HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2016 March ; 25(3): 543–548. doi:10.1016/j.jstrokecerebrovasdis.2015.11.005.

Association between Liver Disease and Intracranial Hemorrhage

Neal S Parikh, MD[1], **Babak B Navi, MD, MS**[1,2], **Sonal Kumar, MD**[3], and **Hooman Kamel, MD**[1,2]

[1]Department of Neurology, Weill Cornell Medical College, New York, NY

[2]Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY

[3]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY

Abstract

Background—Liver disease is common and associated with clinical and laboratory evidence of coagulopathy. The association between liver disease and intracranial hemorrhage remains unclear. Our aim was to assess whether liver disease increases the risk of intracranial hemorrhage.

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 intracranial hemorrhage, 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 intracranial hemorrhage after a diagnosis of liver disease was 1.70% (95% confidence interval [CI], 1.55–1.87%) compared to 0.40% (95% CI, 0.39–0.41%) in patients without liver disease ($P < 0.001$ by the log-rank test). Liver disease remained associated with an increased hazard of intracranial hemorrhage 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 intracranial hemorrhage.

Keywords

Intracranial hemorrhage; intracerebral hemorrhage; liver disease; cirrhosis; coagulopathy; epidemiology

Correspondence to: Neal Parikh, MD, Weill Cornell Medical College, Department of Neurology, 525 E. 68th Street F610, New York, NY 10065, Tel: 212-746-0225, Fax: 212-746-5509, nsp2001@nyp.org.

Introduction

Intracranial hemorrhage (ICH) accounts for at least 10% to 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 pro-coagulant and anticoagulant factors (5). However, it is uncertain as to whether cirrhosis and, broadly, liver disease predispose to hemorrhage in general, since 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.

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, de-identified 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 one 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 one 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 non-residents of these states.

Our primary predictor variable was liver disease of any etiology as defined by *ICD-9-CM* codes. Quan and colleagues 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 including 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 non-traumatic subdural hematoma (9, 10). We performed sensitivity analyses limited to intracerebral hemorrhage, since 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 (CI) 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 a diagnosis of cirrhosis, to determine the effect of non-cirrhotic 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.

In our primary analytical approach, we treated liver disease and all vascular risk factors and comorbidities as time-varying covariates that took on the value recorded at the latest ED visit or hospitalization. In a secondary approach, we treated liver disease and all vascular risk factors and comorbidities as time-fixed covariates that took on the value recorded at the first recorded ED visit or hospitalization. In an alternative secondary analysis, we treated liver disease as a time-varying covariate and all vascular risk factors and comorbidities as time-fixed at baseline.

All analyses were performed using Stata MP (version 13, College Station, TX). The threshold of statistical significance was set at alpha = 0.05.

Results

Among 1,909,816 patients free of ICH at baseline, 56,220 (2.9%) received a diagnosis of liver disease at some point during a mean follow-up period of 4.1 (±1.8) years. At baseline, patients with liver disease were more likely to be older, male, white and beneficiaries of Medicare or Medicaid (Table 1). Additionally, patients with liver disease had a higher Elixhauser comorbidity index and a higher prevalence of established vascular disease and risk factors (Table 1).

We identified 6,772 (0.35%; 95% CI, 0.35–0.36%) first-recorded diagnoses of ICH after the index visit. When liver disease was modeled as a time-varying covariate, the cumulative rate of ICH after a diagnosis of liver disease was 1.70% (95% CI, 1.55–1.87%) compared to 0.40% (95% CI, 0.39–0.41%) in patients without liver disease ($P < 0.001$ by log-rank test). In a Cox proportional hazards model adjusted only for demographic characteristics, liver disease was strongly associated with subsequent ICH (hazard ratio [HR], 3.3; 95% CI, 3.0–3.7). This association was attenuated after adjustment for time-varying vascular risk factors (HR, 1.8; 95% CI, 1.6–2.0) and further attenuated after adjustment for time-varying Elixhauser comorbidities (HR, 1.3; 95% CI, 1.2–1.5).

