Long-Term Risk of Ischemic Stroke among Elderly Survivors of Non-Traumatic Subarachnoid Hemorrhage

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Keywords
Subarachnoid hemorrhage · Ischemic stroke · Outcomes

Abstract
Introduction: Non-traumatic subarachnoid hemorrhage (SAH) is associated with poor long-term functional outcomes, but the risk of ischemic stroke among SAH survivors is poorly understood. Objectives: The aim of this study was to evaluate the risk of ischemic stroke among survivors of SAH. Methods: We performed a retrospective cohort study using claims data from Medicare beneficiaries from 2008 to 2015. The exposure was a diagnosis of SAH, while the outcome was an acute ischemic stroke, both identified using previously validated ICD-9-CM diagnosis codes. We used Cox regression analysis adjusting for demographics and stroke risk factors to evaluate the association between SAH and long-term risk of ischemic stroke. Results: Among 1.7 million Medicare beneficiaries, 912 were hospitalized with non-traumatic SAH. During a median follow-up of 5.2 years (IQR, 2.7–6.7), the cumulative incidence of ischemic stroke was 22 per 1,000 patients per year among patients with SAH, and 7 per 1,000 patients per year in those without SAH. In adjusted Cox models, SAH was associated with an increased risk of ischemic stroke (HR, 2.0; 95% confidence interval, 1.4–2.8) as compared to beneficiaries without SAH. Similar results were obtained in sensitivity analyses, when treating death as a competing risk (sub HR, 3.0; 95% CI, 2.8–3.3) and after excluding ischemic stroke within 30 days of SAH discharge (HR, 1.5; 95% CI, 1.1–2.3). Conclusions: In a large, heterogeneous national cohort of elderly patients, survivors of SAH had double the long-term risk of ischemic stroke. SAH survivors should be closely monitored and risk stratified for ischemic stroke.

Introduction
Non-traumatic subarachnoid hemorrhage (SAH) is associated with high in-hospital mortality and morbidity [1, 2]. A significant proportion of patients who survive an SAH admission continue to have long-term functional and cognitive disability [3, 4]. Cerebral infarction, often attributable to procedural complications related to aneurysm treatment, delayed cerebral ischemia, or cardiac complications such as takotsubo car-
diomyopathy [5, 6], and occurring during the initial hospitalization, is one such factor contributing independently to the mortality and poor functional outcomes in SAH patients [7].

The crude global incidence of SAH has declined over 2 decades, while there has been an increase in SAH incidence in patients over 75 years of age, mainly among women [8]. Moreover, the mortality of SAH has also steadily trended down [1, 9], implying these patients are likely to survive longer after SAH. Several prior studies have suggested that within the first year, survivors of SAH are burdened with myocardial infarction and higher cardiovascular mortality, compared to the general population [2, 10–12]. Whether the risk of ischemic stroke is similarly increased after the initial hospitalization for SAH, particularly in the elderly population is poorly understood. We therefore sought to study the long-term risk of ischemic stroke after SAH using a large, nationally representative sample of Medicare beneficiaries.

Methods

Study Design

We performed a retrospective cohort study using data of both inpatient and outpatient claims on a 5% sample of Medicare beneficiaries. The United States (U.S.) CMS provides health insurance information to a majority of U.S. citizens aged 65 years and older [13]. The CMS provides de-identified claim-based datasets submitted by hospitals and providers. Longitudinal analysis of the care of each beneficiary over time was possible due to a unique and anonymous identifier code linking multiple claims for a patient. The Weill Cornell Medicine institutional review board approved this study.

Patient Population

Data were obtained from inpatient and outpatient claims of Medicare beneficiaries between January 2008 and September 2015. We limited our cohort to beneficiaries with continuous coverage in traditional CMS fee-for-service Medicare (Parts A and B) for at least 1 year or until death to keep within the standard practice of analyzing Medicare data. Although Medicare eligibility begins at 65 years of age, only patients aged 66 years or older were included in our study to allow time for beneficiaries to enter medical care and for their providers to document any preexisting medical comorbidities.

