Incidence of and Risk Factors for Hepatic Encephalopathy in a Population-Based Cohort of Americans With Cirrhosis

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Hepatic encephalopathy (HE) is a devastating complication of cirrhosis. Data are limited regarding the incidence of and risk factors for HE among contemporary patients in the context of the shifting epidemiology of cirrhosis. We examined a 20% random sample of U.S. Medicare enrollees with cirrhosis and Part D prescription coverage from 2008 to 2014. We modelled incident HE using demographic, clinical, and pharmacologic data. Risk factors for HE were evaluated, including demographics/socioeconomics, cirrhosis etiology, severity of liver disease, and pharmacotherapy, along with gastroenterology consultation, as time-varying covariates. Among 166,192 Medicare enrollees with cirrhosis followed for 5.25 (interquartile range [IQR], 2.00-7.00) years, the overall incidence of HE was 11.6 per 100 patient-years. The cohort's median age was 65 years (IQR, 57-72), 31% had alcohol-related cirrhosis, and 49% had likely nonalcoholic fatty liver disease cirrhosis. The two strongest associations with HE were alcohol-related cirrhosis (adjusted hazard ratio [AHR], 1.44; 95% confidence interval [CI], 1.40, 1.47, relative to nonalcoholic nonviral cirrhosis) and the presence of portal hypertension (AHR, 3.42; 95% CI, 3.34, 3.50). Adjusting for confounders, benzodiazepines (AHR, 1.24; 95% CI, 1.21, 1.27), gamma aminobutyric acid (GABA)ergics (AHR, 1.17; 95% CI, 1.14, 1.21), opioids (AHR, 1.24; 95% CI, 1.21, 1.27), and proton pump inhibitors (PPIs) (AHR, 1.41; 95% CI, 1.38, 1.45) were all associated with incident HE. Only benzodiazepines, however, were associated with the risk of hospitalization with HE (incidence-rate ratio, 1.23; 95% CI, 1.20, 1.26). *Conclusion:* Novel data regarding the risk of HE for contemporary patients with cirrhosis are provided. The incidence of HE in an older population of Americans with cirrhosis is high, particularly among those with alcohol-related cirrhosis and portal hypertension. Several medication classes, namely PPIs, opiates, GABAergics, and benzodiazepines, represent potentially modifiable risk factors for HE. (*Hepatology Communications* 2019;3:1510-1519).

Hepatic encephalopathy (HE) is one of the most devastating complications of cirrhosis.[1] Developing HE increases mortality as well as the risk of hospitalization, falls, and motor-vehicle accidents and carries a significant psychosocial burden.[2-4] However, the present and future epidemiology of cirrhosis is shifting with limited data regarding the risk of HE in contemporary patients. Cirrhosis is increasingly prevalent (doubling in the last decade), reflecting a growing population with alcohol-related liver disease and nonalcoholic fatty liver disease (NAFLD).[5,6] Driven by NAFLD, the

Abbreviations: AHR, adjusted hazard ratio; CI, confidence interval; ESRD, end-stage renal disease; GABA, gamma aminobutyric acid; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; ICD-9, International Classification of Diseases, ninth revision; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; PPI, proton pump inhibitor.

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average age of patients with cirrhosis is rising.[7-9] Even as the burden of hepatitis C virus (HCV) wanes given highly effective antiviral therapy,[9] cirrhosis mortality rose by 65% from 2008 to 2016 and is expected to triple by 2030.[10-14] It is unclear how these trends impact the burden of HE.

Older persons with cirrhosis may be at higher risk of HE. Aging is associated with factors that could increase the risk of HE, including sarcopenia,[15,16] renal insufficiency,[17] and diminished cognitive reserve as a function of cardiovascular comorbidities. Aging also carries a greater medication burden,[18] including medications that could precipitate HE by enhancing ammonia's neurotoxicity. For example, opioids increase ammonia absorption through decreased intestinal motility.[19] Benzodiazepines and gabapentin, both increasingly prescribed to older persons,[20] may exacerbate ammonia's neurodepressant effects.[17] Proton pump inhibitors (PPIs) cause dysbiosis and may increase ammonia production.[21] Data are limited, however, on the effects of medications on the risk of HE in patients with cirrhosis. We studied Medicare data to capture the risk of and associations with HE in contemporary patients with cirrhosis who are typically older, have a higher proportion of NAFLD, have multiple comorbidities, and who frequently experience polypharmacy.