Sensitivity analyses limited to intracerebral hemorrhage alone produced similar results. We identified 3,659 incident cases of intracerebral hemorrhage in our sample. Adjusted for demographic characteristics alone, the hazard ratio for liver disease was 3.1 (95% CI, 2.8–3.6). Again, the association was attenuated to 1.7 (95% CI, 1.5–2.0) and 1.3 (95% CI, 1.2–1.5) after adjusting for time-varying vascular risk factors and then Elixhauser comorbidities, respectively.

Furthermore, our findings were similar when patients were censored at the time of a diagnosis of cirrhosis, or conversely when the predictor variable was limited to alcohol-related or non-alcohol related cirrhosis, except for moderately stronger associations between alcohol-related cirrhosis and ICH (Table 2).

Similar patterns were seen in secondary analytical approaches that treated covariates as time-fixed from baseline (Table 2). Our results were essentially unchanged in sensitivity

analyses censoring patients at the time of a diagnosis of stroke, myocardial infarction, venous thromboembolism or atrial fibrillation. In a sensitivity analysis in which we additionally adjusted for documented coagulopathy and thrombocytopenia, we again found an association between liver disease and ICH, although the association was further attenuated (HR, 1.14; 95% CI, 1.04–1.26), as expected given that coagulopathy and thrombocytopenia are very likely to mediate any relationship between liver disease and ICH.

Discussion

In a large, population-based, retrospective cohort study, we found a significantly heightened rate of ICH after a diagnosis of liver disease. The association between liver disease and ICH persisted across multiple analytical approaches accounting for vascular and general comorbidities in a variety of ways. Additionally, the findings were consistent when analyses were limited to intracerebral hemorrhage. Our findings remained essentially the same in models censoring patients likely to be receiving antithrombotic medications and were somewhat more robust in analyses examining more severe forms of liver disease such as cirrhotic liver disease as compared to non-cirrhotic liver disease. Overall, our findings suggest that liver disease—once its numerous associated comorbidities are accounted for—modestly contributes to the risk of ICH.

Though an association between liver disease and ICH was suggested by the results of a retrospective case-control study (9), a subsequent case-cohort study failed to confirm this association (10). However, the latter study showed a non-significantly increased risk of ICH associated with cirrhosis, and the wide confidence intervals suggest that this study was underpowered. Therefore, these prior studies are consistent with our findings that liver disease may increase the risk of ICH. These results, along with studies demonstrating low rates of ischemic cerebrovascular disease (20–23) and coronary heart disease (20, 24) in cirrhosis, support the general conclusion that liver disease predisposes to hemorrhage rather than thrombosis. This association may be mediated by decreased levels of most pro-coagulant factors and thrombocytopenia (5). Alternatively, it is possible that liver disease predisposes to both hemorrhage and thrombosis via a disordered and unstable coagulation system, as some studies have found an association between cirrhotic liver disease and venous thromboembolism (5, 25–28). The finding that the association between liver disease and ICH is somewhat stronger when liver disease is restricted to cirrhotic liver disease, as opposed to all forms and severities of liver disease, raises the possibility of a mechanistic link between severity of liver disease and ICH risk. This relationship requires further investigation.

Our study has several limitations that should be considered. First, due to the modest sensitivity of claims-based algorithms, we likely had incomplete ascertainment of liver disease in our study population as reflected by the 2.9% frequency of liver disease in our cohort, which is lower than the 5% frequency determined by expert chart-review in the algorithm validation cohort (14). It is possible that patients with more severe forms of liver disease were more likely to have a liver disease diagnosis code assigned. However, our methods do not allow for determination of liver disease severity. Additionally, we lacked data on outpatient diagnoses of liver disease. Therefore, our results may not be generalizable

to mild liver disease patients who have not had any ED visits or hospitalizations. Second, given the reliance on ED and inpatient *ICD-9-CM* diagnosis codes, our ascertainment of vascular risk factors and comorbidities may be incomplete, and the association between liver disease and ICH may be further attenuated with more complete covariate ascertainment. However, it is also possible that our models were over-adjusted by inclusion of comorbidities that are actually in the causal pathway between liver disease and ICH (e.g., hemorrhage into a brain metastasis or bleeding induced by liver disease-related thrombocytopenia). Additionally, incomplete ascertainment is also expected to be present in the control group to a similar extent. Third, we lacked data on medication use, particularly in regards to antithrombotic therapies. However, our results were essentially the same when we censored patients at the time of diagnoses that are common indications for antithrombotic therapy. Last, coagulation indices and cell count data were not available or controlled for; however, we believe these variables may mediate the association between liver disease and ICH.

