Association between cirrhosis and aneurysmal subarachnoid hemorrhage

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Abstract

Objective: Cirrhosis has been associated with nontraumatic subarachnoid hemorrhage (SAH). We sought to evaluate the specific association between cirrhosis and aneurysmal SAH. Methods: We performed a retrospective cohort study using a sample of Medicare claims data from 2008 to 2015. Cirrhosis was defined using a validated ICD-9-CM diagnosis code algorithm. Nontraumatic SAH was identified using a validated approach requiring an inpatient claim for its ICD-9-CM diagnosis code. Additionally, we required the presence of an ICD-9-CM procedure code reflecting treatment of a cerebral aneurysm during the same hospitalization to ensure ascertainment of aneurysmal SAH specifically. We used survival statistics to calculate incidence rates and Cox proportional hazards models to evaluate the association between cirrhosis and aneurysmal SAH after adjustment for demographics, stroke risk factors, and comorbidities. Results: We identified 10,658 (0.6%) patients with cirrhosis from among the 1,778,604 beneficiaries in our sample. The mean age of patients with cirrhosis was 73.5 (±7.8) years, and 48% were female. Over a mean of 4.7 (±2.1) years of follow-up, 4,272 patients were hospitalized with aneurysmal SAH. The annual incidence of aneurysmal SAH in patients with cirrhosis was 0.12% (95% confidence interval [CI], 0.08–0.17%) compared to 0.05% (95% CI, 0.05–0.05%) in patients without cirrhosis. In the adjusted model, cirrhosis was independently associated with aneurysmal SAH (hazard ratio, 2.2; 95% confidence interval, 1.5–3.4). Interpretation: Cirrhosis was independently associated with an increased risk of aneurysmal SAH among older individuals. Confirmation of these findings may yield opportunities for risk stratification and prevention.

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) accounts for approximately 4% of strokes in the United States and is associated with substantial morbidity and mortality. Established modifiable risk factors for aneurysmal SAH include hypertension, smoking, and excessive alcohol consumption. In recent studies, we and others have found that chronic liver disease, particularly cirrhosis, is associated with an increased risk of hemorrhagic stroke, including nontraumatic subarachnoid hemorrhage. This raises the possibility that cirrhosis is an independent risk factor for aneurysmal SAH. Cirrhosis has been associated with vascular malformations in the pulmonary circulation, and abnormal vascular tone in other vascular beds. Mechanisms for aneurysm formation and rupture in patients with chronic liver disease may include vascular inflammation, endothelial cell dysfunction, and changes in levels of cellular adhesion molecules that mediate leukocyte adhesion to vascular endothelium. To our knowledge, the association between cirrhosis and aneurysmal SAH has not been previously studied. Therefore, in this follow-up study, we hypothesized that cirrhosis is associated specifically with aneurysmal SAH in a population-based cohort of older Americans.

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Methods

Study design

We performed a retrospective cohort study of a 5% sample of Medicare beneficiaries using inpatient and outpatient claims from 2008 to 2015. The Centers for Medicare and Medicaid Services provides health insurance to individuals 65 years of age and older in the United States. Beneficiaries’ claims from inpatient and outpatient encounters are available in a de-identified form for research purposes; anonymous identifiers facilitate longitudinal analyses. Claims data include up to 25 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes and six ICD-9-CM inpatient procedure codes for each encounter. We adhered to guidelines for research using administrative claims data. This study was approved by the Weill Cornell Medicine institutional review board and was performed in accordance with the ethical standards set forth by the Declaration of Helsinki.

Patient population

As in prior studies, we limited our cohort to beneficiaries with at least 1 year of continuous Medicare coverage (both Part A and B). Additionally, we included only beneficiaries after 1 year of coverage eligibility. These measures were taken to facilitate longitudinal analyses and to allow time for beneficiaries’ files to accrue data regarding baseline comorbidities. Individuals with a prior history of aneurysmal SAH, based on any claims for subarachnoid hemorrhage (ICD-9-CM diagnosis code 430) during this year, were excluded. No additional inclusion or exclusion criteria were applied.