Participants and Methods

STUDY POPULATION

We examined data from a 20% random sample (the second largest available extract of data from this government payer) of U.S. Medicare enrollees with cirrhosis (using a validated algorithm for Medicare data using International Classification of Diseases, ninth revision [ICD-9] 571.2, 571.5, 571.6)[22] and continuous Part D (prescription) coverage from 2008 through 2014 (Supporting Fig. S1). We set 90 days after cirrhosis diagnosis as a landmark and therefore excluded all patients with less than 90 days of outpatient follow-up and those with HE (ICD-9 572.2 or lactulose/neomycin/rifaximin use) at any time before or within 90 days after the cirrhosis diagnosis. To allow for adequate covariate acquisition, we set cohort entry to 365 days before the landmark period, which was effectively 9 months before the first diagnosis of cirrhosis. A summary of diagnostic codes used is provided in Supporting Table S1. Medicare beneficiary claims data from inpatient and outpatient encounters are available in de-identified data sets prepared by the Centers for Medicare and Medicaid Services for research purposes. Each beneficiary is assigned an anonymous identifier allowing for longitudinal analyses. Subjects were followed until death, transplant, or the end of the study (December 31, 2014). In order to evaluate the impact of medication usage, we limited our analyses to beneficiaries who had been continuously enrolled in Medicare Part D for 9 months or more before the index/enrollment visit. We included all patients who met criteria for cirrhosis by using a coding algorithm for administrative data (≥2 validated diagnostic codes for cirrhosis).[23] This study was approved by the institutional review board at the University of Michigan Medical School.

ASCERTAINMENT OF INCIDENT HE

Our primary aim was to describe the incidence of and risk factors for HE. Incident HE was defined if identified for the first time at least 90 days after the

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first cirrhosis diagnosis based on ICD-9 code 572.2 or the prescription of lactulose, neomycin, or rifaximin for >90 days (less if death or transplantation occurred before 90 days), whichever came first. Diagnostic code 572.2 has a specificity of 95%-99%.[23,24] As previously reported,[25] we maximized sensitivity for incident HE using a pharmacy linkage to include prescription of medications that are specific for HE therapy. Chronic lactulose, neomycin, and rifaximin use have few, if any, indications aside from HE and would be expected to be even more specific in a cohort of patients with cirrhosis. These data cannot discern the treatment of covert HE from overt HE. As a functional measure of the severity of HE episodes, we evaluated the risk of hospitalization with HE (defined by inpatient billing codes for HE) associated with medication exposure.

ASCERTAINMENT OF RISK FACTORS FOR HE

Medication use was our principal exposure of interest. We specifically sought to examine the association between incident HE and the use of medication classes that have biological plausibility for the development of HE (opiates, benzodiazepines, gamma aminobutyric acid [GABA]ergics [e.g., gabapentin], and PPIs).[17,26] As described in the analysis section below, associations between medication fills and outcomes were measured as time-varying covariates. For example, consistent fills are more heavily weighted in the model than remote one-time fills. The medications included in each class are described in Supporting Table S2.