Measurements

The exposure was non-traumatic SAH, which is identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code 430.x in any diagnostic position. The code for SAH has a sensitivity of over 90% and a specificity of 96%, when compared with medical record review [14, 15]. Patients with any diagnosis code for trauma were excluded. To identify the underlying cause of non-traumatic SAH, we used ICD-9-CM diagnosis codes to delineate the etiology. These included intracranial aneurysm (437.3), arteriovenous malformation (747.81), and Moyamoya disease (735.5) [16, 17]. We also excluded patients with prevalent SAH or ischemic stroke at the time of enrollment into the Medicare registry, to prevent misclassification of chronic events. Additionally, we did not include patients who had an ischemic stroke concurrently with the SAH hospitalization, given difficulty in establishing which occurred earlier, and consequently, to prevent inclusion of patients who had SAH as a complication of thrombolysis or mechanical thrombectomy for stroke. Furthermore, we only counted the first admission for SAH, since some patients with multiple intracranial aneurysms may experience repeated SAH episodes.

Information on cardiovascular risk factors and relevant comorbidities were collected using previous ICD-9-CM code algorithms: hypertension, diabetes, tobacco use, alcohol use, atrial fibrillation, cardiac valve disease, chronic kidney disease, and peripheral vascular disease. The burden of comorbidities was quantified using the Charlson Comorbidity Index [18, 19], which is a weighted score of 17 comorbidities identified through ICD-9-CM codes, has been used in previous studies using administrative data to adjust for illness burden [20, 21]. The cardiovascular comorbidities have been shown to have good agreement compared with chart review, and are accurate in assessing the risk of stroke [22, 23]. The primary outcome was an incident acute ischemic stroke, which was identified using the ICD-9-CM code 430, 433.x1, 434.x1, and 436. The diagnosis codes for ischemic stroke have a sensitivity of 86% and specificity of 95% [14, 24].

Statistical Analysis

Baseline characteristics were analyzed using Pearson χ2 test for categorical variables, and the Student’s t test for continuous variables. We used Cox regression analysis to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between SAH and ischemic stroke. To ensure that the proportional hazards assumption was met, we performed visual inspection using log-log plots. Participants were followed through until death, outcome, or the last available follow-up. The covariates in the Cox models were chosen a priori, and they included age, sex, race, vascular risk factors including hypertension, diabetes mellitus, atrial fibrillation, valvular heart disease, chronic kidney disease, alcohol and tobacco use, and Charlson comorbidities. These covariates were chosen regardless of their significance level in univariate analyses, as has been done in prior studies [25, 26]. We performed 3 sensitivity analyses. First, we performed a survival analysis treating death as a competing risk. In the second analysis, we excluded all ischemic strokes that occurred in the first 30 days after discharge for an index SAH hospitalization. This conservative step was done to decrease errors from carrying forward any ischemic strokes that occurred due to procedural complications or vasospasm during the index hospitalization for SAH. Third, we excluded beneficiaries with atrial fibrillation and valvular heart disease since these conditions are independent stroke risk factors and this subset of patients are likely to be on antithrombotic therapy, which was not available in the dataset. The covariates in the in the sensitivity analyses were similar to those in the primary analysis. Statistical analyses were performed using Stata (StataCorp, Statistical Software, Release 15, College Station, TX, USA, StataCorp 2019). The threshold for statistical significance was p < 0.05.
Results

Study Population
There were a total of 1.8 million Medicare beneficiaries, of whom we excluded 68,292 (3.8%) with prevalent stroke. Among the 1.7 million beneficiaries, 912 (0.05%) were hospitalized with SAH. The causes of SAH were intracranial aneurysms \( (n = 606, 66.5\%) \), arteriovenous malformations \( (n = 37, 4.1\%) \), and Moyamoya disease \( (n = 2, 0.2\%) \). Patients with SAH were older (77.2 vs. 73.3 years), predominantly women (61%), and had higher prevalent vascular comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, valvular heart disease, alcohol use, tobacco use, and chronic kidney disease (Table 1).

Primary Outcome
During a median follow-up of 5.2 years (interquartile range [IQR], 2.7–6.7), the cumulative incidence of ischemic stroke was 22 per 1,000 patients per year among patients with SAH, and 7 per 1,000 patients per year in those without SAH. In the unadjusted Cox regression analysis, SAH was associated with an increased risk of ischemic stroke (HR, 3.4; 95% CI, 2.5–4.8) (Fig. 1). After adjustment for demographics, vascular risk factors, and Charlson comorbidity index, SAH was associated with an increased risk of ischemic stroke (HR, 2.0; 95% CI, 1.4–2.8) as compared to beneficiaries without SAH (Table 2). We also noted an increased risk of subsequent hemorrhagic stroke after SAH (HR, 6.8; 95% CI, 4.6–10.2).

