of endovascular coiling or microsurgical clipping procedures over the number of years the hospital was included in the dataset.

The effect of hospital teaching status was evaluated using three endpoints: in-hospital deaths, non-routine discharge, and length of stay excluding in-hospital deaths. Time to first aneurysm repair procedure was also compared between teaching and non-teaching hospitals for the ruptured aneurysm subgroup. In-hospital mortality and length of stay in days were directly coded from the NIS database. Discharge disposition was encoded as routine to home, transfer to short-term hospital, transfer to skilled nursing facility or to intermediate care, home health care,

against medical advice, died, and unknown. Non-routine discharge was defined as any disposition other than routine to home.

### *Statistical Analysis*

Patient selection and statistical analysis were performed using STATA 12.0. All statistical analyses were performed using survey commands to account for the complex survey sampling technique of NIS, which incorporates hospital clustering and sampling weight of each discharge. Probability values were considered statistically significant if  $p < 0.05$ .

Statistical analysis was performed for three defined groups for both ruptured and unruptured aneurysms: all patients included in the study, patients with endovascular procedures only, and patients with surgical procedures only. The association between teaching hospital status and the three outcome variables were analyzed using regression models. Length of stay in hospital and days to first aneurysm repair procedure were analyzed using linear regressions to model the effect of teaching hospital status. All regression models were adjusted for patient specific factors relevant to outcome: age, sex, race, the median household income for the patient's zip code, and total number of comorbidities. The median household income for patient's zip code was reported as <\$39,000, \$39,000-\$47,999, \$48,000 to \$62,999, and >\$63,000. The total number of comorbidities was calculated by the summation of all listed comorbidities available in the NIS database (Acquired Immunodeficiency Syndrome, alcohol abuse, anemia deficiency, rheumatoid arthritis, chronic blood loss, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes with or without complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, and valvular disease). The

hospital specific factors affecting patient outcome are also accounted for in the regression models: annual procedural volume of hospital for aneurysm treatment, hospital region (Northeast, Midwest, South, West), and hospital location (rural, urban). Time to aneurysm repair procedure was included as a covariate for statistical analyses of ruptured aneurysms.

## *RESULTS*

### **Study population and Teaching Hospital Status**

Demographics of the study population comparing ruptured and unruptured aneurysms at teaching and non-teaching hospitals are presented in **Table 3**. A total of 34,843 patients were included in the study who had undergone microsurgical clipping or endovascular coiling for unruptured or ruptured aneurysms between January 1, 2001 and December 31, 2010. Of these patients, 16,557 patients had unruptured aneurysms and 18,286 patients had ruptured aneurysms. Overall, there were 9998 males in the study (41%) and the median age for all patients was 54.3. Patients were identified in the NIS database to be White (68.5%), Black (13.1%), Hispanic (11.6%), Asian or Pacific Islander (3.15%), Native American (0.40%), or Other (3.36%).

In both groups with ruptured or unruptured aneurysms, patients were identified as having been treated in a teaching or non-teaching hospital. Mean age was higher in non-teaching hospitals for both unruptured ( $p<0.001$ ) and ruptured aneurysms groups ( $p<0.001$ ). Male to female gender distribution was not different for both ruptured and unruptured aneurysms groups. There was also no difference comparing race distribution of patients with ruptured aneurysms in teaching and non-teaching hospitals, but difference was observed in patients with unruptured aneurysms ( $p=0.029$ ). The total number of comorbidities was higher in patients treated in non-teaching hospitals for both unruptured and ruptured aneurysm cohorts ( $p<0.001$ ).

A total of 669 and 778 hospitals were represented in this study for treatment of unruptured and ruptured aneurysms respectively. Mean number of aneurysm repair procedures and

distribution of hospital regions were significantly different for both unruptured and ruptured aneurysm groups in teaching hospitals ( $p<0.001$ ).

### **Multivariate analysis**

Multivariate logistic and linear regressions were used to study the associations between outcomes and teaching hospital status in patients with ruptured and unruptured aneurysms. The three endpoints assessed were in-hospital mortality, non-routine discharge, and length of stay excluding in-hospital deaths. These results are shown in **Tables 4A and 4B** for ruptured and unruptured aneurysms, respectively.

In the population with unruptured aneurysms, patient age and number of comorbidities were consistently correlated with increased risk of in-hospital deaths, non-routine discharges and increased length of stay. Annual volume of aneurysm repair procedures per hospital was associated with favorable outcome. Independent of hospital volume, no difference was observed in hospital teaching status for the three endpoints.

Similarly, in patients with ruptured aneurysms, patient age and number of comorbidities were correlated with unfavorable endpoints, whereas higher hospital volume for aneurysm treatment was associated with a decrease in mortality and non-routine discharges. In addition, differences between teaching hospital statuses were observed independent of the effect of hospital volume. The likelihood of in-hospital death was reduced by 31% ( $p=0.003$ ) and non-routine discharges were reduced by 23% ( $p=0.042$ ) in teaching hospitals, despite no difference in hospital length of stay.

To analyze whether the differences observed between teaching and non-teaching hospitals in the ruptured aneurysms group were associated with the type of aneurysm repair procedures, the population was stratified into endovascular coiling and microsurgical clipping to analyze in-

hospital deaths, non-routine discharge, and length of stay. Regression of the three endpoints for coiling and clipping are presented in **Table 5A and 5B** for ruptured and unruptured aneurysms respectively. In patients with unruptured aneurysms, no difference was observed for the three endpoints in coiling or clipping of aneurysms. In the ruptured aneurysms group, the likelihood of in-hospital deaths was reduced by 38% in teaching hospitals for microsurgical clipping ( $p=0.002$ ). There were no associations observed between endovascular treatment of ruptured aneurysms and the three outcome measures.