For a complete description of the cohort and risk adjustment, we also included age, sex, race, Charlson comorbidity index (modified to exclude liver disease, with the baseline index defined over a 1-year lookback period before cohort entry),[27] etiology of liver disease, complications of cirrhosis, and baseline evaluation by a gastroenterologist/hepatologist (within 365 days before diagnosis of cirrhosis). In addition, we modeled the effect of gastroenterology consultation after cirrhosis diagnosis as a time-varying covariate. Patients could have multiple causes of cirrhosis (e.g., hepatitis B virus [HBV] and HCV and alcohol-related liver disease). As performed by other investigators,[28,29] we also classified a group of patients with likely NAFLD or nonalcohol nonviral-related cirrhosis (no diagnostic codes for viral hepatitis, alcohol-related use disorder, or alcohol-related organ injury). Liver disease severity was assessed using a combination of codes for diagnosis (e.g., ascites, variceal bleeding), procedures (e.g., paracentesis and transjugular intrahepatic portosystemic shunt [TIPS] placement), or medications (e.g., diuretics for ascites or nonselective beta blockers for variceal bleeding prevention) for decompensated cirrhosis. We created a variable for portal hypertension inclusive of varices, ascites, and TIPS. Finally, we sought to account for confounding by indication for our selected medication exposures. As the reasons for prescribing psychoactive medications and PPIs are not known in this data set and our outcome of interest (HE) can have overlapping features with depression, anxiety, and delirium, we adjusted for mental health pharmacotherapy using antidepressant, antipsychotic, and tricyclic antidepressant use.

DATA ANALYSES

All data were derived from a landmark analysis, setting cohort entry as 1 year before the first diagnosis of cirrhosis in order to mitigate the risk of immortal time bias.[30] The risk of HE was presented as incidence per 100 person-years and hazard ratios (HRs) with 95% confidence intervals (CIs). The incidence rate of HE was estimated using a Poisson generalized linear model. Multivariate Cox proportional hazard models were constructed to examine the effects of baseline predictors (e.g., comorbidities) and time-varying covariates (e.g., drug exposures and incident comorbidities and complications of cirrhosis) using first-order autoregressive modeling. This method accounts for the temporal relationship of covariates, i.e., decompensation events during follow-up and longer duration of exposure to medications or prescription fills closer to the outcomes are more heavily weighted. The incidence of hospitalization with HE was evaluated as an incidence rate per 100 person-years. All analyses were performed using R and SAS (SAS Institute Inc., Cary, NC).

Results

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

We included 166,192 Medicare enrollees with cirrhosis who were followed for a median 5.25

(interquartile range [IQR], 2.00-7.00) years per person. The key features of this cohort are their age (median, 65 years), sex parity (54% men), 41% from the southern United States, and 40% disabled (Table 1). Overall, 33% had alcoholic cirrhosis, 30% had HCV (including some with comorbid alcoholic cirrhosis), and 47% had likely NAFLD or nonalcoholic nonviral hepatitis cirrhosis. At baseline, 19% had evidence of portal hypertension and 3% had hepatocellular carcinoma (HCC). Over the course of follow-up, 39% would develop portal hypertension (32% ascites: 9% requiring paracentesis, 15% varices, and 2% spontaneous bacterial peritonitis) and 7% would develop HCC.

CLINICAL RISK FACTORS FOR HE

Incident HE was diagnosed at a rate of 11.6 per 100 person-years of follow-up. Median time to HE diagnosis was 2.04 (IQR, 0.82-3.95) years. Censoring occurred for 508 patients (<1%) who received liver