Our findings suggest that liver disease is an independent risk factor for ICH. Prospective confirmation of our findings and elucidation of mechanisms of ICH in liver disease may be helpful, particularly for clinicians considering antithrombotic or anticoagulant medications for liver disease patients. Moreover, ICH accounts for an increasing share of the 10% of deaths that are caused by stroke worldwide (29), and liver disease accounts for about 2% of global deaths (30), suggesting that further insights on the association between liver disease and ICH may help global efforts to improve public health.

Acknowledgments

Grant Support: This study was supported by grants K23NS082367 (Kamel) and K23NS091395 (Navi) from the National Institute of Neurological Disorders and Stroke, as well as the Michael Goldberg Stroke Research Fund (Kamel) and the Florence Gould Endowment for Discovery in Stroke (Navi).

References

1. Feigin VL, Lawes CM, Bennett DA, et al. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009; 8(4):355–369. [PubMed: 19233729]
2. Sacco S, Marini C, Toni D, et al. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke. 2009; 40(2):394–399. [PubMed: 19038914]
3. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010; 376(9735): 112–123. [PubMed: 20561675]
4. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010; 362(9):823–832. [PubMed: 20200386]
5. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011; 365(2): 147–156. [PubMed: 21751907]
6. Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med. 2001; 345(9):669–681. [PubMed: 11547722]
7. Huang HH, Lin HH, Shih YL, et al. Spontaneous intracranial hemorrhage in cirrhotic patients. Clin Neurol Neurosurg. 2008; 110(3):253–258. [PubMed: 18194837]
8. Hoya K, Tanaka Y, Uchida T, et al. Intracerebral hemorrhage in patients with chronic liver disease. Neurol Med Chir (Tokyo). 2012; 52(4):181–185. [PubMed: 22522327]

