Cigarette smoking and outcomes after aneurysmal subarachnoid hemorrhage: a nationwide analysis

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OBJECTIVE Although cigarette smoking is one of the strongest risk factors for cerebral aneurysm development and rupture, there are limited data evaluating the impact of smoking on outcomes after aneurysmal subarachnoid hemorrhage (SAH). Additionally, two recent studies suggested that nicotine replacement therapy was associated with improved neurological outcomes among smokers who had sustained an SAH compared with smokers who did not receive nicotine.

METHODS Patients who underwent endovascular or microsurgical repair of a ruptured cerebral aneurysm were extracted from the Nationwide Inpatient Sample (NIS, 2009–2011) and stratified by cigarette smoking. Multivariable logistic regression analyzed in-hospital mortality, complications, tracheostomy or gastrostomy placement, and discharge to institutional care (a nursing or an extended care facility). Additionally, the composite NIS-SAH outcome measure (based on mortality, tracheostomy or gastrostomy, and discharge disposition) was evaluated, which has been shown to have excellent agreement with a modified Rankin Scale score greater than 3. Covariates included in regression constructs were patient age, sex, race/ethnicity, insurance status, socioeconomic status, comorbidities (including hypertension, drug and alcohol abuse), the NIS-SAH severity scale (previously validated against the Hunt and Hess grade), treatment modality used for aneurysm repair, and hospital characteristics. A sensitivity analysis was performed matching smokers to nonsmokers on age, sex, number of comorbidities, and NIS-SAH severity scale score.

RESULTS Among the 5784 admissions evaluated, 37.1% (n = 2148) had a diagnosis of tobacco use, of which 31.1% (n = 1800) were current and 6.0% (n = 348) prior tobacco users. Smokers were significantly younger (mean age 51.4 vs 56.2 years) and had more comorbidities compared with nonsmokers (p < 0.001). There were no significant differences in mortality, total complications, or neurological complications by smoking status. However, compared with nonsmokers, smokers had significantly decreased adjusted odds of tracheostomy or gastrostomy placement (11.9% vs 22.7%, odds ratio [OR] 0.63, 95% confidence interval [CI] 0.51–0.78, p < 0.001), discharge to institutional care (OR 0.71, 95% CI 0.57–0.89, p = 0.002), and a poor outcome (OR 0.65, 95% CI 0.55–0.77, p < 0.001). Similar statistical associations were noted in the matched-pairs sensitivity analysis and in a subgroup of poor-grade patients (the upper quartile of the NIS-SAH severity scale).

CONCLUSIONS In this nationwide study, smokers experienced SAH at a younger age and had a greater number of comorbidities compared with nonsmokers, highlighting the negative ramifications of cigarette smoking among patients with cerebral aneurysms. However, smoking was also associated with paradoxical superior outcomes on some measures, and future research to confirm and further understand the basis of this relationship is needed.

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KEY WORDS cerebral aneurysm; Nationwide Inpatient Sample; nicotine; outcomes; smoking; subarachnoid hemorrhage; tobacco; vascular disorders

ABBREVIATIONS ASA = American Society of Anesthesiologists; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GOS = Glasgow Outcome Scale; NIS = Nationwide Inpatient Sample; NSQIP = National Surgical Quality Improvement Program; OR = odds ratio; SAH = subarachnoid hemorrhage.

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CIGARETTE smoking is one of the most detrimental behaviors to health, and an estimated 18% of deaths in the US are attributable to smoking.¹⁶ Among the many negative consequences of cigarette smoking include that it is a well-known risk factor for the development and rupture of cerebral aneurysms.^{4,9,17,21,22,33,34,36,39,43} An estimated 29% of the attributable risk of aneurysmal subarachnoid hemorrhage (SAH) is due to smoking, and smoking cessation decreases the risk of SAH.²¹ Although cigarette smoking has decreased internationally, approximately 17.8% of the adult population in the US are current smokers.³¹

While smoking is a potent risk factor for SAH, the impact of smoking on the outcomes following rupture of cerebral aneurysms is poorly understood. Prior studies have found that smokers sustain rupture at a younger age⁵¹ and have an increased risk of delayed cerebral ischemia.^{18,29,40,51} However, analyses of the association of smoking with outcomes after SAH have reported conflicting results.³⁷ Notably, two studies suggested that nicotine replacement therapy in smokers who sustained aneurysmal SAH was associated with superior outcomes,^{12,45} and this observation has been hypothesized to potentially be attributable to neuroprotective properties of nicotine.

Given the prevalence of smoking, additional data evaluating the association of smoking with outcomes following SAH are needed, which may inform the treatment of ruptured aneurysms. In this study, a national administrative claims database, the Nationwide Inpatient Sample (NIS; Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality), and a prospective registry, the National Surgical Quality Improvement Program (NSQIP), were queried to evaluate the association between smoking and outcomes after SAH. It was hypothesized that due to increased odds of delayed cerebral ischemia, smoking would be associated with higher odds of mortality and poor outcomes.