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY COHORT

	Total (N = 166,192)	Did not Develop HE (n = 117,433)	Developed HE (n = 48,759)	*P* Value†
Age, median (IQR)	65 (57, 72)	65 (58, 73)	63 (55, 71)	*P* < 0.001
Sex, male, n (%)	90,416 (54)	69,901 (54)	27,515 (56)	*P* < 0.001
Race, n (%)				
White	129,561 (78)	91,485 (78)	38,076 (78)	*P* < 0.001
Black	19,711 (12)	14,429 (12)	5,282 (11)	
Other	16,920 (10)	11,519 (10)	5,401 (11)	
Medicaid status, n (%)				
Full	37,491 (23)	25,088 (21)	12,403 (25)	*P* < 0.001
Partial	8,137 (5)	5,247 (4)	2,890 (6)	
None	120,564 (73)	87,098 (74)	33,466 (69)	
Urban/rural status: urban n (%)	135,990 (82)	96,250 (82)	39,740 (82)	*P* = 0.047
Gastroenterology/hepatology consult, n (%)	48,788 (29)	45,722 (39)	3,066 (6)	*P* < 0.001
Region, n (%)				
Midwest	32,938 (20)	24,086 (21)	8,852 (18)	*P* < 0.001
Northeast	31,188 (19)	22,679 (19)	8,509 (17)	
South	67,510 (41)	46,806 (40)	20,704 (42)	
West	34,556 (21)	23,862 (20)	10,694 (22)	
Charlson comorbidity index, n (%)				
0	43,662 (26)	27,547 (23)	17,259 (35)	*P* < 0.001
1	45,561 (27)	29,319 (25)	17,714 (36)	
2	31,183 (19)	20,919 (18)	10,462 (21)	
3 or more	45,786 (28)	39,648 (34)	3,324 (7)	
ESRD, n (%)	6,255 (4)	4,427 (4)	1,828 (4)	*P* = 0.118
Disabled, n (%)	65,774 (40)	43,515 (37)	22,259 (46)	*P* < 0.001
Characteristics of cirrhosis				
Alcoholic cirrhosis*	54,194 (33)	30,011 (26)	24,183 (50)	*P* < 0.001
Hepatitis C cirrhosis*	49,599 (30)	31,247 (27)	18,352 (38)	*P* < 0.001
Nonalcoholic nonviral cirrhosis	78,111 (47)	62,433 (53)	15,678 (32)	*P* < 0.001
Ascites	24,406 (15)	21,584 (18)	410 (1)	*P* < 0.001
Varices	9,826 (6)	8,131 (7)	245 (1)	*P* < 0.001
HCC	4,851 (3)	4,343 (4)	508 (0)	*P* < 0.001

Note that the baseline burden of portal hypertension is lower among patients who developed HE because cohort entry was backdated by 180 days for many patients.
*Many patients had both hepatitis C and alcoholic cirrhosis. Patients with cirrhosis but neither viral hepatitis nor any alcohol use disorder or injury were classified as nonalcoholic nonviral cirrhosis.
†Two-tailed *P* values were obtained using chi-squared testing for categorical variables and the Student *t* test for continuous variables.

transplant, 2,806 patients (2%) who died before HE, and 27,620 patients (15%) who were lost to follow-up. We present unadjusted incident rates for HE in Table 2. Persons with alcohol-related cirrhosis had a higher incidence of HE (17.6 per 100 person-years; IQR, 17.4-17.8) compared to HCV cirrhosis (14.3 per 100 person-years; IQR, 14.1-14.5) or nonalcoholic/nonviral cirrhosis (8.1 per 100 person-years; IQR, 8.0-8.2). The incidence of HE was highest among those with portal hypertension (26.1 per 100 person-years; IQR, 25.8-26.4).

Results of adjusted analyses of demographic and clinical factors associated with incident HE accounting for baseline and time-varying covariates, such as portal hypertensive events and Charlson comorbidities, are presented in Table 3. Some subsets of the cohort with lower crude risks in Table 2 (e.g., women, persons with advanced age) were found to have higher adjusted risks after accounting for the impact of disease severity. Overall, the strongest associations with HE were alcohol-related cirrhosis (adjusted HR [AHR], 1.44) and portal hypertension (AHR, 3.42).