## *DISCUSSION*

In this study, we retrospectively reviewed data from the NIS from 2001 to 2010 to determine whether hospital teaching status is an independent factor associated with patient outcome after treatment of cerebral aneurysms. Consistent with previous studies, patient specific factors such as age and comorbidities are associated with poorer outcome measures, while average volume for aneurysm treatment for each hospital was correlated with decreased mortality, non-routine discharges and hospital length of stay(85). We examined whether the teaching status of a hospital is associated with patient outcome measures independent of the effect of patient volume. For patients with ruptured aneurysms, academic institutions were associated with lower mortality rate (12.9% vs. 17.5%,  $p=0.003$ ) and lower likelihood of non-routine discharge (59.9% vs. 68.8%,  $p=0.042$ ). Moreover, the disparity in mortality rate in teaching versus non-teaching hospitals seemed even more pronounced for those treated with clipping. Such differences in outcome parameters were not observed in the unruptured population, in which mortality, non-routine discharge, and length of stay were not statistically different between those treated at teaching and non-teaching hospitals independent of aneurysm treatment volume. The results for the ruptured population are consistent with findings from prior reports of SAH(83), whereas the relationship



between hospital teaching status and patient outcome for the treatment of unruptured aneurysm has not been previously investigated. The associations between favorable patient outcomes and the surgical clipping of ruptured aneurysms, but not with the endovascular treatment of ruptured aneurysms or either treatments for unruptured aneurysms, further support the hypothesis that teaching hospitals are correlated with better outcomes with more invasive procedures and can possibly explain the variations in teaching status' effect on patient outcome observed in prior studies.

It has been shown that the treatment pattern and patient outcome for intracranial aneurysms can be highly variable based on the geographic location (86) and volume of the treating hospitals (81). Nevertheless, controversies continue to exist on how hospital teaching status can affect patient outcome. While one report demonstrated that teaching hospitals are associated with higher likelihood of severe maternal non-routine discharge and length of stay for women with type 2 and gestational diabetes(87), multiple studies suggest that teaching hospitals may produce better outcome for patients requiring complex surgical procedures and multi-disciplinary therapy(83, 88, 89). Our study analyzed the outcome of patients undergoing endovascular coiling and microsurgical clipping and appears to support the latter observation. In-hospital death was reduced by 38% in teaching hospitals for patients who had undergone clipping. These findings are independent of demographic and hospital associated factors, including hospital location and aneurysm repair volume.

Previous speculations of the association between academic institutions and better patient outcomes for invasive procedures are that teaching hospitals have a higher patient volume. However, our study suggests that teaching hospital status has an independent association with favorable outcome independent of patient and treatment volume. There are several potential reasons for the observed positive outcome for patients undergoing microsurgical clipping for

ruptured intracerebral aneurysms in teaching hospitals. Academic institutions possess dedicated intensive care units managed by specialists to manage patients with severe and critical conditions. Although less-experienced physician trainees are an important part of teaching hospitals, more rigorous practice guidelines and standardized clinical care practices may be more stringently enforced in teaching hospitals to ensure better outcome. The increased overnight staffing at teaching hospitals may also contribute to better management of critical conditions. Third, academic institutions are actively involved in clinical research and may be more likely to practice the most updated standards of care. Finally, the higher complexity of cases in teaching hospitals in general may also reflect and augment the surgical skills of individual surgeons, which may be more apparent in the more complicated procedures involving ruptured aneurysms. These differences may explain the significantly reduced mortality of patients undergoing the complex surgical procedures.

Caveats for our analyses include the retrospective nature of the study and the inability to demonstrate causality. NIS does not provide specific clinical information on admission, such as presenting neurological condition, Hunt and Hess Grade, or the size and location of the aneurysm, and therefore these factors are not included in any analysis. In this study, we have included certain prognostic factors which affect outcome relevant to SAH and recovery, such as patient age, sex, race, total number of comorbidities, and hospital demographics. However, these adjustments do not entirely represent all factors that can affect outcome measures. For example, there is no information in the NIS database on the complexity of cases. As patients with complex medical problems are more often referred to academic centers, our study may underestimate the outcome advantages of teaching institutes. Coding inaccuracies remain a concern for any outcome study using NIS data and ICD-9-CM identifiers(90), and hospitals of comparable quality based teaching status may not be represented equally among the NIS database. Despite these caveats, the large

size and well-established nationwide representativeness made NIS a standard tool for large-sample analyses in multiple medical fields and the codes used here have been previously validated and generally used in examination of treatment of aneurysm patients.

### *CONCLUSIONS*

Our findings suggest that in-hospital mortality and non-routine discharges were reduced in patients treated in teaching hospitals, independent of aneurysm procedure volume. Mortality was reduced in patients with ruptured aneurysms who have undergone microsurgical clipping, but not endovascular coiling, in teaching hospitals. These analyses support the hypothesis that teaching hospitals are associated with better outcome for patients requiring complex procedures and critical care, and suggest that the teaching status of hospitals should be an important consideration when triaging patients for the treatment of ruptured aneurysms.