Methods

Data Source

The NIS was queried from the years 2009–2011. The NIS is the largest all-payer administrative database in the US, is a 20% sample of nonfederal hospitals, and has been extensively used to evaluate the outcomes of patients with SAH.^{5–8,10,11,14,15,20,25–28,30,35,38,41,42,47–50} The year 2009 was the first year included as this was the first year that there were more encoded diagnosis codes (from 15 to 25) for each patient; in 2012, new survey weights were introduced that prohibit variance calculations using combined populations before and after the redesign. Our IRB has determined that studies utilizing the NIS are exempt from individual review.

Inclusion and Exclusion Criteria

Patients were included who 1) had an ICD-9-CM diagnosis of subarachnoid hemorrhage (430) or intracerebral hemorrhage (431, 432.9), 2) underwent microsurgical clipping (39.51) or coil embolization (39.72, 39.75, 39.76, 39.79) of an intracranial aneurysm, 3) were at least 18 years of age, and 4) had a nonelective admis-

sion. Admissions with a diagnosis of a cerebrovascular malformation (747.81) and cerebral arteritis (437.4) or a procedure code of treatment of an arteriovenous malformation surgically (39.53) or by radiosurgery (923.x) were excluded.

Patient Stratification and ICD-9-CM Validation

Patients were stratified by the ICD-9-CM codes for current (305.1) or a personal history of (V15.82) tobacco use. Prior validation studies of patients treated in an outpatient setting have suggested that the combination of these codes is effective at identifying smoking status.⁵²

To validate these ICD-9-CM codes in patients with cerebral aneurysms, those who underwent microsurgical or endovascular cerebral aneurysm repair at our institution between 2009 and 2015 were evaluated. Documented smoking status was compared with recorded ICD-9-CM codes for tobacco use from billing data. This ICD-9-CM code validation was performed after approval from our IRB.

Covariates

Patient age and sex were extracted. The Elixhauser index, which includes drug and alcohol abuse, was used to evaluate comorbidities. However, neurological deficits, paralysis, and electrolyte complications were not included in the comorbidity score given the potential misclassification with SAH and its associated complications. Comorbidities encoded in fewer than 20 patients were also excluded from the total score. Insurance status, race or ethnicity, and hospital characteristics are encoded in the NIS. Socioeconomic status was measured indirectly as the median household income in the patient's ZIP code.

The NIS-SAH severity scale,⁵⁰ an externally validated scale that has been shown to have strong concordance with Hunt and Hess grade, was used for severity adjustment. The score was calculated using published methodology, using the ICD-9-CM diagnosis codes for coma, hydrocephalus, hemiparesis, aphasia, and cranial nerve deficits, as well as ICD-9-CM procedure codes for CSF diversion and mechanical ventilation. Treatment modality selected for aneurysm repair was included as a covariate to partially account for differences in institutional practice and aneurysm location. Additionally, decompressive craniectomy (01.25) and cerebral edema (348.5) were evaluated to partially adjust for documented elevated intracranial pressure.

Outcomes

Outcomes evaluated included in-hospital mortality, complications, and length of hospital stay. Total complications included: neurological (seizures 345.xx, stroke 433.x and 434.x, transient cerebral ischemia [used as an approximation for delayed cerebral ischemia] 435.x, and neurological complications after procedure 997.01, 997.09), cardiac (410.xx, 248.xx, 427.5, 785.xx), pulmonary (514.x, 518.xx, 512.x), renal (584.x), gastrointestinal (578.x, 5601, 00845), venous thromboembolic (453.x, 415.x), hematological (285.x and 998.1x, as well as red blood cell transfusion 94.04), sodium abnormalities (253.5, 253.6, 276.0,

TABLE 1. Demographics of the NIS study population, stratified by cigarette smoking status

Variable	Total Population	Nonsmoker	Former Smoker	Current Smoker	p Value
No. of patients	5784	3636	348	1800	
Mean age in yrs (SD)	54.9 (13.7)	56.2 (14.6)	58.8 (13.2)	51.4 (11.2)	<0.001
Female sex	68.4	71.6	62.4	63.0	<0.001
Race/ethnicity					
Caucasian	48.9	45.1	56.0	55.4	<0.001
African American	13.7	14.2	12.1	13.2	
Hispanic	11.1	13.4	8.6	6.8	
Asian or Other	8.6	9.9	8.1	5.9	
Missing	17.7	17.5	15.2	18.7	
Socioeconomic status					
Lower quartile	27.4	25.5	27.9	31.2	<0.001
2nd quartile	25.7	25.7	23.0	26.3	
3rd quartile	24.6	24.0	26.2	25.5	
Upper quartile	19.5	21.6	21.8	15.0	
Missing	2.7	3.2	1.2	2.1	
Insurance status					
Private	47.3	46.5	49.7	48.4	<0.001
Medicare	24.4	27.8	34.5	15.7	
Medicaid	16.4	15.8	7.2	19.3	
Self pay or other	12.0	10.0	8.6	16.6	
Alcohol abuse	6.7	3.8	5.5	12.7	<0.001
Anemia (deficiency)	20.5	22.0	20.7	17.6	0.001
Arthritis	2.2	2.4	2.3	1.8	0.34
Blood loss anemia	1.4	1.5	1.7	1.1	0.40
CHF	4.8	5.5	5.8	3.3	0.001
Chronic pulmonary disease	12.7	9.1	20.4	18.4	<0.001
Coagulopathy	5.2	5.6	4.0	4.7	0.25
Diabetes mellitus	10.9	12.1	10.6	8.5	<0.001
Diabetes w/ complications	0.9	1.2	0.9	0.3	0.002
Drug abuse	5.7	3.5	3.2	10.6	<0.001
Hypertension	65.3	64.6	69.3	66.0	0.17
Hypothyroidism	6.8	7.1	10.6	5.4	0.001
Liver disease	1.3	1.4	1.4	1.2	0.76
Obesity	7.5	7.3	9.5	7.5	0.34
Peripheral vascular disease	6.2	6.0	5.5	6.7	0.51
Pulmonary hypertension	2.8	3.1	3.7	2.0	0.03
Renal failure	2.6	3.2	3.7	1.3	<0.001
Valvular disease	2.7	3.1	2.9	1.9	0.04
Weight loss	10.5	11.7	8.6	8.4	<0.001
No. of comorbidities					
0	15.3	16.2	13.5	13.7	0.02
1	30.1	30.0	26.4	31.1	
2	27.4	27.9	29.9	26.1	
≥3	27.2	26.0	30.2	29.1	
Mean NIS-SAH Severity Scale score (SD)	6.8 (11.8)	7.5 (12.7)	6.9 (12.5)	5.2 (9.7)	<0.001
Microsurgical clipping	42.1	42.5	33.3	43.1	0.003
Intracerebral hemorrhage	10.5	11.4	11.5	8.4	0.002
Cerebral edema	14.7	16.2	13.5	11.8	<0.001
Craniectomy	1.4	1.8	0.9	0.7	0.003