TABLE 2. CRUDE (UNADJUSTED) RATES OF HE BY RISK FACTOR

Clinical Category	Subset (Range)	No. of HE Events	Unadjusted Incidence (per 100 Person-Years)*	*P* value
Overall	-	48,763	11.6 (11.5, 11.6)	-
Sex	Women	21,307	10.7 (10.6, 10.8)	<0.001
	Men	27,565	12.4 (12.3, 12.6)	
Race	White	38,165	11.6 (11.5, 11.8)	<0.001
	Black	5,292	10.6 (10.3,10.9)	
	Other	5,415	12.4 (12.1, 12.7)	
Age (years)	(19, 50)	5,651	13.6 (13.3, 13.8)	<0.001
	(50, 55)	5,585	13.0 (12.8, 13.1)	
	(55, 59)	6,255	12.4 (12.3, 12.5)	
	(60, 65)	4,940	11.9 (11.7, 12.0)	
	(66, 70)	12,511	11.3 (11.2, 11.4)	
	(70, 75)	6,260	10.8 (10.7, 11.0)	
	(75, 80)	4,234	10.3 (10.2, 10.5)	
	80+	3,436	10.0 (9.7, 10.1)	
Charlson comorbidity index	0	17,300	15.2 (14.9, 15.4)	<0.001
	1	17,745	12.0 (11.8, 12.1)	
	2	10,489	12.1 (11.9, 12.4)	
	≥3	3,338	6.6 (6.4, 6.8)	
Etiology of liver disease	Alcohol	24,240	17.6 (17.4, 17.8)	<0.001
	Hepatitis B	2,589	12.0 (11.6, 12.6)	
	Hepatitis C	18,395	14.3 (14.1, 14.5)	
	Nonalcohol nonviral	15,715	8.1 (8.0, 8.2)	
Portal hypertension (varices, ascites)	No	29,429	7.4 (7.3, 7.5)	<0.001
	Yes	19,335	26.1 (25.8,26.4)	
Region	Midwest	8,873	10.6 (10.4, 10.9)	<0.001
	Northeast	8,530	10.7 (10.5,11.0)	
	South	20,757	12.1 (12.0, 12.3)	
	West	10,712	12.2 (12.0, 12.4)	
Community	Rural	9,042	11.6 (11.4,11.9)	0.43
	Urban	39,830	11.6 (11.5,11.7)	
ESRD	No	47,034	11.5 (11.4, 11.6)	<0.001
	Yes	1,838	14.7 (14.0, 15.3)	
Disability before HE	No	26,576	10.7 (10.6,10.9)	<0.001

*Estimates are unadjusted incidence rates and 95% CI. See Table 3 for adjusted risks. This distinction is important to consider and is most pertinent to advanced age where the incidence of HE is lower owing to the competing risk of death but the risk of HE is higher adjusting for disease severity.

TABLE 3. ASSOCIATION BETWEEN INCIDENT HE AND CLINICAL AND DEMOGRAPHIC FACTORS

Baseline Variable	AHR (95% CI)*	*P* Value
Age (per year)	1.00 (1.00, 1.01)	$P < 0.001$
Male	0.98 (0.96, 1.01)	$P = 0.166$
Gastroenterology consult (within 1 year before diagnosis)	0.13 (0.13, 0.14)	$P < 0.001$
ESRD	1.07 (1.00, 1.13)	$P < 0.046$
Disability	1.07 (1.04, 1.11)	$P < 0.001$
Urban	1.05 (1.02, 1.08)	$P = 0.003$
Region (relative to the Midwest)		
Northeast	1.02 (0.99, 1.06)	$P = 0.24$
South	1.16 (1.13, 1.20)	$P < 0.001$
West	1.11 (1.07, 1.15)	$P < 0.001$
Race (relative to white)		
Black	0.86 (0.83, 0.89)	$P < 0.001$
Other	1.02 (0.98, 1.06)	$P = 0.30$
Cirrhosis class (relative to nonalcoholic nonviral)		
Alcoholic cirrhosis	1.44 (1.40, 1.47)	$P < 0.001$
Hepatitis C	1.26 (1.23, 1.29)	$P < 0.001$
Hepatitis B	0.89 (0.84, 0.94)	$P < 0.001$
Time-varying covariates		
Gastroenterology consultation (after cirrhosis diagnosis)	2.08 (2.04, 2.13)	$P < 0.001$
Portal hypertension	3.42 (3.34, 3.50)	$P < 0.001$
CCI (relative to CCI 0)		
CCI = 1	0.83 (0.80, 0.86)	$P < 0.001$
CCI = 2	0.95 (0.91, 0.99)	$P = 0.007$
CCI ≥ 3	1.09 (1.06, 1.13)	$P < 0.001$

*HRs are derived from Cox proportional models using baseline and time-varying covariates as described above. All values are adjusted simultaneously for the other variables in the table.
Abbreviation: CCI, Charlson comorbidity index.