Sensitivity Analysis
In prespecified sensitivity analyses, SAH was associated with an increased risk of ischemic stroke when treating death as a competing risk (sub HR, 2.0; 95% CI, 1.4–2.8) as compared to beneficiaries without SAH (Table 2). We also noted an increased risk of subsequent hemorrhagic stroke after SAH (HR, 6.8; 95% CI, 4.6–10.2).

Post hoc Analysis
Given the differences in baseline characteristics of beneficiaries with and without SAH, we performed a propensity score analysis, where participants were matched on age, sex, race, hypertension, diabetes mellitus, and atrial fibrillation. All 912 patients with SAH were matched with controls based on the propensity score using 1:1 matching. A univariate Cox proportional hazards model was then fitted using the matched sample. Robust variance estimator was used to account for the clustering within matched sets. In the final analytical cohort, SAH was independently associated with an increased risk of ischemic stroke (HR, 2.0; 95% CI, 1.3–3.0).

Table 1. Characteristics of patients stratified by presence of subarachnoid hemorrhage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAH ( (N = 912) )</th>
<th>No SAH ( (N = 1,751,791) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>77.2 (7.7)</td>
<td>73.3 (7.7)</td>
</tr>
<tr>
<td>Female</td>
<td>554 (61)</td>
<td>998,807 (57)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>764 (84)</td>
<td>1,507,729 (86)</td>
</tr>
<tr>
<td>Black</td>
<td>76 (8)</td>
<td>137,363 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>72 (8)</td>
<td>106,699 (6)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter flu</td>
<td>256 (28)</td>
<td>135,810 (8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>831 (91)</td>
<td>973,048 (56)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>411 (45)</td>
<td>406,282 (23)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>269 (30)</td>
<td>122,315 (7)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>197 (22)</td>
<td>95,844 (5)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>293 (32)</td>
<td>205,654 (12)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>222 (24)</td>
<td>124,981 (7)</td>
</tr>
</tbody>
</table>

SAH, subarachnoid hemorrhage; SD, standard deviation. Data are presented as \( n (\%) \) unless otherwise specified.

Fig. 1. Kaplan-Meier survival analysis showing the risk of an ischemic stroke after subarachnoid hemorrhage. SAH, subarachnoid hemorrhage.
Discussion

In a large, heterogeneous cohort of Medicare beneficiaries, we observed a 2-fold heightened long-term risk of ischemic stroke after SAH compared to those without. The risk was similarly elevated after excluding SAH patients who had an ischemic stroke in the first 30 days after SAH discharge.

Several prior studies have evaluated the risk of major cardiovascular complications after SAH. In a Danish nationwide cohort study, a higher incidence of cardiovascular disease and death was observed in SAH patients than in the general population [11]. However, little is known about the cerebrovascular complications after SAH discharge. In this context, our study provides a novel finding of an elevated risk of ischemic stroke among SAH survivors.

From a pathophysiologic standpoint, the risk of ischemic stroke after SAH may be attributed to shared vascular risk factors, mainly hypertension and smoking, and other mechanisms such as cessation of antithrombotic medications or a systemic inflammatory response that occurs after SAH [8, 27, 28]. In fact, troponin elevation in the acute phase of SAH predicts cardiovascular events in the first year, suggesting a potential underlying role of myocardial injury [29, 30]. Additionally, takotsubo or stress cardiomyopathy, an acute complication of SAH is independently associated with ischemic stroke, myocardial infarction, and vascular death, as late as 10 years after diagnosis, further bolstering the early myocardial injury hypothesis [5, 31]. A noteworthy finding in our study was the heightened risk of subsequent hemorrhagic stroke after SAH, highlighting the need to carefully assess the risk-benefit ratio of secondary stroke prevention therapies. Since many patients with SAH have multiple aneurysms, these may play a role in future hemorrhagic stroke events. Larger prospective studies are therefore needed to further explore mechanisms of ischemic stroke after SAH, and potential prevention strategies.