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TABLE 1. Demographics of the NIS study population, stratified by cigarette smoking status

Variable	Total Population	Nonsmoker	Former Smoker	Current Smoker	p Value
Hospital metropolitan area (population)					
≥1,000,000	59.2	62.1	57.8	53.6	<0.001
250,000–999,999	15.4	15.6	11.8	15.7	
50,000–249,999	8.7	7.4	12.4	10.6	
<50,000	16.8	14.9	18.1	20.2	
Hospital size					
Small/medium	14.5	13.8	17.2	15.5	0.08
Large	85.5	86.2	82.8	84.5	
Teaching hospital	88.4	88.7	90.2	87.6	0.27
Hospital region					
Northeast	16.3	18.4	10.3	13.2	<0.001
Midwest	24.6	20.9	29.0	31.1	
South	33.8	33.3	32.2	35.2	
West	25.4	27.4	28.5	20.6	
Yr of admission					
2009	30.3	31.2	26.4	29.3	0.07
2010	37.0	37.2	35.9	36.7	
2011	32.7	31.5	37.6	34.1	

CHF = congestive heart failure.

All data are presented as percentage except for patient age and NIS-SAH severity scale score. Boldface type indicates statistical significance.

276.1), and infections (595.0, 996.64, 481–486, 507.0, 997.31, 38.x, 995.9x, 320.x, 041.x, 324.1, 790.7, 999.31, and 998.59). The proportion of patients who underwent tracheostomy (311, 312.1, 312.9) and gastrostomy or jejunostomy (431.1, 431.9, 463.2) was evaluated. An extended hospitalization was defined as a hospital stay longer than the upper quartile of the interquartile range of the entire study population. A nonroutine discharge was defined as any discharge other than to home; discharge to institutional care was a designation of a nursing facility, extended care facility, or hospice, but does not include discharge to acute rehabilitation. Analyses of tracheostomy or gastrostomy, length of stay, and discharge disposition were only conducted for patients discharged alive, to distinguish these outcomes from mortality.

Finally, the composite NIS-SAH outcome measure was calculated. This externally validated end point defines a poor outcome based on in-hospital mortality, discharge to institutional care, or tracheostomy or gastrostomy placement, and has been shown to have 95% agreement with a modified Rankin scale score greater than 3.⁵⁰

Missing Data

Patients with missing data for covariates (race/ethnicity and socioeconomic status) were placed in a separate stratum for that variable to maintain the total study population and appropriately account for missing data. Although data on most outcomes including death and nonroutine discharge were available from all states, data are not provided on discharge to institutional care (which is a component of the NIS-SAH outcome measure) for patients from California, Maryland, or Maine. Patients from these states

constituted 12.1% (n = 700) of the patient population and were excluded from analyses of discharge to institutional care or of poor outcome. A sensitivity analysis was performed using multiple imputations for the missing data on discharge status on these patients.

Sensitivity and Subgroup Analyses

A matched-pairs sensitivity analysis was performed after matching current smokers and nonsmokers by age, sex, NIS-SAH severity scale score, and number of comorbidities. An additional sensitivity analysis performed propensity adjustment by evaluating the probability of smoking based on patient demographics and comorbidities, and this propensity score was used as a covariate in regression models. Another sensitivity analysis accounted for the potential misclassification of smoking status based on the calculated classification accuracy of ICD-9-CM coding from our institutional review. Moreover, a subgroup of patients with a poor grade, defined as an NIS-SAH severity scale score in the upper quartile for the entire population, was evaluated. Additional regression constructs analyzed the interaction between smoking and age, sex, or treatment modality for aneurysm repair, as well as between patient age and severity of SAH.