Many other factors were associated with the adjusted risk of incident HE, including comorbidities associated with Medicare insurance, such as disability (AHR, 1.07) and end-stage renal disease (ESRD) (AHR, 1.07). Urban patients and those in the south or west were more likely to develop HE, with respective AHRs of 1.05, 1.16, and 1.11. Black Americans were least likely to develop incident HE (AHR, 0.86). Gastroenterology consultation displayed a complex association with incident HE. Baseline consultation (HR, 0.13) was inversely associated with incident HE; however, when modeling consultation as a time-varying covariate, it was strongly associated with HE (AHR, 2.08; 95% CI, 2.04, 2.13).

Details of how clinical and demographic factors for those who did and did not develop HE changed by year of cohort entry are shown in Supporting Tables S4 and S5. Age, sex, and race differed little over time for either subgroup. Notably, the etiology of cirrhosis shifted substantially over time. The prevalence of HCV rose among those who did not develop HE (23% to 27%), while it fell among those who did develop HE (41% to 34%). Patients became more medically complex overall, with the proportion having extrahepatic comorbidities (Charlson >0) climbing over time for both those who did and did not develop HE. Portal hypertension became more common in both groups, with 40%-58% among those who developed HE and 36%-41% among those who did not. Similarly, the prevalence of HCC rose in both groups (5%-8% in those who developed HE, 6%-9% in those who did not).

MEDICATION USE IS ASSOCIATED WITH HE

The association between incident HE and medication use is described in Table 4. Benzodiazepines (AHR, 1.19; 95% CI, 1.16, 1.22) GABAergics (AHR, 1.17; 95% CI, 1.14, 1.21), opioids (AHR, 1.24; 95% CI, 1.21, 1.27), and PPIs (AHR, 1.41; 95% CI, 1.38, 1.45) were each associated with increased risk of incident HE. These effect estimates were adjusted for comorbidities, etiology of cirrhosis, severity of cirrhosis (cirrhosis complications and medications used for portal hypertension), demographic factors, baseline and time-varying gastroenterology consultation, and the concomitant use of antidepressants, antipsychotics, and tricyclics.

The trends in medication use for patients who did and did not develop incident HE are detailed in Supporting Fig. S2. For each medication, the number and proportion of person-years of prescription are shown. For example, in 2008, 20.6% of the person-years evaluated had PPI prescriptions, while in 2014, the proportion was 27.5%. Benzodiazepines and GABAergics had the largest rise, from 4.5% and 4.1%, respectively, in 2008 to 15.4% and 12.7%, respectively, in 2014. This paralleled the rise in opiate use from 9.0% to 20.2%. Medications associated with liver disease severity, such as diuretics and nonselective beta blockers, did not rise (36.7% and 15.0%, respectively, in 2008 to 34.2% and 17.8%, respectively, in 2014). Medications that are not associated with liver disease severity, such as statins, did rise, but the difference was not statistically significant between those who did and those who did not develop HE (6.6% and 5.4%,

TABLE 4. EFFECTS OF CHRONIC MEDICATION USE ON INCIDENT HE

Medication Class	10,000* Person-Years at Risk	No. of HE Events	Unadjusted HR (95% CI)	Adjusted† HR (95% CI)
Medications with plausible effects on HE pathophysiology				
Benzodiazepines	6.5	9,374	1.23 (1.20, 1.26)	1.19 (1.16, 1.22)
GABAergics	6.0	8,579	1.24 (1.21, 1.27)	1.17 (1.14, 1.21)
Opioids	12.5	18,200	1.37 (1.34, 1.39)	1.24 (1.21, 1.27)
Proton pump inhibitors	12.6	19,677	1.58 (1.55, 1.61)	1.41 (1.38, 1.45)
Medications as markers of mental health treatment				
Antipsychotics	1.8	2,420	1.14 (1.10, 1.19)	1.12 (1.06, 1.18)
Antidepressants	9.8	13,827	1.31 (1.29, 1.34)	1.24 (1.21, 1.27)
Tricyclic antidepressants	3.6	5,100	1.20 (1.16, 1.23)	1.10 (1.05, 1.14)
Medications as markers of liver disease severity				
Diuretics	10.8	23,085	2.70 (2.65, 2.76)	2.08 (2.03, 2.13)
Nonselective beta blockers	5.6	11,398	2.01 (1.97, 2.06)	1.39 (1.35, 1.43)
Medications without direct effects on HE pathophysiology				
Statins	9.3	10,774	1.02 (1.00, 1.04)	1.08 (1.05, 1.11)