## V. Insurance status on the outcome of aneurysmal subarachnoid hemorrhage<sup>3</sup>

### *INTRODUCTION*

Legislation impacting healthcare insurance has remained at the forefront of politics, policy, and media in the United States for more than half a century. Medicare and Medicaid enrollments have been steadily increasing for several decades: in the most recent census, the two programs were the primary payer for more than 108 million Americans(92). Despite this increase in coverage, disparities based on insurance status have been increasingly recognized for patients with varied medical and surgical conditions. Medicare and Medicaid patients undergoing a range of operations have been found to have greater mortality and morbidity, an observation partially attributable to complexities in the American healthcare delivery system and socioeconomic factor (93-97). Although investigation into differences in outcomes by insurance status for patients undergoing neurosurgical intervention has been limited, a recent retrospective institutional study found that patients with public or no insurance were more likely to sustain a complication after craniotomy(98). However, no nationwide study to date has evaluated the impact of primary payer on the outcomes after surgical or endovascular securing of ruptured cerebral aneurysms.

Prior studies have found hospitalization costs for both endovascular and surgical treatment of ruptured aneurysms to be higher than Medicare payments (99). However, no analysis to date has evaluated the relationship between insurance status and outcomes after aneurysmal SAH. This is the first nationwide study to investigate the impact of primary payer status on the in-hospital outcomes—mortality, length of stay, and discharge disposition—after surgical or endovascular treatment of ruptured intracranial aneurysms.

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<sup>3</sup> This work was previously published in Lai *et al.* 2013 (91).

## *METHODS*

### *Inclusion Criteria and Outcome Measures*

Patients from the NIS database were included in the analysis if they had an *ICD-9-CM* diagnosis code for SAH, (ICM-9-CM 430) or intracerebral hemorrhage (ICH, ICM-9-CM 431) and at least one procedural code for aneurysm repair, by “clipping of aneurysm” (ICM-9-CM 39.51), “endovascular repair or occlusion” (ICM-9-CM 39.72), or “other repair of aneurysm” (ICM-9-CM 39.79). Patients were identified by primary payer status, which is directly encoded in the NIS, and stratified into four groups: Medicare, Medicaid, private insurance, and uninsured. Patients were classified as uninsured if their insurance status was coded as self-pay or no charge. In-hospital mortality, hospital discharge disposition, and length of hospital stay were selected as outcome measures.

### *Statistical Analysis*

Analyses were performed using STATA 12.0 using survey commands to account for the complex survey sampling of NIS, which incorporates hospital clustering and sampling weight of each discharge. Probability values were considered statistically significant if  $p < 0.05$ .

Univariate analysis of two-group mean comparison test and F-test were used to compare study population demographics. The Wilcoxon rank sum test and Kruskal-Wallis test were used for non-normal distributions, identified by the Shapiro-Wilk normality test.

Multivariable hierarchical logistic and linear regression analyses were performed to evaluate the outcomes of patients undergoing repair of ruptured cerebral aneurysms by primary payer. Potential confounding variables included as covariates included patient demographics (patient age, sex, race, comorbidities, and the median household income for the patient’s ZIP code); hospital demographics (teaching status, region, location, and procedural volume); year of

admission; differences in the severity of presentation (the proportion of patients who underwent ventriculostomy and the presence of intracerebral hemorrhage); and variations in management (treatment modality, time to aneurysm repair, and time to ventriculostomy) . Patient age, sex, and comorbidities (using the Elixhauser *et al.* categories of comorbid disease(100)) are directly coded in the NIS. Year of admission was included to account for temporal changes in insurance policies and health care delivery.

Ventriculostomy was used as a surrogate for severity of neurological deficit upon presentation—as this procedure is traditionally reserved for patients with a Hunt-Hess grade of 3 or greater—and identified by procedural codes (ICM-9-CM 02.2). Likewise, the presence of intracerebral hemorrhage was also utilized as a potential maker of severity of presentation, as these patients by definition have a higher Fisher grade. The proportion of patients treated via microsurgical clipping was included as a covariate to adjust for differences in treatment modality.

Time to aneurysm repair and ventriculostomy were calculated by identifying time to the first coiling or clipping procedure code. Finally, to analyze the degree to which any differences which may be present based on insurance status are impacted by the procedural approach utilized to secure the aneurysm, subgroup analyses were performed separately for patients who underwent surgical clipping and endovascular coiling.

## *RESULTS*

### *Study Population*

17,559 patients with aneurysmal SAH underwent microsurgical clipping or endovascular coiling between 2001 and 2010; the demographics of the study population are presented in **Table 6**. The majority of patients were covered by private insurance (50.6%), followed by Medicare (23.3%), Medicaid (14.7%), and no insurance (11.4%). Medicare patients were older (mean age 69,  $p<0.0001$ ), while Medicaid (mean age 46,  $p<0.0001$ ) and uninsured patients (mean age 47,

$p<0.0001$ ) were younger, compared to those with private insurance (mean age 50). The Medicare group had a higher proportion of females (74% versus 67% of privately insured patients,  $p<0.0001$ ), while the uninsured group had a lower proportion (62%,  $p<0.0001$ ).

We investigated the baseline characteristics of the hospitals in which the patient population was treated (**Table 7**). A greater proportion of Medicaid (67%,  $p=0.0065$ ) and uninsured patients (66%,  $p=0.0199$ ) were treated at a teaching hospital compared to those with private insurance (59%). Hospital location and region did not differ significantly by primary payer. Those with Medicare underwent intervention at hospitals with higher annual volume of ruptured aneurysms ( $p=0.0075$ ). Time to aneurysm treatment was significantly longer for Medicare and Medicaid patients ( $p<0.0001$ ). Time to ventriculostomy was not different among the four insurance groups.

