Cirrhosis is associated with extrahepatic hemorrhagic and thrombotic processes, such as gastrointestinal bleeding and venous thromboembolism. The cerebrovascular complications of cirrhosis are comparatively less well understood. Early studies reported a reduced prevalence of stroke in patients with cirrhosis at the time of autopsy. More recent studies similarly found a reduced risk of all stroke and ischemic stroke, but these studies had small and narrowly defined study cohorts. With regard to hemorrhagic stroke, a previous study found that liver disease is associated with an increased risk of intracranial hemorrhage, but other studies have not found this to be the case. Because of the continued uncertainty, we sought to assess the association between cirrhosis and various stroke types in a large, nationally representative sample of Medicare beneficiaries.

**Methods**

**Study Design**

We performed a retrospective cohort study of 1,618,059 Medicare beneficiaries using a 5% sample of inpatient and outpatient Medicare claims data from January 1, 2008, through December 31, 2014, for a random 5% sample of 1,618,059 Medicare beneficiaries older than 66 years.
ters are made available in deidentified data sets by the Centers for Medicare & Medicaid Services for research purposes. Each beneficiary is given an anonymous identifier code so that longitudinal analyses can be performed. Up to 25 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, 6 ICD-9-CM inpatient procedure codes, and 13 Current Procedural Terminology inpatient or outpatient procedure codes are provided for each encounter. Although some granular data, such as medication use and laboratory results, are not included, administrative claims data allow for population-based epidemiologic studies of putative stroke risk factors, especially those with relatively low prevalence, such as cirrhosis. We adhered to the Report of Studies Conducted Using Observational Routinely Collected Health Data guidelines for studies using administrative claims data. One of the investigators (H.K.) was responsible for data set acquisition and data stewardship. This study was approved by the Weill Cornell Medicine Institutional Review Board, which deemed that informed consent was not required.

**Patient Population**

To facilitate longitudinal analysis, we followed the convention of limiting our cohort to beneficiaries with at least 1 year of continuous Medicare coverage (Parts A and B). We further refined our cohort by including beneficiaries only after 1 year of coverage eligibility to allow time for beneficiaries’ records to accrue claims that reflected their baseline comorbidities, such as prior stroke. Thus, patients with a diagnosis of stroke before 1 year of coverage eligibility were excluded.

**Measurements**

Our primary predictor was cirrhosis, defined by an algorithm that requires the presence of at least 1 ICD-9-CM inpatient or outpatient claim for cirrhosis or its complications. 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. We slightly modified this approach by excluding the diagnosis code for ascites because it has poor specificity and by requiring at least 2 claims for cirrhosis or its complications for beneficiaries included on the basis of outpatient codes alone. The original approach has 67% sensitivity and 88% positive predictive value for identifying cirrhosis and has been used in the study of Medicare data. Administrative claims data have been used to identify patients with cirrhosis with good reliability in multiple additional settings. In secondary analyses, we analyzed separately beneficiaries with alcohol-related and non-alcohol-related cirrhosis, for which individual ICD-9-CM diagnosis codes have also been validated to have fair accuracy. Non-alcohol-related cirrhosis includes metabolic and infectious cirrhosis. In addition, we analyzed separately beneficiaries with decompensated cirrhosis, defined as the presence of an individual diagnosis code for alcohol-related or non-alcohol-related cirrhosis in addition to a diagnosis code for any decompensation event. This algorithm has a positive predictive value of 91% for hepatic decompensation. We did not include patients with biliary cirrhosis in our analyses because of the diagnosis code’s low specificity. To prevent detection bias, we ascertained only cirrhosis diagnoses documented before the occurrence of stroke and did not include cirrhosis documented for the first time during the stroke hospitalization.

The primary outcome was hospital admission for any stroke, and the secondary outcomes were hospital admission for ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). Outcomes were defined by validated ICD-9-CM algorithms, which required the presence of the following diagnosis codes in any discharge diagnosis position: ischemic stroke codes 433.x1, 434.x1, or 436, ICH code 431, and SAH code 430. For all outcomes, the diagnosis code algorithms were designed to facilitate ascertainment of incident stroke by excluding claims with concomitant codes for rehabilitation. For hemorrhagic stroke outcomes, patients with concomitant diagnosis codes for trauma were excluded to exclude patients with traumatic ICH and SAH. The ICD-9-CM diagnosis code algorithm for identifying ischemic stroke is 86% sensitive and 95% specific. The code used to identify ICH is 82% sensitive and 93% specific, and the code used to identify SAH is 98% sensitive and 92% specific. Transient ischemic attack was not included as an outcome.