9. Grønbaek H, Johnsen SP, Jepsen P, et al. Liver cirrhosis, other liver diseases, and risk of hospitalisation for intracerebral haemorrhage: a Danish population-based case-control study. BMC Gastroenterol. 2008; 8:16. [PubMed: 18501016]
10. Lai CH, Cheng PY, Chen YY. Liver cirrhosis and risk of intracerebral hemorrhage: a 9- year follow-up study. Stroke. 2011; 42(9):2615–2617. [PubMed: 21757678]
11. Donovan LM, Kress WL, Strnad LC, et al. Low Likelihood of Intracranial Hemorrhage in Patients With Cirrhosis and Altered Mental Status. Clin Gastroenterol Hepatol. 2015; 13(1):165–169. [PubMed: 24907500]
12. Barrett, M.; Steiner, C.; Andrews, R., et al. [cited 30 May 2015] Methodological Issues when Studying Readmissions and Revisits Using Hospital Adminstrative Data. HCUP Methods Series Report # 2011-01. 2011. [updated 2011;]; Available from: http://www.hcup-us.ahrq.gov/reports/methods/2011_01.pdf.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–1139. [PubMed: 16224307]
14. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008; 43(4):1424–1441. [PubMed: 18756617]
15. Nehra MS, Ma Y, Clark C, et al. Use of administrative claims data for identifying patients with cirrhosis. J Clin Gastroenterol. 2013; 47(5):e50–e54. [PubMed: 23090041]
16. Tirschwell DL, Longstreth WT. Validating administrative data in stroke research. Stroke. 2002; 33(10):2465–2470. [PubMed: 12364739]
17. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009; 373(9675): 1632–1644. [PubMed: 19427958]
18. Yurkovich M, Avina-Zubieta JA, Thomas J, et al. A systematic review identifies valid comorbidity indices derived from administrative health data. J Clin Epidemiol. 2015; 68(1):3–14. [PubMed: 25441702]
19. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care. 1998; 36(1):8–27. [PubMed: 9431328]
20. Berzigotti A, Bonfiglioli A, Muscari A, et al. Reduced prevalence of ischemic events and abnormal supraortic flow patterns in patients with liver cirrhosis. Liver Int. 2005; 25(2):331–336. [PubMed: 15780058]
21. Chen YH, Chen KY, Lin HC. Non-alcoholic cirrhosis and the risk of stroke: a 5-year follow-up study. Liver Int. 2011; 31(3):354–360. [PubMed: 20860634]
22. Kane WC, Aronson SM. Cerebrovascular disease in an autopsy population. 4. Reduced frequency of stroke in patients with liver cirrhosis. Trans Am Neurol Assoc. 1971; 96:259–260. [PubMed: 5159099]
23. Melato M, Mucli E, Poldrugo F, et al. Stroke-cirrhosis relationship: an autopsy study in a heavy drinking population. Ital J Gastroenterol. 1991; 23(4):211–214. [PubMed: 1751817]
24. Howell WL, Manion WC. The low incidence of myocardial infarction in patients with portal cirrhosis of the liver: A review of 639 cases of cirrhosis of the liver from 17,731 autopsies. Am Heart J. 1960; 60:341–344. [PubMed: 14403495]
25. Vieira da Rocha EC, D'Amico EA, Caldwell SH, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol. 2009; 7(9):988–993. [PubMed: 19410018]
26. Ogren M, Bergqvist D, Björck M, et al. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol. 2006; 12(13):2115–2119. [PubMed: 16610067]
27. Aggarwal A, Puri K, Liangpunsakul S. Deep vein thrombosis and pulmonary embolism in cirrhotic patients: systematic review. World J Gastroenterol. 2014; 20(19):5737–5745. [PubMed: 24914335]
28. Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009; 137(6):2105–2111. [PubMed: 19706293]

29. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. The Lancet Global health. 2013; 1:e259–e281. [PubMed: 25104492]

30. Mokdad AA, Lopez AD, Shahraz S, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC medicine. 2014; 12:145. [PubMed: 25242656]

Table 1

Baseline Characteristics of Patients, Stratified by Liver Disease

Characteristic*	Liver Disease (N = 56,220)	No Liver Disease (N = 1,853,596)	*P* value
Age, mean (SD), y	56.2(15.3)	46.6(20.1)	<0.001
Female	25,715(45.7)	1,031,823(55.7)	<0.001
Race†			<0.001
White	33,583 (62.2)	1,037,921 (58.7)	
Black	6,288 (11.7)	243,267 (13.8)	
Hispanic	10,150 (18.8)	326,859 (18.5)	
Asian	2,168 (4.0)	75,311 (4.3)	
Other	1,789(3.3)	85,201 (4.8)	
Payment source‡			<0.001
Medicare	17,991 (32.0)	380,095 (20.5)	
Medicaid	8,019 (14.3)	191,124 (10.3)	
Private	18,655 (33.2)	840,805 (45.4)	
Self-pay	7,553 (13.4)	309,728 (16.7)	
Other	3,982 (7.1)	130,629 (7.1)	
Hypertension	19,129 (34.0)	369,605 (19.9)	<0.001
Diabetes	10,548 (18.8)	160,926 (8.7)	<0.001
Coronary heart disease	5,424 (9.7)	103,572 (5.6)	<0.001
Congestive heart failure	3,703 (6.6)	46,169 (2.5)	<0.001
Peripheral vascular disease	1,497 (2.7)	22,317 (1.2)	<0.001
Chronic obstructive pulmonary disease	4,331 (7.7)	66,666 (3.6)	<0.001
Chronic kidney disease	2,090 (3.7)	23,003(1.2)	<0.001
Atrial fibrillation	2,905 (5.2)	51,563(2.8)	<0.001
Transient ischemic attack	236 (0.4)	7,218(0.4)	0.26
Ischemic stroke	357 (0.6)	10,330(0.6)	0.02
Myocardial infarction	554(1.0)	9,545 (0.5)	<0.001
Venous thromboembolism	687(1.2)	10,780(0.6)	<0.001
Tobacco use	2,632 (4.7)	44,947 (2.4)	<0.001
Alcohol use	12,248 (21.8)	135,756 (7.3)	<0.001
Elixhauser comorbidities§, mean (SD), no.	3.1 (1.8)	1.4 (1.5)	<0.001