#### *Univariate Analysis*

First, univariate analysis was performed to evaluate the unadjusted difference in outcomes by primary payer. In-hospital mortality was higher for patients with Medicare (20%,  $p<0.0001$ ), Medicaid (12%,  $p=0.0299$ ) and no insurance (14%,  $p=0.0008$ ) compared to patients with private insurance (11%). The proportion of patients with a non-routine discharge was higher for Medicare patients (83%,  $p<0.0001$ ), not different for Medicaid patients (59%,  $p=0.06$ ), and lower for those without insurance (43%,  $p<0.0001$ ) compared to the privately insured. Medicaid patients had the longest unadjusted length of hospital stay ( $25\pm 23$  days,  $p<0.001$ ), followed by those with Medicare ( $21\pm 14$  days,  $p<0.001$ ), no insurance ( $19\pm 15$  days,  $p=0.211$ ), and private insurance ( $19\pm 13$  days).

#### *Multivariate Analyses*

Subsequently, hierarchical multivariate regression models were constructed to evaluate differences in outcomes by insurance status after adjusting for several potential confounding

variables (**Table 8**). The initial multivariate regression model included patient and hospital demographics, year of admission, and severity of presentation as independent variables. A second multivariate model was also constructed including all of the variables in the first model as well as timing of intervention—time to aneurysm repair and time to ventriculostomy.

In the initial model, the adjusted odds of in-hospital mortality were significantly higher for Medicare (OR 1.23,  $p<0.001$ ), Medicaid (OR 1.23,  $p<0.001$ ) and uninsured patients (OR 1.49,  $p<0.001$ ) compared to patients with private insurance. Additionally, Medicare and Medicaid beneficiaries had higher adjusted odds of non-routine discharges (OR 1.62,  $p<0.001$  and OR 1.08,  $p=0.044$ ) while uninsured patients had lower adjusted odds of a non-routine discharge. Length of stay was longer for Medicaid patients (by 6 days,  $p<0.001$ ) but not significant for those with Medicare or uninsured status. In the second model, when adjusted for timing of intervention, both Medicaid (OR 0.75,  $p<0.001$ ) and uninsured patients (OR 0.42,  $p<0.001$ ) had reduced non-routine discharges despite longer length of stay (by 8.35 days,  $p<0.001$  for Medicaid and by 2.45,  $p=0.05$  for uninsured).

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$p=0.044$ ) while uninsured patients had lower adjusted odds of a non-routine discharge. Length of stay was longer for Medicaid patients (by 6 days,  $p<0.001$ ) but not significant for those with Medicare or uninsured status. In the second model, when adjusted for timing of intervention, both Medicaid (OR 0.75,  $p<0.001$ ) and uninsured patients (OR 0.42,  $p<0.001$ ) had reduced non-routine discharges despite longer length of stay (by 8.35 days,  $p<0.001$  for Medicaid and by 2.45,  $p=0.05$  for uninsured) (**Table 8**).

To determine whether differences in outcome measures were associated with the procedural approach utilized for securing the aneurysm, subgroup analyses were subsequently performed separately for patients who underwent microsurgical clipping and endovascular coiling (**Table 9A and 9B**). Compared with those with private insurance, Medicare patients who underwent surgical clipping had a higher adjusted odds of in-hospital mortality (OR 1.36,  $p<0.001$ ) and non-routine discharges (OR 1.50,  $p<0.001$ ) but not difference in length of hospital stay. Medicaid patients had a higher in-hospital mortality (OR 1.18,  $p=0.025$ ) and no difference in non-routine discharges despite an increased in hospital length of stay (by 7.63 days,  $p<0.001$ ). Uninsured patients had a lower adjusted odds of a non-routine discharge (OR 0.30,  $p<0.001$ ) and longer length of stay (by 2.93 days,  $p=0.018$ ). Patients who underwent endovascular coiling had no difference in mortality by insurance status (**Table 9B**).

## *DISCUSSION*

The association between socioeconomic disadvantage and poor health has been well-established. The factor of insurance status, which was often treated as a binary parameter and a surrogate for socioeconomic status, has recently been considered an independent variable in public-health analyses(101). Numerous reports have suggested that uninsured patients and patients with public insurance have inferior outcomes after certain medical and surgical treatments compared to patients covered by private insurance(93, 95, 97, 98, 102-106). LaPar *et al.* reported

that primary payer status affects mortality after a range of different major surgical operations, including lung resection, colectomy, abdominal aortic aneurysm repair, total hip replacement, and coronary artery bypass grafting (95). On the other hand, other studies have suggested insurance status does not influence surgical outcome (107). Nonetheless, investigation into the impact of payer status on patients undergoing neurosurgical interventions has been limited. El-Sayed *et al.* analyzed outcomes after craniotomy from a single institution and found that patients with public insurance or no insurance were more likely to sustain a complication(98); likewise, those with cranial and spinal tumors have been found to have differential post-operative mortality by primary payer(108, 109). However, no study to date has analyzed the impact of insurance status on the outcomes after aneurysmal SAH: we report the first nationwide study evaluating if those with government-sponsored or no insurance have differential outcomes compared to those with private insurance after microsurgical clipping or endovascular coiling for ruptured intracranial aneurysms.

In this study, 17,559 patients with aneurysmal SAH from across the United States who presented over a ten year period were evaluated. After adjusting for many potential confounding variables in multivariate regression models—including patient and hospital demographics including age, sex, comorbidities, race, socioeconomic status, procedural volume, and the need for ventriculostomy—patients with Medicaid or no insurance had a higher adjusted odds of in-hospital mortality compared to those with private insurance. However, when also adjusting for timing of intervention, these differences in mortality were no longer statistically significant. Medicaid or no insurance coverage was associated with lower adjusted odds of a non-routine hospital discharge: by 28% and 55% respectively. Moreover, length of hospital stay was significantly longer by 9 days for Medicare patients and 4 days for uninsured patients. When subgroup analyses evaluated patients undergoing clipping and coiling separately, differences based upon insurance status were more profound for those who underwent clipping compared to endovascular coiling.