Additional covariates were demographic characteristics and traditional stroke risk factors and comorbidities. Patients’ age, sex, and race/ethnicity (as reported by the patient or surrogate) were determined from the Medicare denominator file. The following traditional stroke risk factors and relevant comorbidities were ascertained using ICD-9-CM codes: hypertension, diabetes, 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.

**Statistical Analysis**

Patients’ baseline characteristics were compared using the χ² test and the 2-tailed, unpaired t test, as appropriate. Crude rates were reported using descriptive statistics with exact 95% CIs. Survival statistics were used to calculate incidence rates, and cumulative incidence functions accounting for the competing risk of death were used to calculate the cumulative incidence of stroke. Patients entered observation after 1 year of continuous Medicare eligibility and were censored at the time of death, loss of Medicare insurance, or on December 31, 2014. Cox proportional hazards regression analysis was used to evaluate the association between cirrhosis and stroke while adjusting for age, sex, race, and the aforementioned stroke risk fac-
tors and comorbidities. All covariates were included in Cox proportional hazards regression models regardless of significance at the univariate level.

We performed 2 prespecified sensitivity analyses to test the robustness of our results by further refining our cohort of patients with cirrhosis. First, we used provider codes to limit our cohort of patients with cirrhosis to those diagnosed by a gastroenterologist. Second, we used procedure codes to limit our cohort of patients with cirrhosis to those who had undergone abdominal imaging or biopsy of the liver.

We performed several post hoc analyses. First, we determined the association of mild, noncirrhotic liver disease with our outcomes. Mild liver disease was identified using ICD-9-CM codes selected from its Charlson Comorbidity Index definition.27 Second, we repeated our primary analysis while additionally adjusting for all the remaining comorbidities listed in the Charlson Comorbidity Index.28 Third, we determined the association between cirrhosis and embolic vs nonembolic stroke. Embolic stroke was defined by ICD-9-CM code 434.11, which is reasonably specific.29 Fourth, we limited our outcomes to stroke diagnoses with a concomitant procedure code for brain imaging during the hospitalization. Fifth, we separately examined associations with fatal vs nonfatal stroke.

Statistical analyses were performed (H.K.) using STATA/MP software, version 13 (StataCorp). The threshold of statistical significance was set at α = .05.

### Results

Among the 1618 059 beneficiaries in our sample, we identified 15 586 patients (1.0%) with cirrhosis (mean [SD] age, 74.1 [6.9] years; 7263 [46.6%] female). Compared with patients without cirrhosis, patients with cirrhosis were more frequently male and had higher rates of stroke risk factors (Table 1). During a mean (SD) follow-up of 4.3 (1.9) years, 77 268 patients were hospitalized with stroke. Patients with stroke were older, were more often female, and had a higher burden of stroke risk factors (Table 2). During the duration of follow-up, 198 293 patients (12.3%) in the cohort were censored because of a change in insurance status.

The incidence of stroke was 2.17% (95% CI, 1.99%-2.36%) per year among patients with cirrhosis and 1.11% (95% CI, 1.10%-1.11%) per year among patients without cirrhosis (Figure). The annual incidence of ischemic stroke was 1.80% (95% CI, 1.64%-1.98%) among patients with cirrhosis and 0.96% (95% CI, 0.96%-0.97%) among patients without cirrhosis. The annual incidence of ICH was 0.31% (95% CI, 0.25%-0.39%) among patients with cirrhosis and 0.14% (95% CI, 0.13%-0.14%) among patients without cirrhosis. Last, the annual incidence of SAH was 0.13% (95% CI, 0.09%-0.18%) among patients with cirrhosis and 0.04% (95% CI, 0.04%-0.05%) among patients without cirrhosis.

