Association between Liver Disease and Intracranial Hemorrhage

Neal S. Parikh, MD,* Babak B. Navi, MD, MS,*† Sonal Kumar, MD, MPH,‡ and Hooman Kamel, MD*†

Background: Liver disease is common and associated with clinical and laboratory evidence of coagulopathy. The association between liver disease and intracranial hemorrhage (ICH) remains unclear. Our aim was to assess whether liver disease increases the risk of ICH. *Methods:* We performed a retrospective cohort study based on administrative claims data from California, Florida, and New York acute care hospitals from 2005 through 2011. Of a random 5% sample, we included patients discharged from the emergency department or hospital after a diagnosis of liver disease and compared them to patients without liver disease. Patients with cirrhotic liver disease were additionally analyzed separately. Kaplan–Meier survival statistics were used to calculate cumulative rates of incident ICH, and Cox proportional hazard analysis was used to adjust for demographic characteristics, vascular disease, and Elixhauser comorbidities. Multiple models tested the robustness of our results. *Results:* Among 1,909,816 patients with a mean follow-up period of 4.1 (±1.8) years, the cumulative rate of ICH after a diagnosis of liver disease was 1.70% (95% confidence interval [CI], 1.55%-1.87%) compared to .40% (95% CI, .39%-.41%) in patients without liver disease ($P < .001$ by the log-rank test). Liver disease remained associated with an increased hazard of ICH after adjustment for demographic characteristics and vascular risk factors (hazard ratio [HR], 1.8; 95% CI, 1.6-2.0). This was attenuated in models additionally adjusted for general comorbidities (HR, 1.3; 95% CI, 1.2-1.5). *Conclusions:* There is a modest, independent association between liver disease and the risk of ICH. **Key Words:** Intracranial hemorrhage—intracerebral hemorrhage—liver disease—cirrhosis—coagulopathy—epidemiology.

Introduction

Intracranial hemorrhage (ICH) accounts for at least 10%-20% of all strokes and often leads to severe disability or death.[1,2] Established risk factors for ICH include hypertension, diabetes, smoking, and alcohol use.[3] Given that patients with cirrhosis often develop major bleeding from the gastrointestinal tract,[4] they may also face an increased risk of major bleeding elsewhere, including ICH. Cirrhosis is associated with multiple hematological abnormalities, including of procoagulant and anticoagulant levels.[5] However, it is uncertain as to whether cirrhosis and, broadly, liver disease predispose to hemorrhage in general, because the gastrointestinal bleeding seen in cirrhosis may be mostly due to portal hypertension rather than an intrinsic coagulopathy.[5,6] Therefore, it remains unclear whether liver disease is a risk factor for ICH.

From the *Department of Neurology, Weill Cornell Medical College, New York, New York; †Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, New York; and ‡Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, New York.

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Address correspondence to Neal S. Parikh, Department of Neurology, Weill Cornell Medical College, 525 E. 68th Street F610, New York, NY 10065. E-mail: nsp2001@nyp.org.

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While the clinical characteristics of ICH in cirrhosis have been described,[7,8] the two available studies on ICH risk in liver disease, including cirrhosis, produced conflicting results.[9,10] Further, a recent study, though not designed to assess the degree of ICH risk associated with liver disease, revealed ICH to be an infrequent cause of altered mental status in cirrhotic patients.[11] Given this uncertainty, we examined the association between liver disease and ICH in a large, heterogeneous, population-based cohort.

Methods

We used administrative claims data from California, Florida, and New York. The Agency for Healthcare Research and Quality provides standardized, quality-checked, deidentified discharge data from all patient visits to nonfederal emergency departments (EDs) and admissions to nonfederal acute care hospitals in these states. Each patient is assigned an anonymous, unique identifier to allow longitudinal tracking across ED visits and hospitalizations.[12] These publicly available data include demographic characteristics and a list of up to 25 *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes. Our analysis of these data was approved by the Weill Cornell Medical College Institutional Review Board.