Time to ventriculostomy and aneurysm repair have been associated with clinical outcomes in patients with ruptured intracranial aneurysms (110), but their usage as covariates in previous administrative database analyses has been limited. In this study, time to aneurysm securing was significantly longer for Medicare and Medicaid patients compared to those with private insurance; likewise, time to ventriculostomy was longer for Medicaid patients. When timing of intervention was added to multivariate regression models, the impact of insurance status on outcomes diminished. In fact, after for adjusting for timing of intervention, no significant difference in mortality by insurance status was found.

The reason for the differences in outcomes and timing of intervention by primary payer seen in this study may be multifactorial. Prior studies have suggested that disparities based on insurance status are largely attributable to underlying societal variations and the structure of the healthcare delivery system in the United States rather than individual provider or hospital bias. It has been hypothesized that inferior outcomes for patients with government-sponsored or no insurance undergoing surgical procedures may be partially attributable to three factors—access to high-quality care, comorbidities, and acuity of presentation (111). Those with government-sponsored or no insurance are known to have prohibitive language and transportation barriers to receiving quality care. Individuals with private insurance may possess better access to primary care, have greater health-care literacy, and additional pre- and post-operative support (98, 101, 102). Patients with limited access to primary care may have poorly controlled comorbidities, which are known to negatively impact surgical outcomes and may delay procedural intervention. While twenty-nine comorbidities were included as covariates in multivariate analyses, this may not fully account for differences in severity of the diseases. Moreover, patients with limited access to primary care and preventive medicine may have reduced pre-morbid referral to specialists—including cerebrovascular neurosurgeons—potentially decreasing the likelihood of undergoing

elective securing of the cerebral aneurysm. Additionally, prior studies have suggested that patients with government or no insurance are more likely to be treated at hospitals with limited resources and reduced staffing, which may decrease the likelihood of undergoing early intervention.

Notably, Medicaid coverage was associated in this study with a 45% lower adjusted odds of a non-routine hospital discharge, despite having a statistically and clinically significant longer hospitalization (by 12.5 days). Similar trends were seen for uninsured patients. These observations are consistent with prior studies which have found restricted access to rehabilitation services for uninsured patients after traumatic injury (112). Although governmental programs such as Medicaid are designed to provide coverage for acute conditions, there may be variability in extension to include short- and long-term rehabilitation facilities. This may explain why Medicaid patients were less likely to have a non-routine discharges and had longer hospital stays: those that were medically eligible for acute rehabilitation may have remained in the hospital until they were ready to be discharged home.

The limitations of this study merit closer evaluation. The mortality rates in this study only represent patients who underwent procedural treatment for ruptured aneurysms and do not include patients who died before intervention. This may bias towards better outcomes, as those with decreased access to healthcare may have a higher chance of dying prior to receiving treatment.

Nonetheless, the NIS has many unique advantages that make it well-suited to evaluate the impact of insurance status on surgical outcomes in the United States. The NIS is the largest all-payer database in the United States, providing a broader perspective than state-wide or single-payer datasets. The NIS includes data on many important potential confounding variables—including patient and hospital demographics—that were utilized as covariates in multivariate analyses. The large size and well-established nationwide perspective of the NIS have rendered it a standard dataset for large-sample analyses on health care utilization and outcomes in the United

States. Further research, particularly with data collected in a prospective fashion, may provide additional insight into strategies to reduce differential outcomes based on primary payer for patients undergoing procedural intervention for aneurysmal SAH.

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**TABLES**

**Table 1.** Meta-analysis of 12 aneurysm-associated SNPs using the random-effects model (GWAS) and differential gene expression associated with significant SNPs (Gene Omnibus). \*P-values were adjusted using Bonferroni correction.