In the primary analysis after adjustment for demographic characteristics, stroke risk factors, and relevant comorbidities, patients with cirrhosis experienced a higher risk of any stroke (hazard ratio [HR], 1.4; 95% CI, 1.3-1.5). However, the degree of association appeared to be higher for ICH (HR, 1.9; 95% CI, 1.5-2.4) and SAH (HR, 2.4; 95% CI, 1.7-3.5) than for ischemic stroke (HR, 1.3; 95% CI, 1.2-1.5). In terms of ischemic stroke subtypes, cirrhosis was weakly associated with nonembolic stroke (HR, 1.4; 95% CI, 1.3-1.5) and not associated with embolic stroke (HR, 1.0; 95% CI, 0.8-1.3). In secondary analyses in which alcohol-related and non-alcohol-related
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Table 3. Association Between Cirrhosis and Stroke in Medicare Beneficiaries by Type of Cirrhosis and Type of Stroke

<table>
<thead>
<tr>
<th>Type of Cirrhosis</th>
<th>No. of Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Stroke</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>15,586</td>
<td>1.4 (1.3-1.5)</td>
</tr>
<tr>
<td>Alcohol-related cirrhosis</td>
<td>3255</td>
<td>1.5 (1.2-1.8)</td>
</tr>
<tr>
<td>Non-alcohol-related cirrhosis</td>
<td>11,164</td>
<td>1.5 (1.3-1.6)</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>6043</td>
<td>1.7 (1.5-2.0)</td>
</tr>
<tr>
<td>Cirrhosis diagnosed by GI</td>
<td>5542</td>
<td>1.5 (1.3-1.7)</td>
</tr>
<tr>
<td>Cirrhosis with imaging or biopsy*</td>
<td>13,384</td>
<td>1.4 (1.3-1.6)</td>
</tr>
</tbody>
</table>

Abbreviations: GI, gastroenterologist; HR, hazard ratio; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

*This definition of cirrhosis required preceding abdominal imaging or liver biopsy.

cirrhosis were the predictors of interest, 3255 patients with alcohol-related and 11,164 patients with non-alcohol-related cirrhosis were identified. In this analysis, results were largely consistent with the primary analysis (Table 3) with the exception of the risk of SAH in patients with alcohol-related cirrhosis, for which the HR was not statistically significant (HR, 1.6; 95% CI, 0.7-4.0). In addition, 6043 patients with decompensated cirrhosis were identified, for whom the risk of stroke and all individual stroke types appeared to be slightly higher (Table 3). In contrast, mild liver disease was not associated with stroke (HR, 0.8; 95% CI, 0.7-0.8), ischemic stroke (HR, 0.7; 95% CI, 0.7-0.8), ICH (HR, 1.1; 95% CI, 0.96-1.4), or SAH (HR, 1.2; 95% CI, 0.8-1.6).

In sensitivity analyses, we separately analyzed 5542 patients diagnosed with cirrhosis by a gastroenterologist and 13,384 patients with cirrhosis who had undergone abdominal imaging or liver biopsy; results were consistent with the primary analysis (Table 3). We performed a number of post hoc sensitivity analyses. Adjustment for additional comorbidities did not significantly change our results. The results of the primary analysis were unchanged when we required documentation of brain imaging at the time of an outcome. Last, cirrhosis was similarly associated with fatal and nonfatal stroke.

Discussion

In a large, nationally representative sample of Medicare beneficiaries, we found that patients with cirrhosis faced an increased risk of stroke after adjustment for patient demographic characteristics, traditional stroke risk factors, and relevant comorbidities. Cirrhosis appeared to be more strongly associated with hemorrhagic stroke than ischemic stroke. Similar associations were seen regardless of cirrhosis type, although decompensated cirrhosis appeared to have the strongest association with stroke.

To our knowledge, this is the first comprehensive study of the association between cirrhosis and various stroke types in a large, representative sample. A prior smaller study that sought to clarify this association exclusively in patients with non-alcohol-related cirrhosis found, in contrast to our results, that cirrhosis was associated with a lower risk of stroke. Although the risk of ischemic stroke in that study was significantly lower among patients with cirrhosis, hemorrhagic stroke risk was not statistically significantly lower. Important differences in study design and patient characteristics may explain our discrepant findings. The study by Chen et al used a single diagnosis code to include only patients with non-alcohol-related cirrhosis, whereas we used a validated algorithm to include patients with various forms of cirrhosis. In addition, the patients in our study cohort were older, were more diverse, and had a greater burden of baseline stroke risk factors. Other compelling data regarding specific stroke subtypes are limited. Small studies have suggested a reduced prevalence and incidence of ischemic stroke in patients with cirrhosis. With regard to hemorrhagic stroke, early studies reported conflicting results. However, a subsequent study demonstrated an independent association between liver disease, including cirrhosis, and the risk of intracranial hemorrhage, but this study was limited by the lack of outpatient data. In this context, our findings challenge the weakly supported notion that cirrho-
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Risk of stroke among patients with cirrhosis