Additional Data Source

To evaluate for consistency with the NIS, data were extracted from the prospective NSQIP registry (2007–2013), which has been previously used to analyze patients with SAH.^{2,46} The NSQIP was exempted from individual review by our IRB. Patients were included who were 1) 18

years of age or older, 2) had an ICD-9-CM diagnosis code for SAH or intracerebral hemorrhage (430, 431, 432.9), and 3) underwent a craniotomy under general anesthesia for clipping of a carotid (CPT codes 61697, 61700, 61703, or 61705) or vertebrobasilar circulation intracranial aneurysm (CPT codes 61698 or 61702) by a neurosurgeon. The NSQIP does not systematically collect data on intracranial endovascular interventions. Patients were stratified by cigarette smoking, which is defined by the NSQIP as having smoked any cigarettes within the past year, and is directly recorded by surgical reviewers, not designated by ICD-9-CM codes.¹

Covariates extracted were patient age, sex, race or ethnicity, American Society of Anesthesiologists (ASA) class, baseline functional status, body habitus, comorbidities (hypertension, cardiac disease, chronic obstructive pulmonary disease [COPD], diabetes mellitus, hyponatremia, and alcohol abuse), endotracheal intubation, case urgency, and operative time. The 30-day outcomes evaluated were mortality, complications, length of hospital stay, reoperation, and discharge disposition. Complications extracted were neurological (cerebrovascular accident, intracranial hemorrhage, or coma), cardiac (cardiac arrest or acute myocardial infarction), extubation failure, prolonged mechanical ventilation, venous thromboembolic, infectious, and packed red blood cell transfusions. Reoperation is defined by the NSQIP as any return to the operating room, including tracheostomy, gastrostomy, or ventricular shunt placement.

Statistical Analyses

Statistical analyses were performed using Stata (version 13, StataCorp LLC) accounting for the survey design of the NIS, with the hospital identification as the sampling unit, the discharge weight as the sampling weight variable, and the NIS stratum as the strata. Descriptive statistics were performed and baseline characteristics were compared using the chi-square test for categorical variables and the ANOVA for continuous variables. Thereafter, multivariable logistic regression models were constructed with all analyzed characteristics as covariates, given their association with SAH outcomes. Conditional logistic regression analyzed the matched analysis, after including matching criteria. Concordance statistics assessed the discrimination of regression constructs. A *p* value < 0.05 was considered significant.

Results

Validation of ICD-9-CM Codes

Among 275 patients with cerebral aneurysms treated at our institution, 39.3% (*n* = 108, 95% CI 33.4%–45.1%) were current smokers and 28.0% (*n* = 77, 95% CI 22.7%–33.3%) had a history of smoking. When evaluating the ICD-9-CM code for current tobacco use, the accuracy was 82.9%, sensitivity 62.6%, specificity 96.4%, positive predictive value 91.8%, and negative predictive value 79.7%. The ICD-9-CM code for a history of tobacco use was less robustly coded: the accuracy was 74.9%, sensitivity 36.3%, specificity 89.9%, positive predictive value 58.3%, and negative predictive value 78.4%.

Demographics of the NIS Population

Within the NIS patient population, 5784 patients were included, and 37.1% (*n* = 2148, 95% confidence interval [CI] 35.9%–38.4%) were documented smokers. Of these patients, 31.1% (*n* = 1800, 95% CI 29.9%–32.3%) had a diagnosis code indicating current tobacco use and 6.0% (*n* = 348, 95% CI 5.4%–6.6%) a history of tobacco use. The demographics of the NIS population are stratified by smoking status in Table 1. The differences in the crude rates of in-hospital mortality, discharge to institutional care, and poor outcome as stratified by cigarette smoking status are shown in Fig. 1.

Multivariable Regression Models

Multivariable logistic regression models evaluating the association of smoking with outcomes are shown in Table 2. Due to differences in patient age, sex, number of comorbidities, and severity of SAH by smoking status, a matched-pairs analysis compared current smokers to nonsmokers after matching on these 4 criteria (Table 2). In both the total population and the matched pair analysis, there was no difference in mortality, total complications, neurological complications, or delayed cerebral ischemia. However, cigarette smoking was associated with decreased odds of a poor outcome in both the total population (odds ratio

FIG. 1. Bar graphs showing differences in the crude rates (and associated errors) of in-hospital mortality, discharge to institutional care, and poor outcome (defined by the NIS-SAH outcome measure) in the total population (A) and the subgroup of poor-grade patients (B), stratified by cigarette smoking status.