Gene	Chr	Position	SNP	Allele	Major Allele	SNPs			Gene Expression		
						OR (95%CI)	P	P <sub>adj</sub> *	OR (95%CI)	Rando <sub>m</sub> <sub>adj</sub> *	Fixed <sub>adj</sub> *
<i>THEM4</i>	1	151874041	rs13320	A/G	G	2.81 (2.3-3.4)	2.14x10 <sup>-26</sup>	6.21x10 <sup>-25</sup>	1.14 (0.9-1.5)	<i>I</i>	<i>I</i>
<i>PNKD</i>	2	218345073	rs921970	A/C	C	2.65 (1.6-4.4)	1.06x10 <sup>-4</sup>	3.07x10 <sup>-3</sup>	4.19 (1.0-18)	0.58	<b>0.01</b>
<i>EFHD1</i>	2	232682275	rs7286	C/T	C	2.06 (1.6-2.7)	1.69x10 <sup>-7</sup>	4.78 x10 <sup>-6</sup>	0.4 (0.2-1.1)	<i>I</i>	<i>I</i>
<i>SH3BP5</i>	3	15300094	rs826423	A/G	A	3.51 (1.8-6.9)	2.85x10 <sup>-4</sup>	8.25 x10 <sup>-3</sup>	0.68 (0.5-1.0)	0.74	0.21
<i>SUCLG2</i>	3	67401619	rs1490265	A/C	A	2.61 (2.1-3.2)	5.10x10 <sup>-14</sup>	1.48x10 <sup>-14</sup>	0.91 (0.5-1.8)	<i>I</i>	<i>I</i>
<i>FAM162A</i>	3	122409547	rs1127343	A/G	A	2.62 (4.5-3.5)	4.81x10 <sup>-4</sup>	1.40 x10 <sup>-2</sup>	0.96 (0.6-1.6)	<i>I</i>	0.64
<i>RAI14</i>	5	34698588	rs889319	C/T	T	3.45 (2.8-4.2)	2.44x10 <sup>-33</sup>	7.08x10 <sup>-32</sup>	1.02 (0.8-1.4)	<i>I</i>	<i>I</i>
<i>PPP2R2B</i>	5	147075262	rs1480150	C/T	C	3.75 (2.3-6.2)	1.67x10 <sup>-7</sup>	4.84 x10 <sup>-6</sup>	0.47 (0.1-2.2)	<i>I</i>	0.002
<i>RARS</i>	5	168491658	rs244896	G/T	T	2.39 (1.6-3.6)	3.02x10 <sup>-5</sup>	8.76x10 <sup>-4</sup>	1.02 (0.8-1.4)	0.58	<i>I</i>
<i>PARK2</i>	6	162180689	rs1954948	C/T	T	2.48 (2.0-3.1)	7.32x10 <sup>-16</sup>	1.93x10 <sup>-14</sup>	0.64 (0.2-2.1)	<i>I</i>	0.14
<i>GLRX5</i>	14	95541473	rs1007813	C/T	C	2.58 (1.6-4.2)	1.77x10 <sup>-4</sup>	5.13 x10 <sup>-3</sup>	0.76 (0.6-1.1)	0.58	0.64
<i>RAB4B</i>	19	40796801	rs7937	C/T	C	2.71 (1.8-4.1)	1.19x10 <sup>-6</sup>	3.46x10 <sup>-5</sup>	1.74 (1.2-2.5)	0.02	0.02

**Table 2.** Multivariate analysis evaluating the association between meteorological parameters by state and (A) annual state population-adjusted hospital admission rate for, as well as (B) in-hospital mortality after aneurysmal SAH, adjusted for sex.

A.

<b>State-Adjusted Hospital Admission</b>	<b>Coefficient</b>	<b>95% Confidence Interval</b>	<b>P value</b>
<b>Average Daily Temperature</b>	0.012	(0.002, 0.02)	0.021
<b>Average Daily Precipitation</b>	-0.044	(-0.2, 0.07)	0.426
<b>Average Percent Daily Sunlight</b>	-0.061	(-0.08, -0.04)	<0.001
<b>Average Morning Humidity</b>	-0.041	(-0.05, -0.03)	<0.001

B.

<b>In-hospital Mortality</b>	<b>Coefficient</b>	<b>95% Confidence Interval</b>	<b>P value</b>
<b>Average Daily Temperature</b>	0.0007	(-0.003, 0.002)	0.158
<b>Average Daily Precipitation</b>	-0.017	(-0.03, -0.007)	0.001
<b>Average Percent Daily Sunlight</b>	-0.001	(-0.003, 0.0003)	0.119
<b>Average Morning Humidity</b>	-0.004	(-0.002, -0.0008)	0.512



**Table 3.** Characteristics of patients with ruptured and unruptured intracranial aneurysms by teaching hospital status.

Study Population Characteristics	Unruptured Aneurysms			Ruptured Aneurysms		
	Teaching	Non-Teaching	P value	Teaching	Non-Teaching	P value
<b>Patient Characteristics</b>						
<b>Patients</b>	14763	1794		15628	2658	
<b>Mean Age (mean±SE)</b>	55.4±0.2	57.8±0.4	<0.001	53.5±0.2	55.7±0.4	<0.001
<b>Male gender (%)</b>	23.4	25.1	0.127	32.6	30.8	0.256
<b>Race (%)</b>			0.029			0.678
White	7986(75)	1036(80)		6877 (61)	1337 (64)	
Black	1062(10)	96(7.4)		1881 (17)	247 (12)	
Hispanic	958(9.0)	128(9.9)		1500 (13)	337 (16)	
Asian or Pacific Islander	221 (2.1)	13(1.0)		468 (4.2)	94 (4.5)	
Native American	49(0.5)	3 (0.2)		41 (0.4)	6 (0.3)	
Other	310(2.9)	22(1.7)		436 (3.9)	81 (3.9)	
<b>Total Comorbidities (mean±SE)</b>	1.53±0.02	1.77±0.06	<0.001	1.97±0.04	2.24±0.07	0.001
<b>Hospital Characteristics</b>						
<b>Hospitals (%)</b>	405 (61)	264 (39)		436 (56)	342 (44)	
<b>Annual Aneurysm Procedure Volume per Hospital (mean±SE)</b>	18.6±1.6	3.8±0.5	<0.001	16.4±1.3	3.5±0.3	<0.001
<b>Time to Aneurysm Procedure (Days, (mean±SE)</b>	0.54±0.04	0.65±0.08	0.255	1.8±0.1	2.0±0.1	0.550

<b>Hospital Regions</b>			<0.001			<0.001
Northeast	82 (20.2)	25 (9.47)		37 (11)	96 (22)	
Midwest	116 (28.6)	36 (13.6)		45 (13)	120 (28)	
South	129 (31.9)	122 (46.2)		153 (45)	133 (31)	
West	78 (19.3)	81 (30.7)		107 (31)	87 (20)	
<b>Hospital Location (%)</b>			0.391			0.015
Urban	11 (2.5)	10 (2.9)		10 (2.3)	16 (4.7)	
Rural	381 (97.5)	233 (68.1)		426 (97.7)	326 (95.3)	

**Table 4.** Adjusted odds ratio for outcome and difference in length of stay in patients who underwent treatment of ruptured (A) and unruptured (B) aneurysms in teaching vs non-teaching hospital.