Measurements

Our primary exposure was cirrhosis. Cirrhosis was ascertained using a previously validated ICD-9-CM diagnosis code algorithm that requires the presence of at least one ICD-9-CM inpatient or outpatient claim for cirrhosis or its complications. We slightly modified the original approach by excluding the low-specificity code for ascites and requiring at least two claims whenever cirrhosis or its complications were defined by outpatient encounter data alone. The specific codes included were: 571.2, 571.5, 572.2, 572.3, 572.4, 456.0, 456.1, 456.20, 456.21, and 567.23. The original approach has 67% sensitivity and 88% positive predictive value for identifying cirrhosis. The specificity of the individual codes used for cirrhosis ranges from 68% to 99%. Administrative claims data have been used to identify patients with liver cirrhosis with good reliability in multiple additional settings. We did not include patients with biliary cirrhosis because of the diagnosis code’s low specificity. In a prespecified sensitivity analysis, we removed the code for alcohol-related cirrhosis (571.2) from this algorithm to reduce the influence of alcohol abuse on our results.

For a prespecified secondary analysis, mild, noncirrhotic chronic liver disease was defined using a modified coding schema created for the Charlson Comorbidity Index. After excluding acute liver disease and cirrhosis, the following codes were included: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 571.0, 571.3, 571.4, 571.8, 571.9, 573.3, 573.8, and 573.9. We chose these codes to identify individuals with chronic infectious hepatitis, noninfectious chronic liver disorders such as nonalcoholic fatty liver disease, and other chronic conditions. The original schema has been validated to have positive predictive value of 80.2% and specificity of 99.5% for mild liver disease as compared to expert chart review.

The outcome was hospital admission for aneurysmal SAH, which was defined using a combination of diagnosis and procedure codes. The ICD-9-CM diagnosis code algorithm for broadly identifying nontraumatic SAH required an inpatient claim for ICD-9-CM diagnosis code 430 for nontraumatic SAH in the absence of codes for trauma or rehabilitation. This algorithm has been found to be 98% sensitive and 92% specific for nontraumatic SAH. We further required that an ICD-9-CM procedure code for endovascular or surgical treatment of a cerebral aneurysm be present in the claim for the same hospitalization. The surgical treatment procedure code was 39.51. The endovascular treatment procedure codes were 39.52, 39.72, 39.75, 39.76, and 39.79. This approach has been used to identify patients with aneurysmal SAH in administrative data. Hospital discharge procedure codes have high face validity and have been shown to be important for strategies that seek to more accurately identify aneurysmal SAH.

In addition to demographic variables, covariates included stroke risk factors and medical comorbidities. Stroke risk factors were: hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure, valvular disease, peripheral vascular disease, chronic kidney disease, chronic obstructive pulmonary disease, alcohol abuse, and tobacco use. We chose to conservatively include all stroke risk factors, and not only SAH risk factors, to account for overall differences in health status between individuals with and without cirrhosis. The additional medical comorbidities were included from the Charlson Comorbidity Index: dementia, pulmonary disease, rheumatologic disease, peptic ulcer disease, cancer, metastatic cancer, and acquired immunodeficiency syndrome. This strategy was used to
further adjust for potential confounders related to between-group differences in overall health status.24

Statistical analyses

Baseline characteristics were compared using the chi-squared test and the t-test, as appropriate. Survival statistics were used to calculate crude incidence rates with exact 95% confidence intervals (CI) and cumulative incidence functions were used to present cumulative rates. Beneficiaries entered observation after 1 year of continuous Medicare enrollment and were censored at the time of death, loss of Medicare coverage, or on 31 December 2015. Cox proportional hazards models were used to evaluate the association between exposures and aneurysmal SAH while adjusting for demographic variables, stroke risk factors, and medical comorbidities. All covariates were included in regression models regardless of significance at the univariate level. The threshold of statistical significance was set at \( \alpha = 0.05 \). Statistical analyses were performed by HK using Stata/MP version 14 (College Station, TX).