Our finding of an increased risk of stroke among patients with cirrhosis has multiple possible explanations. There is increasing evidence that cirrhosis is accompanied by a mixed coagulopathy with potential implications for hemorrhagic and thrombotic processes. Clinically, cirrhosis is often associated with bleeding complications, most commonly portal hypertensive hemorrhage in the gastrointestinal tract. Patients with liver fibrosis were also recently found to have an increased burden of cerebral microhemorrhages on brain magnetic resonance imaging. Our findings further support a hemorrhagic tendency in cirrhosis that is independent of portal hypertension. On the other hand, a propensity for venous thromboembolism in cirrhosis is increasingly recognized. At a minimum, cirrhosis does not appear to be protective against thrombotic events. Studies of coagulation factors in patients with cirrhosis have revealed an unstable imbalance of prothrombotic and prohemorrhagic derangements. The increased risk of ischemic and hemorrhagic stroke observed in our study may reflect these complex coagulation system aberrations, particularly for patients with more advanced, decompensated cirrhosis because these patients appeared to have a higher risk of all stroke types. The risk of stroke conferred by the patients’ underlying vascular risk factors may be amplified by cirrhosis, perhaps because of the mixed coagulopathy. The underlying causes of cirrhosis, such as alcohol abuse, hepatitis C infection, and metabolic disease, may also contribute to stroke risk, although we did not find mild, noncirrhotic liver disease to be associated with stroke. Alternatively, with regard to ischemic stroke, clinicians’ perceptions of the risk of bleeding or further hepatic toxicity may limit the aggressiveness of stroke prevention with antithrombotic medications and statin therapy, for example. Last, although we adjusted for baseline stroke risk factors, it is possible that cirrhosis reflects poor health in general and that residual confounding contributed to our findings. However, residual confounding would not explain the seemingly stronger associations with hemorrhagic compared with ischemic stroke. Furthermore, our findings were unchanged when adjusting for additional comorbidities. In addition, the magnitude of the associations for ICH and SAH and the robustness of these associations in sensitivity analyses make confounding less likely in those cases.

Limitations

We adhered to relevant guidelines on the use of administrative claims data. However, a number of inherent limitations warrant mention. First, the diagnosis code algorithm used to ascertain cirrhosis prioritizes positive predictive value over sensitivity. It is possible that some patients in the control group also had cirrhosis; however, this bias serves to increase the confidence in our findings. The generalizability of our results to mild cirrhosis may be limited because the diagnosis code algorithm used to ascertain cirrhosis in the primary analysis includes some patients based on the presence of complications of cirrhosis. Although our results were largely unchanged in secondary analyses of patients with alcohol-related and non–alcohol-related cirrhosis regardless of the presence or absence of complications, the associations with stroke appeared to be weaker in a post hoc analysis of patients with mild, noncirrhotic liver disease. Regardless, the inability to ascertain the duration of cirrhosis before inclusion in our cohort is an additional limitation because rates of stroke may be lower during this period. Second, vascular risk factor ascertainment may be incomplete, although this limitation is expected to be equally present in the control group. Third, relatively few patients had alcohol-related cirrhosis; thus, this secondary analysis may have been underpowered, which may have contributed to the nonsignificant and imprecise association observed with SAH. Fourth, there may be misclassification among outcomes. However, we used a reliable algorithm to identify outcomes; furthermore, our results were unchanged in an analysis that required documentation of brain imaging at the time of stroke diagnosis. Similarly, although we used strategies to exclude patients with prior stroke, we cannot be certain that all outcomes were first-ever outcomes. Fifth, because our analysis was of Medicare beneficiaries, our results may not be generalizable to younger patients. Sixth, the fact that 12.3% of our cohort was censored because of a change in insurance is also a limitation. Seventh, we cannot determine the association of antithrombotic medication use or laboratory derangements with our predictors and outcomes because the Medicare data set used for our analysis does not include these data. Additional research to delineate whether and to what extent such variables mediate the association between cirrhosis and stroke is warranted.

Conclusions

In a nationally representative sample of elderly patients with vascular risk factors, cirrhosis was associated with an increased risk of stroke, particularly hemorrhagic stroke. Additional investigation into the epidemiology and pathophysiology of this association may yield opportunities for stroke risk reduction and prevention.

ARTICLE INFORMATION

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Author Contributions: Dr Kamel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Parikh, Navi, Kamel.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Parikh.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kamel.
Administrative, technical, or material support: Navi, Kamel.
Study supervision: Navi, Jesudian, Kamel.

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REFERENCES