TABLE 2. Multivariable logistic regression models evaluating the association of cigarette smoking with outcomes after SAH in the NIS population

Outcome	Total Population					Matched-Pairs Analysis		
	Crude %	OR	95% CI	p Value*	C Statistic	OR	95% CI	p Value*
In-hospital mortality								
Nonsmokers	13.3	Ref	—	—	0.80	Ref	—	—
Former smokers	12.1	0.79	0.52–1.18	0.24		—	—	—
Current smokers	8.8	0.87	0.69–1.09	0.23		1.56	0.75–3.22	0.23
Total complications								
Nonsmokers	84.6	Ref	—	—	0.83	Ref	—	—
Former smokers	82.2	0.80	0.55–1.14	0.22		—	—	—
Current smokers	78.9	0.91	0.77–1.09	0.31		1.36	0.94–1.96	0.10
Neurological complications								
Nonsmokers	34.1	Ref	—	—	0.63	Ref	—	—
Former smokers	32.2	0.95	0.74–1.22	0.67		—	—	—
Current smokers	33.9	1.00	0.85–1.16	0.95		0.96	0.75–1.22	0.71
Delayed cerebral ischemia								
Nonsmokers	14.9	Ref	—	—	0.65	Ref	—	—
Former smokers	16.7	1.15	0.81–1.62	0.44		—	—	—
Current smokers	17.8	1.16	0.95–1.40	0.14		0.85	0.60–1.19	0.33
Gastrostomy or tracheostomy (n = 5100)								
Nonsmokers	22.7	Ref	—	—	0.84	Ref	—	—
Former smokers	13.7	0.54	0.36–0.82	0.004		—	—	—
Current smokers	11.9	0.63	0.51–0.78	<0.001		0.50	0.30–0.86	0.01
Extended hospitalization (n = 5100)*								
Nonsmokers	26.7	Ref	—	—	0.77	Ref	—	—
Former smokers	18.3	0.68	0.49–0.94	0.02		—	—	—
Current smokers	16.2	0.63	0.52–0.76	<0.001		0.47	0.30–0.73	0.001
Nonroutine discharge (n = 5100)								
Nonsmokers	62.0	Ref	—	—	0.81	Ref	—	—
Former smokers	55.6	0.73	0.56–0.95	0.02		—	—	—
Current smokers	47.8	0.76	0.66–0.89	<0.001		0.73	0.53–1.00	0.05
Discharge to institutional care (n = 4487)								
Nonsmokers	21.6	Ref	—	—	0.83	Ref	—	—
Former smokers	17.9	0.73	0.48–1.12	0.15		—	—	—
Current smokers	11.5	0.71	0.57–0.89	0.002		0.24	0.08–0.69	0.008
Poor outcome (by the NIS-SAH outcome measure, n = 5084)								
Nonsmokers	41.1	Ref	—	—	0.85	Ref	—	—
Former smokers	33.3	0.66	0.47–0.94	0.02		—	—	—
Current smokers	24.5	0.65	0.55–0.77	<0.001		0.47	0.30–0.72	0.001

C statistic = concordance statistic; Ref = reference.

All multivariable logistic regression models include characteristics described in Table 1 as covariates, including patient age, sex, race/ethnicity, socioeconomic status, insurance status, comorbidities, NIS-SAH severity scale, and hospital characteristics. In all relevant tables, regression analyses of tracheostomy or gastrostomy placement, length of stay, and discharge disposition ("nonroutine discharge") were only performed for patients discharged from the hospital alive. Boldface type indicates statistical significance.

* In all relevant tables, an extended hospitalization was defined as longer than 24 days, the upper quartile for the entire population.

[OR] 0.65, 95% CI 0.55–0.77, $p < 0.001$) and the matched pair analysis (OR 0.47, 95% CI 0.30–0.72, $p = 0.001$). In a sensitivity analysis in which missing discharge status was imputed, smoking remained associated with lower odds of discharge to institutional care and a poor outcome (data not shown).

Sensitivity and Subgroup Analyses

Given the potential for misclassification of smoking by ICD-9-CM coding, a sensitivity analysis was performed accounting for its sensitivity, specificity, and positive and negative predictive values (calculated from our institutional data). In this analysis, after excluding prior smokers,

TABLE 3. Sensitivity analyses evaluating the association of cigarette smoking with outcomes after SAH in the NIS population

Outcome	ICD-9-CM Codes Sensitivity Analysis			Propensity Score*		
	OR	95% CI	p Value	OR	95% CI	p Value
In-hospital mortality						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.85	0.71–1.02	0.08	0.97	0.87–1.08	0.54
Total complications						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	1.01	0.86–1.19	0.92	0.95	0.88–1.02	0.17
Neurological complications						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	1.01	0.90–1.13	0.87	1.00	0.93–1.09	0.92
Delayed cerebral ischemia						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	1.10	0.94–1.28	0.22	1.07	0.87–1.18	0.18
Gastrostomy or tracheostomy						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.77	0.64–0.92	0.005	0.80	0.30–0.86	0.01
Extended hospitalization						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.77	0.66–0.91	0.002	0.80	0.74–0.88	<0.001
Nonroutine discharge						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.84	0.73–0.96	0.01	0.88	0.82–0.95	0.001
Discharge to institutional care						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.87	0.73–1.05	0.14	0.81	0.73–0.91	<0.001
Poor outcome (by the NIS-SAH outcome measure)						
Nonsmokers	Ref	—	—	Ref	—	—
Current smokers	0.76	0.65–0.89	<0.001	0.81	0.75–0.89	<0.001

The ICD-9-CM codes sensitivity analysis included reclassification of a random set of 148 classified smokers and 738 classified nonsmokers, to mimic the expected distribution of smoking status based on our institutional validation of ICD-9-CM coding for smoking among patients with cerebral aneurysms. These multivariable logistic regression models include characteristics described in Table 1 as covariates, including patient age, sex, race/ethnicity, socioeconomic status, insurance status, comorbidities, NIS-SAH severity scale score, and hospital characteristics. Boldface type indicates statistical significance.