Results

Among the 1,778,604 beneficiaries in our sample, we identified 10,658 (0.60%) individuals with cirrhosis. The mean age of individuals with cirrhosis was 73.5 (±7.8) years. Individuals with cirrhosis were more frequently male and had higher rates of stroke risk factors and medical comorbidities (Table 1).

Over a mean follow-up of 4.7 (±2.1) years, 4272 patients were hospitalized with aneurysmal SAH. Of these, 23 patients had cirrhosis and 4249 did not. The annual incidence of aneurysmal SAH was 0.12% (95% CI, 0.08–0.17%) in individuals with cirrhosis and 0.05% (95% CI, 0.05–0.05%) in those without cirrhosis (Fig. 1). In univariate analysis, cirrhosis was associated with aneurysmal SAH (hazard ratio [HR], 2.52; 95% confidence interval [CI], 1.67–3.80).

After adjustment for demographics and stroke risk factors, individuals with cirrhosis had a higher risk of aneurysmal SAH (HR, 2.1; 95% CI, 1.4–3.1). Results were similar after additional adjustment for medical comorbidities (HR, 2.3; 95% CI, 1.5–3.4). The HR for select covariates are provided in Table 2 for comparison. The results of a sensitivity analysis excluding individuals with alcohol-related cirrhosis were similar to the primary analysis (HR, 2.4; 95% CI, 1.5–3.6).

In a secondary analysis, we identified 20,081 individuals with noncirrhotic chronic liver disease. The incidence of aneurysmal SAH in this group was 0.07% (95% CI, 0.05–1.0%) per year. In the most adjusted model, individuals with noncirrhotic chronic liver disease had a nonsignificantly increased risk of aneurysmal SAH (HR, 1.4; 95% CI, 1.0–2.0; \( P = 0.08 \)).

Discussion

In this analysis of older Americans, cirrhosis was associated with an increased risk of aneurysmal SAH. Individuals with milder forms of liver disease had a nonsignificantly increased risk of aneurysmal SAH, and the magnitude of the association appeared attenuated.

Our findings are consistent with multiple prior studies that demonstrated an increased risk of hemorrhagic stroke among individuals with cirrhosis.4,5,25 Additionally, these findings build on our prior work5 in which we observed an increased risk of nontraumatic SAH, but not specifically aneurysmal SAH, among Medicare beneficiaries. These studies included nontraumatic SAH in composite hemorrhagic stroke outcomes and did not use stringent criteria to identify aneurysmal SAH. To our knowledge, this is the first study that sought to determine whether cirrhosis is associated specifically with aneurysmal SAH using a population-based sample and a stringent outcome definition.

Table 1. Characteristics of patients, stratified by liver cirrhosis.

| Characteristic1 | Liver cirrhosis (N = 10,658) | No liver cirrhosis (N = 1,767,946) |
|----------------|------------------------------|------------------------------------|
| Age, mean (SD), year | 73.2 (6.5) | 73.5 (7.8) |
| Female | 5114 (48) | 1,009,622 (57) |
| Race2 | | |
| White | 8980 (84) | 1,522,149 (86) |
| Black | 707 (7) | 139,636 (8) |
| Other | 971 (9) | 106,161 (6) |
| Hypertension | 7791 (73) | 922,875 (52) |
| Diabetes | 5323 (50) | 374,113 (21) |
| Atrial fibrillation | 1924 (18) | 135,606 (8) |
| Coronary heart disease | 3217 (30) | 307,908 (17) |
| Peripheral vascular disease | 1443 (14) | 113,429 (6) |
| Congestive heart failure | 2357 (22) | 114,786 (6) |
| Valvular disease | 1561 (15) | 114,187 (6) |
| Chronic kidney disease | 2026 (19) | 87,557 (5) |
| Chronic pulmonary disease | 2408 (23) | 190,385 (11) |
| Alcohol abuse | 1740 (16) | 47,324 (3) |
| Tobacco use | 820 (8) | 24,850 (1) |