A)

	<b>% of Patients</b>	<b>Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>P value</b>
<b>Mortality</b>	13.4			
Teaching	12.9	0.69	[0.54, 0.88]	0.003
Non-Teaching	17.5			
<b>Non-Routine Discharges</b>	61.0			
Teaching	59.9	0.77	[0.60, 0.99]	0.042
Non-Teaching	68.8			
	Mean Number of Days	Difference (Days)		
<b>Length of Stay</b>	20.4			
Teaching	20.4	0.22	[-1.48, 1.92]	0.801
Non-Teaching	20.1			

B)

	<b>% of Patients</b>	<b>Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>P value</b>
<b>Mortality</b>	0.74			
Teaching	0.69	0.84	[0.38, 1.88]	0.677
Non-Teaching	1.18			
<b>Non-Routine Discharges</b>	14.9			
Teaching	14.6	1.00	[0.73, 1.36]	0.976
Non-Teaching	17.3			
	Mean Number of Days	Difference (Days)		
<b>Length of Stay</b>	4.70			
Teaching	4.65	0.47	[-0.26, 1.20]	0.208
Non-Teaching	5.05			

\*Regression model includes covariates adjusted for patient age, sex, race, total number of comorbidities, median household income, hospital region, hospital location and average hospital volume of aneurysm procedure. Ruptured aneurysms (A) also includes time to aneurysm repair procedure as covariate.

**Table 5.** Adjusted odds ratios for outcome and difference in length of stay in patients with ruptured (A) and unruptured (B) aneurysms who had undergone endovascular coiling or microsurgical clipping based on hospital teaching status.

A)

Outcome Procedure	% of Patients		Odds Ratio	95% Confidence Interval	P Value
	Teaching	Non-Teaching			
<b>Mortality</b>					
Clipping	11.9	17.8	0.62	[0.46, 0.84]	0.002
Coiling	14.2	17.0	0.73	[0.51, 1.05]	0.085
<b>Non-Routine Discharge</b>					
Clipping	59.9	70.0	0.83	[0.61, 1.13]	0.239
Coiling	59.6	67.4	0.76	[0.57, 1.01]	0.060
	Mean Number of Days		Difference (Days)		
<b>Length of Stay</b>					
Clipping	21.0	20.5	1.22	[-0.86, 3.30]	0.249
Coiling	19.2	19.0	-0.32	[-2.58, 1.94]	0.782

B)

Outcome Procedure	% of Patients		Odds Ratio	95% Confidence Interval	P Value
	Teaching	Non-Teaching			
<b>Mortality</b>					
Clipping	0.91	1.36	0.95	[0.30, 3.05]	0.949
Coiling	0.45	1.01	0.86	[0.28, 2.62]	0.789
<b>Non-Routine Discharge</b>					
Clipping	23.5	29.1	0.87	[0.63, 1.20]	0.402
Coiling	8.21	10.6	0.96	[0.56, 1.64]	0.872
	Mean Number of Days		Difference (Days)		
<b>Length of Stay</b>					
Clipping	6.53	6.96	0.48	[-0.39, 1.36]	0.276
Coiling	2.92	3.11	0.05	[-0.83, 0.93]	0.904

**Table 6.** The demographics of patients with aneurysmal SAH who underwent surgical clipping or endovascular coiling, by primary payer.

	Private	Medicare		Medicaid		Uninsured		F
			<i>p</i> *		<i>p</i> *		<i>p</i> *	
<b>No. of patients</b>	8883	4096		2578		2002		
<b>Age (mean±SD)</b>	50±11	69±11	<0.0001	46±13	<0.0001	47±11	<0.0001	<0.0001
<b>Female (%)</b>	67	74	<0.0001	67	0.7680	62	<0.0001	<0.0001
<b>Race (%)</b>			0.0020		<0.0001		<0.0001	<0.0001
White	68	72		40		50		
Black	14	12		25		22		
Hispanic	10	9.2		25		20		
Asian/Pacific Islander	4.5	4.0		3.8		3.4		
Native American	0.3	0.27		0.7		0.2		
Other	3.7	3.0		5.2		4.8		
<b>Number of Comorbidities (median±range)<sup>†</sup></b>	1 (0-8)	2 (0-9)	<0.0001	2 (0-9)	<0.0001	1 (0-8)	0.0009	0.0001
<b>Median Household Income (%)</b>			<0.0001		<0.0001		<0.0001	<0.0001
< \$25,000	18	25		37		34		
\$25,000-34,999	23	27		27		28		
\$35,000-44,999	26	23		22		23		
>\$44,999	33	24		14		16		
<b>Microsurgical Clipping (%)</b>	60	52	<0.0001	60	0.5014	63	0.0498	<0.0001
<b>Ventriculostomy (%)</b>	26	34	<0.0001	34	<0.0001	20	0.0002	<0.0001
<b>Intracerebral Hemorrhage (%)</b>	8.8	11	0.0060	9.7	0.2142	6.8	0.0094	0.0002

\*P values are for comparison with private insurance.

<sup>†</sup>For non-normal distributions, Wilcoxon rank sum and Kruskal-Wallis tests were used.

**Table 7.** Characteristics of the hospitals treating patients with aneurysmal SAH via surgical clipping or endovascular coiling, by insurance status.