* The propensity-score adjusted sensitivity analysis only included the propensity score as a covariate, which was based on the probability that an individual was a documented smoker based on patient demographics and comorbidities.

smoking was randomly reclassified for 148 documented smokers to nonsmokers and for 738 documented nonsmokers as smokers. This created a sample mimicking the expected distribution of smoking status if the ICD-9-CM codes had perfect classification. In this analysis, smoking remained associated with decreased odds of tracheostomy or gastrostomy placement, an extended hospitalization, nonroutine discharge, and poor outcome (Table 3), suggesting that smoking misclassification alone does not account for the observed statistical differences. An additional sensitivity analysis was performed of outcomes using propensity score adjustment, with similar associations as the primary analysis (Table 3). There is a potential reporting bias, whereby tobacco use may be less robustly documented in poor-grade patients with altered sensorium. Thus, a subgroup analysis was performed exclusively of patients with documented poor grades (Table 4), the results of which were similar to the primary analysis.

Interactions

Additional regression constructs evaluated an interaction between smoking and patient age, sex, or treatment modality used for aneurysm repair in mortality, delayed cerebral ischemia, or poor outcome. No effect measure modification was observed by age or sex. However, after accounting for the interaction of smoking and treatment modality, smoking was associated with decreased odds of in-hospital mortality (OR 0.69, 95% CI 0.50–0.96, $p = 0.03$), increased odds of delayed cerebral ischemia (OR 1.29, 95% CI 1.02–1.64, $p = 0.03$), and decreased odds of a poor outcome (OR 0.53, 95% CI 0.41–0.69, $p = 0.001$). Finally, an interaction between patient age and severity of SAH (using the NIS-SAH severity scale) was considered: while the interaction itself was significant ($p = 0.02$), suggesting a synergistic relationship between age and severity of SAH, the association of smoking with death, delayed

TABLE 4. Multivariable logistic regression evaluating the outcomes of poor-grade patients, stratified by cigarette smoking

Outcome	Crude %	OR	95% CI	p Value	C Statistic
In-hospital mortality (n = 1785)					
Nonsmokers	24.8	Ref	—	—	0.72
Former smokers	28.7	0.97	0.57–1.65	0.92	
Current smokers	23.4	1.08	0.80–1.45	0.62	
Neurological complications (n = 1785)					
Nonsmokers	42.1	Ref	—	—	0.63
Former smokers	38.3	0.86	0.53–1.39	0.53	
Current smokers	45.2	0.98	0.76–1.26	0.85	
Delayed cerebral ischemia (n = 1785)					
Nonsmokers	17.4	Ref	—	—	0.68
Former smokers	16.0	0.86	0.45–1.63	0.65	
Current smokers	22.6	1.20	0.88–1.64	0.24	
Gastrostomy or tracheostomy (n = 1344)					
Nonsmokers	49.5	Ref	—	—	0.71
Former smokers	44.8	0.89	0.52–1.53	0.62	
Current smokers	38.9	0.74	0.58–0.95	0.02	
Extended hospitalization (n = 1344)					
Nonsmokers	52.0	Ref	—	—	0.68
Former smokers	47.8	0.95	0.56–1.61	0.85	
Current smokers	45.9	0.79	0.60–1.05	0.10	
Discharge to institutional care (n = 1168)					
Nonsmokers	38.0	Ref	—	—	0.77
Former smokers	40.4	0.94	0.52–1.70	0.83	
Current smokers	27.7	0.69	0.49–0.96	0.03	
Poor outcome (by the NIS-SAH outcome measure, n = 1550)					
Nonsmokers	69.8	Ref	—	—	0.74
Former smokers	70.7	0.89	0.52–1.52	0.66	
Current smokers	58.9	0.75	0.58–0.96	0.03	

All multivariable logistic regression models include characteristics described in Table 1 as covariates, including patient age, sex, race/ethnicity, socioeconomic status, insurance status, comorbidities, NIS-SAH severity scale, and hospital characteristics. Boldface type indicates statistical significance.

cerebral ischemia, and a poor outcome remained similar to the primary analysis (data not shown).

NSQIP Population

Within the NSQIP population, 373 patients were included, 36.5% (n = 136, 95% CI 31.6%–41.4%) of whom were smokers, and their baseline demographics are compared in Table 5. Similar to the NIS population, smokers were significantly younger and more likely to abuse alcohol. The crude rates of reoperation, nonroutine discharge, and discharge to institutional care were lower for smokers. However, in multivariable analyses (Table 6), these differences were not statistically significant, likely due to the comparatively small sample size of this population.