Our study has several important limitations. First, our study may have been subject to surveillance bias as patients with SAH are more likely to undergo serial work up and neuroimaging resulting in a higher incidence of ischemic stroke. Second, inclusion of patients over 66 years likely limited the generalizability of our results to the general population. Third, the use of claims data is subject to errors in misclassification of events and diagnostic codes. For example, SAH may have been misclassified as “stroke” in subsequent hospitalizations. However, the ICD-9-CM codes for SAH and ischemic stroke used in this study have been validated to have high sensitivity and specificity [24]. Furthermore, our results were similar after a 30-day washout period that ensured that only new ischemic stroke events were captured in the analysis. Fourth, while we did not obtain information on aneurysm treatment procedures such as clipping or endovascular coiling; this likely did not influence our findings particularly because these procedures tend to increase the risk of stroke intra- or perioperatively, and not long-term after the index SAH [32, 33]. Information on medications often used for secondary stroke prevention such as antithrombotic, lipid lowering, and antihypertensive therapy were not available. Nevertheless, these medications are known to reduce the risk of ischemic stroke, and this risk was there-

<table>
<thead>
<tr>
<th>Cox regression models</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary unadjusted analysis(^1) (entire cohort)</td>
<td>3.4 (2.5–4.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary adjusted analysis(^1) (entire cohort)</td>
<td>2.0 (1.4–2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensitivity analyses</td>
<td></td>
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<tr>
<td>Competing risk analysis(^2)</td>
<td>3.0 (2.8–3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exclusion of events in first 30 days(^1)</td>
<td>1.5 (1.1–2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exclusion of beneficiaries with atrial fibrillation and valvular heart disease(^1)</td>
<td>1.7 (1.1–3.0)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Propensity score analysis(^3)</td>
<td>2.0 (1.3–3.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) Models adjusted for age, sex, race, hypertension, diabetes mellitus, atrial fibrillation, valvular heart disease, chronic kidney disease, alcohol use, tobacco use, and Charlson comorbidities. \(^2\) Death was treated as competing risk. Sub-hazard ratios were calculated. \(^3\) Propensity score analysis where subjects were matched on age, sex, race, hypertension, diabetes mellitus, and atrial fibrillation.
fore presumably underestimated in our analysis. Finally, we did not have information on SAH severity like the Hunt-Hess score or the modified Fisher Scale score.

Conclusion

In a large, heterogeneous sample of Medicare beneficiaries, SAH was independently associated with an increased risk of ischemic stroke. This finding warrants further study to better delineate the risk and identify optimal prevention strategies in this high-risk group of SAH patients.

Acknowledgment

The authors are grateful to Kelsey Lansdale for her editing and clerical assistance.

Statement of Ethics

The Center for Medicare Services CMS provides de-identified claim-based datasets submitted by hospitals and providers. The Weill Cornell Medicine institutional review board approved the study and waived the requirement for informed consent (reference number: 1507016424).

Conflict of Interest Statement

A.M. is supported by the NIH (grant KL2TR002385), the American Heart Association (18CDA34110419), and the Leon Levy Foundation. Bard reports grants from Hyperfine, Biogen, and Astrocyte unrelated to this work. B.B.N. is supported by the NIH (K23NS091395) and the Florence Gould Endowment for Discovery in Stroke. H.K. is supported by the NIH (U01NS095869 and R01NS097443) and the Michael Goldberg Research Fund; serves as a member of the data and safety monitoring board for the Patient-Centered Outcomes Research Institute (PCORI)-funded Transapetal versus Retrograde Aortic Ventricular Entry to Reduce Systemic Emboli (TRAVERSE) trial; and has received personal fees for medicolegal consulting on stroke. HK reports serving as co-PI for the NIH-funded ARCADIA trial (NINDS U01NS095869) which receives in-kind study drug from the BMS-Pfizer Alliance for Eliquis® and ancillary study support from Roche Diagnostics, serving as Deputy Editor for JAMA Neurology, serving as a steering committee member of Medtronic’s Stroke AF trial (uncompensated), serving on an end point adjudication committee for a trial of empagliflozin for Boehringer-Ingelheim, and having served on an advisory board for Roivant Sciences related to Factor XI inhibition. All remaining authors declare no competing interests.

Data Availability Statement

The claims data used in this analysis are restricted per the terms of Medicare’s data use agreement and therefore cannot be shared directly with other investigators. However, investigators can obtain access to these data by application to the Centers of Medicare and Medicaid Services (CMS).

References