We included a random 5% sample of adults with at least 1 ED visit or hospitalization between 2005 and 2010 in California, 2005 and 2011 in Florida, and 2006 and 2011 in New York. This sample was not weighted by the frequency of visits, so patients with 1 visit were as likely to be included as those with numerous visits. The dates above were chosen to provide at least 1 year of follow-up data for all patients. We excluded patients with any history of ICH because we were interested in first-ever recorded ICH. To maximize follow-up, we excluded nonresidents of these states.

Our primary predictor variable was liver disease of any etiology as defined by *ICD-9-CM* codes. Quan et al developed[13] and validated[14] an enhanced *ICD-9-CM* coding algorithm to identify liver disease as originally represented as an Elixhauser comorbidity. The algorithm includes all forms and grades of liver disease; codes in this algorithm (070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7) include a history of liver disease, acute liver disease, cirrhosis, and some complications of liver cirrhosis. This method has a positive predictive value of 80.2% and specificity of 99.5% for any liver disease as compared to expert chart review.[14] Given the heterogeneity of this liver disease sample and in concordance with prior studies on this topic, we performed secondary analyses that attempt to isolate patients with liver cirrhosis. We used *ICD-9-CM* codes 571.2 and 571.5, respectively, to identify patients with alcohol and non–alcohol-related cirrhosis. These codes have been validated to identify these specific forms of liver disease with moderate specificity.[15] We opted to use these single codes as opposed to more complex algorithms, which include codes for complications of cirrhosis, as this latter approach appears to reduce specificity.[15]

The primary outcome was ICH, defined as per prior studies on this topic as a composite of intracerebral hemorrhage, subarachnoid hemorrhage, or nontraumatic subdural hematoma.[9,10] We performed sensitivity analyses limited to intracerebral hemorrhage, as this type of hemorrhage is the most likely to reflect spontaneous bleeding (i.e., without an underlying vascular lesion or trauma), and its *ICD-9-CM* code has been well-validated.[16]

To account for potential confounders in the relationship between liver disease and ICH, we adjusted for demographic characteristics such as age, sex, race, and insurance status. Additionally, we used *ICD-9-CM* codes to determine the presence of vascular disease and its risk factors, such as hypertension, diabetes, coronary heart disease, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, atrial fibrillation, transient ischemic attack, stroke, myocardial infarction, venous thromboembolism, tobacco use, and alcohol use.[3,17] Lastly, we ascertained the following Elixhauser comorbidities[14,18,19]: acquired immunodeficiency syndrome, anemia, arthritis, blood loss, chronic lung disease, depression, drug use, hypothyroidism, lymphoma, metastatic cancer, obesity, psychiatric disorder, tumor, peptic ulcer disease, and valve disease.

Descriptive statistics with exact confidence intervals (CIs) were used to report crude rates. We used Kaplan–Meier survival statistics and the log-rank test to compare cumulative rates of outcomes among patients with and without liver disease. Patients entered the cohort at their first-recorded ED visit or hospital discharge and were censored at the time of an outcome, last available follow-up date, or documented in-hospital death. We performed sensitivity analyses to minimize the effects of antiplatelet and anticoagulant drugs by censoring patients upon diagnosis with venous thromboembolism, myocardial infarction, stroke, or atrial fibrillation. In additional sensitivity analyses, we censored patients at the time of diagnosis of cirrhosis, to determine the effect of noncirrhotic liver disease on ICH risk.

Multivariable Cox proportional hazards analysis was used to examine the relationship between liver disease and ICH while adjusting for the covariates above. Models were built in a stepwise fashion, first adjusting only for demographic characteristics, then additionally for vascular risk factors, and then additionally for Elixhauser comorbidities. All covariates were left in the model regardless of statistical significance to maximally isolate the contribution of our predictor variable. In a sensitivity analysis, we additionally adjusted for documented coagulopathy and thrombocytopenia.