Discussion

Because cigarette smoke is a mixture of more than 4000 chemicals, the exact mechanisms by which smoking promotes cerebral aneurysm formation remain largely unknown.^{13,19,24} Few studies have evaluated how the outcomes after aneurysmal SAH vary by smoking status. In

a single-institution study, Lasner et al. found that smoking and Fisher Grade 3 were predictors of symptomatic vasospasm.⁴⁰ Likewise, when evaluating 3441 patients from 5 randomized controlled trials, Weir et al. reported that smoking was associated with younger age at rupture and a 1.2 times higher odds of clinical vasospasm; however, mortality and neurological status were not examined.⁵¹ Proberskin reported that younger age and cigarette smoking were protective against mortality after rupture,⁴⁴ hypothesizing that smoking may cause immediate vasospasm and platelet activation, diminishing the initial volume of hemorrhage.⁴⁴ Nonetheless, this study was criticized for not fully accounting for confounding.³² Krishnamurthy et al. found a higher rate of delayed neurological deterioration for smokers, but no difference in Glasgow Outcome Scale (GOS) scores in multivariable models.³⁷

A notable observation from two retrospective studies was that transdermal nicotine replacement after SAH was associated with superior outcomes among smokers. After matching by age, Hunt and Hess grade, and radiographic findings, Seder et al. found that smokers who received nicotine replacement had significantly decreased odds

of death 3 months after rupture, but similar rates of delayed cerebral ischemia, compared with smokers who did not receive nicotine.⁴⁵ Likewise, Carandang et al. found no significant difference in angiographic vasospasm, but lower odds of clinical vasospasm and a poor GOS score among smokers who received nicotine replacement compared with smokers treated without nicotine.¹² Moreover, in an analysis of patients with ischemic stroke enrolled in the “Get With The Guidelines-Stroke” registry, Ali et al. found decreased odds of death for smokers.³

In this study, the NIS administrative claims database and the NSQIP surgical registry were used to evaluate the association of smoking with outcomes after aneurysmal SAH. In both populations, smokers were significantly younger and had increased comorbidities; given the morbidity associated with SAH, this earlier age of rupture highlights the negative ramifications of smoking in patients with cerebral aneurysms. However, in both data sets, smoking was associated with lower crude rates of reoperation, an extended hospitalization, and discharge to institutional care. The magnitude of the difference was comparable between the two data sets in extended hospitalization (NIS 26.7% vs 16.2%, NSQIP 29.3% vs 21.1%), the reduction of reoperation (NIS 22.7% vs 11.9%, NSQIP 20.5% vs 13.0%), and discharge to institutional care (NIS 21.6% vs 11.5%, NSQIP 16.4% vs 10.1%). Additionally, in the NIS population, smoking was associated with decreased adjusted odds of tracheostomy or gastrostomy, discharge to institutional care, and poor outcome in the entire population, the matched-pairs analysis, and the subgroup of poor-grade patients. Although smoking was not associated with delayed cerebral ischemia in the total population, after accounting for the interaction of cigarette smoking and microsurgical clipping, smoking was associated with increased odds of delayed cerebral ischemia. This may partially explain why some prior studies showed that smoking was associated with vasospasm, as these studies were primarily analyzing patients treated surgically; some research has suggested that endovascular treatment is associated with decreased delayed cerebral ischemia,²³ which may be particularly pertinent for smokers.

One possible explanation for the superior outcomes associated with smoking may be due to the neuroprotective effects of nicotine. The impact of nicotine on the cerebral vasculature has been reviewed elsewhere; Carandang et al. concluded from a comprehensive review that nicotine might have antiinflammatory and neurogenic vasodilatory effects that are mediated by nicotinic acetylcholine receptors on intracranial vessels.¹² Nevertheless, this does not necessarily mean that nicotine administration to non-smokers would have clinical benefit, and any underlying pathophysiology cannot be discerned from the present study.

However, the differences in outcomes by smoking status may also be due to bias from study design. One potential source of bias is confounding, including by age, sex, number of comorbidities, or severity of SAH, all of which differed significantly according to smoking status. Due to the possibility of residual confounding, a matched-pairs sensitivity analysis was performed, which had similar statistical associations with the primary analysis. Reporting bias is

TABLE 5. Demographics of the NSQIP study population, stratified by smoking status

Characteristic	Total Population	Smoking Status		p Value
		Smoker	Nonsmoker	
No. of patients	373	136	237	
Mean age in yrs (SD)	54.9 (13.3)	51.9 (10.1)	56.6 (14.6)	0.001
Female sex	71.1	66.9	73.4	0.18
Race/ethnicity				
Caucasian	45.6	48.5	43.9	0.02
African American	14.8	19.9	11.8	
Hispanic	9.7	5.2	12.2	
Asian	7.8	4.4	9.7	
Other or not reported	22.3	22.1	22.4	
Hypertension	46.4	43.4	48.1	0.38
Prior cardiac revascularization				
No	60.1	66.9	56.1	0.11
Yes	3.2	2.2	3.8	
Missing	36.7	30.9	40.1	
COPD	3.5	2.9	3.8	0.66
Diabetes mellitus	9.7	11.0	8.9	0.50
Alcohol abuse				
No	58.2	58.8	57.8	0.001
Yes	5.1	10.3	2.1	
Missing	36.7	30.9	40.1	
Body mass index				
Non-obese	56.6	64.7	51.9	0.11
Obese	23.1	17.7	26.2	
Morbidly obese	6.4	5.9	6.8	
Missing	13.9	11.8	15.2	
ASA physical status class				
1 or 2	8.3	5.9	9.7	0.32
3	34.9	38.2	32.9	
4 or 5	56.8	55.9	57.4	
Functional status				
Independent	78.3	79.4	77.6	0.97
Dependent	20.9	21.5	19.9	
Missing	0.8	0.7	0.8	
Carotid circulation aneurysm	83.7	85.3	82.7	0.51
Preop ventilation	30.6	24.3	34.2	0.045
Preop sodium (mEq/L)				
≥135	84.2	82.4	85.2	0.76
<135	12.6	14.0	11.8	
Missing	3.2	3.7	3.0	
Emergency op	60.6	55.9	63.3	0.16
Op time (mins)				
<270	52.8	51.5	53.6	0.53
270–330	21.2	24.3	19.4	
>330	26.0	24.3	27.0	