	Private	Medicare		Medicaid		Uninsured		F
			<i>p</i> *		<i>p</i> *		<i>p</i> *	
<b>Teaching hospital (%)</b>	59	60	0.5920	67	0.0065	66	0.0199	0.0131
<b>Rural location (%)</b>	3.3	3.0	0.7950	1.8	0.1464	2.7	0.6146	0.5340
<b>Hospital region (%)</b>			0.9994		0.6112		0.6298	0.8517
Northeast	17	17		16		15		
Midwest	22	22		22		23		
South	36	37		36		43		
West	24	24		26		18		
<b>Annual Aneurysm Procedure Volume (median+range)<sup>+</sup></b>	27(0.14-134)	30.5 (0.14-134)	0.0075	25.8 (0.25-134)	0.2128	25.8 (0.25-134)	0.7574	
<b>Time to Aneurysm Repair, days (median+range)<sup>+</sup></b>	1 (0-69)	1 (0-50)	<0.0001	1 (0-106)	<0.0001	1 (0-40)	0.1138	<0.0001
<b>Time to Ventriculostomy, days (median+range)<sup>+</sup></b>	0 (0-52)	0 (0-62)	0.2955	0 (0-77)	0.4034	0 (0-42)	0.6828	0.209



**Table 8.** Hierarchical analysis\* evaluating the impact of primary payer status on the outcomes after aneurysmal SAH, utilizing patients with private insurance as the reference.

<b>Outcome</b>	<b>Medicare</b>	<b>Medicaid</b>	<b>Uninsured</b>
	<b>OR [95% CI]</b>	<b>OR [95% CI]</b>	<b>OR [95% CI]</b>
<b>In-hospital Mortality</b>	1.23 [1.14, 1.34] <i>P</i> <0.001	1.23 [1.14, 1.34] <i>P</i> <0.001	1.49 [1.36, 1.63] <i>P</i> <0.001
<b>Non-routine Discharge</b>	1.62 [1.48, 1.76] <i>P</i> <0.001	1.08 [1.002, 1.16] <i>P</i> =0.044	0.53 [0.49, 0.58] <i>P</i> <0.001
	<b>Coef. [95% CI]</b>	<b>Coef. [95% CI]</b>	<b>Coef. [95% CI]</b>
<b>Length of Stay</b>	0.80 [-0.046, 1.65] <i>P</i> =0.064	6.00 [4.76, 7.23] <i>P</i> <0.001	0.64 [-0.22, 1.49] <i>P</i> =0.144

\*The independent variables included as covariates in regression analyses were patient age, sex, race, comorbidities, median household income of the patient’s zip code, hospital region, hospital location, teaching status, procedural volume, the presence of intracerebral hemorrhage, the performance of a ventriculostomy, year of admission, and aneurysm treatment modality (clipping or coiling).

**Table 9.** Subgroup hierarchical analyses investigating the impact of primary payer on the outcomes after aneurysmal SAH, evaluating patients who underwent microsurgical clipping (A) or endovascular coiling (B) separately.

A)

	<b>Private Insurance</b>	<b>Medicare</b>		<b>Medicaid</b>		<b>Uninsured</b>	
	<b>%</b>	<b>%</b>	<b>OR [95% CI]</b>	<b>%</b>	<b>OR [95% CI]</b>	<b>%</b>	<b>OR [95% CI]</b>
<b>In-hospital Mortality</b>	10.5	19.3	1.36 [1.16, 1.58] <i>P</i> <0.001	12.3	1.18 [1.02, 1.36] <i>P</i> =0.025	13.4	1.09 [0.88, 1.36] <i>P</i> =0.438
<b>Non-routine Discharge</b>	59.2	84.4	1.50 [1.32, 1.71] <i>P</i> <0.001	57.8	1.03 [0.93, 1.14] <i>P</i> =0.632	42.5	0.30 [0.25, 0.35] <i>P</i> <0.001
	Days	Days	Coef. [95% CI]	Days	Coef. [95% CI]	Days	Coef. [95% CI]
<b>Length of Stay</b>	19±13	23±15	0.13 [-1.30, 1.56] <i>P</i> =0.857	26±24	7.63 [5.38, 9.87] <i>P</i> <0.001	20±15	2.93 [0.49, 5.36] <i>P</i> =0.018

B)

	<b>Private Insurance</b>	<b>Medicare</b>		<b>Medicaid</b>		<b>Uninsured</b>	
	<b>%</b>	<b>%</b>	<b>OR [95% CI]</b>	<b>%</b>	<b>OR [95% CI]</b>	<b>%</b>	<b>OR [95% CI]</b>
<b>In-hospital Mortality</b>	11.5	21.6	0.85 [0.58, 1.26] <i>P</i> =0.418	12.5	1.31 [0.95, 1.81] <i>P</i> =0.104	13.8	1.26 [0.75, 2.10] <i>P</i> =0.381
<b>Non-routine Discharge</b>	54.0	80.9	2.06 [1.45, 2.93] <i>P</i> <0.001	60.5	1.76 [1.29, 2.40] <i>P</i> <0.001	43.8	0.39 [0.26, 0.58] <i>P</i> <0.001
	Days		Coef. [95% CI]	Days	Coef. [95% CI]	Days	Coef. [95% CI]
<b>Length of Stay</b>	18±13	20±13	-3.08 [-7.76, 1.60] <i>P</i> =0.197	24±20	12.1 [4.85, 19.4] <i>P</i> =0.001	18±14	8.49 [-1.41, 18.4] <i>P</i> =0.093

\*The independent variables included as covariates in regression analyses were patient age, sex, race, comorbidities, median household income of the patient’s ZIP code, hospital region, hospital location, teaching status, procedural volume, the proportion of patients who underwent ventriculostomy, year of admission, the proportion of patients who presented with intracerebral hemorrhage, and aneurysm treatment modality (clipping or coiling).