SD, standard deviation.
1Data are presented as number (%) unless otherwise specified.
2As reported by patients or their surrogates.
These results raise the possibility that cirrhosis is an independent risk factor for aneurysmal SAH. Indeed, increased liver fibrosis – a precursor to cirrhosis – has been associated with cerebral small vessel disease as evidenced by microhemorrhages detected on magnetic resonance imaging. Further, cirrhosis is associated with abnormal systemic vascular tone and microscopic and macroscopic vascular malformations in the pulmonary circulation. Last, cirrhosis-associated coagulopathy may be implicated because pharmacologically induced coagulopathy has been associated with SAH. Alternatively, although we adjusted for alcohol abuse and our results were unchanged when excluding individuals with alcohol-related cirrhosis, the observed association may be due to residual confounding by unmeasured alcohol abuse, a suspected risk factor for aneurysmal SAH. However, we do not suspect this to be the case because the prevalence of alcohol abuse among older Americans is low. Our findings, while preliminary and in need of confirmation, suggest that cirrhosis has vascular sequela outside of the portal and pulmonary vascular beds, and conversely, that the cerebral vasculature is vulnerable to systemic aberrations resulting from cirrhosis. Identifying mechanisms of vascular injury in cirrhosis may improve our understanding of aneurysmal SAH and yield opportunities to prevent cerebrovascular and other vascular complications.

Large administrative datasets facilitate the study of uncommon diseases, such as cirrhosis and aneurysmal SAH. However, this study has several limitations in addition to its retrospective observational design. First, while we adjusted our models for stroke risk factors and major medical comorbidities, residual unmeasured confounding may be present. Explicitly, differences in other important risk factors such as smoking and renal disease may be imperfectly captured by administrative claims data. However, we used the conservative strategy of adjusting for all vascular risk factors and medical comorbidities, as opposed to only variables that directly confound the association between cirrhosis and aneurysmal SAH, to maximally account for overall differences in health status.
Second, albeit validated, ICD-9-CM diagnosis code algorithms have inherent misclassification error. Nondifferential misclassification of the exposure may have attenuated the estimate of the association between cirrhosis and aneurysmal SAH. Reassuringly, individuals with cirrhosis in our study population were similar in demographic characteristics and vascular risk factor burden to individuals with cirrhosis in another cohort of older Americans. Relatedly, the low prevalence of noncirrhotic chronic liver disease in our sample reflects the high specificity and correspondingly low sensitivity of the individual diagnosis codes used. Additionally, the duration of disease and precise severity of cirrhosis are not reflected in administrative coding, so the included sample is clinically heterogeneous. Fourth, because our definition of aneurysmal SAH required a claim for aneurysm treatment and medical comorbidities.

### Conclusions

Cirrhosis may be an independent risk factor for aneurysmal SAH among older individuals. It may be worthwhile to further investigate whether cirrhosis is associated with aneurysm formation or rupture, and by what mechanisms.

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### Authors’ Contributions

Dr. Parikh drafted and revised the manuscript for content, was responsible for the study concept and design, interpreted the data, and gave final approval for submission. Dr. Merkler revised the manuscript for important intellectual content, interpreted the data, and gave final approval for submission. Dr. Jesudian revised the manuscript for important intellectual content, interpreted the data, and gave final approval for submission. Dr. Kamel revised the manuscript for important intellectual content, was responsible for the study concept and design, analyzed and interpreted the data, provided study supervision, and gave final approval for submission.

### Conflicts of Interest

The authors do not report any conflicts of interest.

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