All data are presented as percentages, with the exception of patient age. Boldface type indicates statistical significance.

TABLE 6. Multivariable logistic regression models evaluating the outcomes of the NSQIP patient population, stratified by smoking status

Variable	Crude %		OR	95% CI	p Value	C Statistic
	Nonsmokers	Smokers				
30-day mortality	13.5	9.6	0.66	0.27–1.62	0.37	0.88
Any complication	56.1	48.5	0.81	0.48–1.38	0.44	0.80
Reop (n = 328)	20.5	13.0	0.67	0.31–1.41	0.29	0.78
Extended hospitalization (n = 328)	29.3	21.1	0.77	0.42–1.42	0.41	0.75
Nonroutine discharge (n = 214)	52.6	36.4	0.58	0.27–1.26	0.17	0.82
Discharge to institutional care (n = 214)	16.1	10.4	0.78	0.25–2.45	0.67	0.82

All multivariable logistic regression models include baseline characteristics described in Table 4 as covariates. Data on discharge disposition were only available from 2011 to 2014.

an additional concern: smoking may be less robustly documented in patients with poor grade and altered sensorium, spuriously causing smoking to appear to be associated with superior outcomes.³² Therefore, a subgroup analysis was performed exclusively of patients with a documented poor grade, in which smoking remained associated with decreased odds of tracheostomy or gastrostomy and of a poor outcome.

There are many limitations of this study. First, clinical data were recorded in the NIS using ICD-9-CM indicators. The prevalence of tobacco use was similar in the two data sets: 37.1% in the NIS population (of whom 31.1% were current smokers) and 36.5% in the NSQIP population (where smoking is encoded directly by surgical reviewers and not through ICD-9-CM codes). Our institutional validation showed relatively high accuracy and positive and negative predictive values for the ICD-9-CM code for current tobacco use; encoding of a history of tobacco use was less robust. While the prevalence of smoking has decreased in the US, tobacco use may be undercoded in the NIS. However, a sensitivity analysis showed that misclassification of smoking status did not explain the observed significant effect estimates.

Moreover, data were not available on the duration or dose of cigarette smoking. While severity adjustment was performed using the externally validated NIS-SAH severity scale, other clinical variables not encoded through ICD-9-CM identifiers could not be evaluated, including Hunt and Hess grade, World Federation of Neurological Surgeons scale grade, Fisher grade, aneurysm size, and location. Additionally, a nuanced assessment of delayed cerebral ischemia was not possible, as ICD-9-CM identifiers do not distinguish between radiographic vasospasm, delayed cerebral ischemia, and delayed ischemic neurological deficit. Also, long-term data were not available.

However, there are many advantages to the use of large data sets to evaluate the association of cigarette smoking with outcomes after SAH. Both the NIS and NSQIP accrue patients from across the US, providing a broad perspective. The NIS includes several demographics, such as insurance status, race/ethnicity, and socioeconomic status, as well as comorbidities (including drug and alcohol abuse and hypertension) that may confound the association of cigarette smoking with outcomes and were included as covariates in multivariable analyses. Finally, the large sample size of the NIS provides greater statistical power to

evaluate more subtle associations that may not be detected with smaller populations.

Conclusions

In this nationwide analysis, the association of cigarette smoking with outcomes after SAH was evaluated. Smoking was associated with a younger age of rupture and increased number of comorbidities, highlighting the negative impact of smoking in patients with cerebral aneurysms. However, cigarette smoking was also associated with paradoxically superior outcomes on many measures, including reduced odds of a poor outcome in the entire population and in poor-grade patients. These data, along with two recent studies showing that nicotine replacement therapy among smokers who sustain SAH was associated with superior outcomes, suggests that further research, including prospective studies, are needed to confirm these findings and further elucidate the underlying pathophysiology.

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Disclosures

Dr. Ali Aziz-Sultan reports being a consultant for Covidien and Codman. Dr. Gormley reports being a consultant for Codman.

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Conception and design: Du, Dasenbrock. Acquisition of data: Dasenbrock, Rudy, Lai. Analysis and interpretation of data: Dasenbrock, Rudy. Drafting the article: Dasenbrock, Rudy. Critically revising the article: Du, Dasenbrock, Smith, Frerichs, Gormley, Aziz-Sultan. Reviewed submitted version of manuscript: Du, Dasenbrock, Smith, Frerichs, Gormley, Aziz-Sultan. Approved the final version of the manuscript on behalf of all authors: Du. Statistical analysis: Dasenbrock. Study supervision: Du.

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