Abbreviations: SD, standard deviation.

*Data are presented as number (%) unless otherwise specified.

†Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing race/ethnicity data in 4.6% of patients.

‡Numbers do not sum to group totals because of missing payment-source data in <0.01% of patients.

§Numbers represent the number of Elixhauser comorbid conditions, which comprise a comprehensive set of 28 comorbidity measures for use with large administrative datasets. (19)

Table 2

Hazard Ratios for Intracranial Hemorrhage in Liver Disease

Model	Hazard Ratio (95%CI)
Liver disease as a time-varying covariate	
Model 1:Unadjusted	4.3 (3.9–4.7)
Model 2:Adjusted for demographic characteristics*	3.3 (3.0–3.7)
Model 3: Model 2 plus baseline vascular risk factors†	3.1 (2.8–3.4)
Model 4: Model 3 plus baseline comorbidities‡	2.2 (2.0–2.4)
Model 5: Model 2 plus time-varying vascular risk factors	1.8 (1.6–2.0)
Model 6: Model 5 plus time-varying comorbidities	1.3 (1.2–1.5)
Liver disease as a time-fixed covariate	
Model 1:Unadjusted	2.4 (2.0–2.8)
Model 2:Adjusted for demographic characteristics	1.8 (1.5–2.1)
Model 3: Model 2 plus baseline vascular risk factors	1.6 (1.3–1.9)
Model 4: Model 3 plus baseline comorbidities	1.2 (1.1–1.4)
Non-cirrhotic liver disease as a time-varying covariate	
Model 1:Unadjusted	4.0 (3.6–4.5)
Model 2:Adjusted for demographic characteristics	3.3 (3.0–3.7)
Model 3: Model 2 plus baseline vascular risk factors	3.1 (2.8–3.5)
Model 4: Model 3 plus baseline comorbidities	2.2 (2.0–2.5)
Model 5: Model 2 plus time-varying vascular risk factors	1.9 (1.7–2.1)
Model 6: Model 5 plus time-varying comorbidities	1.4 (1.2–1.5)
Alcohol-related cirrhosis as a time-varying covariate	
Model 1:Unadjusted	7.0 (5.9–8.5)
Model 2:Adjusted for demographic characteristics	5.7 (4.8–6.9)
Model 3: Model 2 plus baseline vascular risk factors	5.0 (4.1–6.0)
Model 4: Model 3 plus baseline comorbidities	3.4 (2.8–4.1)
Model 5: Model 2 plus time-varying vascular risk factors	2.3 (1.9–2.8)
Model 6: Model 5 plus time-varying comorbidities	1.7 (1.4–2.0)
Non-alcohol related cirrhosis as a time-varying covariate	
Model 1:Unadjusted	6.3 (5.3–7.4)
Model 2:Adjusted for demographic characteristics	3.9 (3.2–4.6)
Model 3: Model 2 plus baseline vascular risk factors	3.6 (3.0–4.3)
Model 4: Model 3 plus baseline comorbidities	2.6 (2.2–3.1)
Model 5: Model 2 plus time-varying vascular risk factors	2.0 (2.2–3.1)
Model 6: Model 5 plus time-varying comorbidities	1.5 (1.2–1.8)

* The demographic characteristics that were included were age, sex, race, and insurance status.

[†]Vascular risk factor were defined 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.

[‡]Included Elixhauser comorbid conditions were 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 value disease.