*Person-years at risk integrates the duration of prescriptions (before any HE event) for all subjects.
†In addition to adjustment for the other medications in this table, covariates used for adjustment included age, sex, race, etiology of cirrhosis, ESRD, disability, portal hypertension (varices, ascites diagnosis, paracentesis, portosystemic shunt placement), and management by a gastroenterologist.

respectively, in 2008 to 12.8% and 12.7%, respectively, in 2014) (Supporting Fig. S3).

HOSPITALIZATIONS WITH HE

As a measure of the intensity of the associations between the clinical covariates and HE, we evaluated the incidence of hospitalization with HE. Persons with severe liver disease manifested by portal hypertension experienced an incidence rate of 27.11 (95% CI, 26.84, 27.38) hospitalizations per person-years compared to 4.25 (95% CI, 4.18, 4.31) hospitalizations per person-years for those without, giving an incidence rate ratio (IRR) of 6.38 (95% CI, 6.27, 6.51). The respective IRR for PPIs, opiates, and benzodiazepines was 0.49 (95% CI, 0.48, 0.50), 0.69 (95% CI, 0.67, 0.70), and 1.23 (95% CI, 1.20, 1.26).

Discussion

HE is a watershed moment in the natural history of chronic liver disease. After HE, morbidity and mortality sharply rise.[2-4] HE is the most potent risk factor for hospitalization, with frequent readmissions, accidental trauma, diminished quality of life, and death or transplantation.[3,4,31-35] Long-term data regarding the risk of HE are limited among contemporary patients, particularly those with NAFLD, the elderly, and those with comorbidities and polypharmacy. To evaluate the incidence of and risk factors for HE, we examined a very large sample from the Medicare database (>160,000 patients with cirrhosis), which offers long-term follow-up, detailed patient-level characteristics and medication usage, and is enriched with patients who are both older and often have significant comorbidities.

These data extend our understanding of the natural history of cirrhosis in multiple ways. First, our study describes a high rate of incident HE (11.6 per 100 patient-years) among Medicare enrollees with cirrhosis, with the highest (as expected) among those with portal hypertension. Second, we found that alcohol-related cirrhosis was associated with a 1.44-fold higher risk of incident HE compared to patients with likely NAFLD cirrhosis. Third, we found that benzodiazepines, opiates, GABAergics, and PPIs were frequently and increasingly prescribed to patients with cirrhosis and that the use of these medications, even after adjusting for confounders, was significantly associated with incident HE.

NAFLD CIRRHOSIS IS LEAST LIKELY TO PROGRESS TO HE

We demonstrated distinct differences in the risk of HE related to the etiology of liver disease. For patients with nonalcoholic nonviral cirrhosis, the incidence rate of HE was lower than for other causes of

cirrhosis. Data on the prediction of decompensation and HE have been drawn from younger (<60 years old) cohorts of patients with predominantly HCV or alcohol-related cirrhosis.[25,36-40] However, many, perhaps most, new diagnoses of cirrhosis in the United States are related to NAFLD.[5,10] The clinical course of NAFLD cirrhosis is poorly characterized. Prior data from smaller cohorts suggest that the natural history of NAFLD may be more benign than alcohol-related disease, presumably because alcohol use leads to a more progressive course.[41] As patients with NAFLD cirrhosis tend to be older at presentation with extrahepatic comorbidities,[7] population-based data from Medicare are well suited to fill this critical knowledge gap. It should be noted that some individuals with NAFLD cirrhosis are at increased risk of HE, namely those with portal hypertension, ESRD, or a high burden of (particularly disabling) comorbidities. We also found that patients from the southern and western United States, white Americans, and those living in urban centers were at a higher risk of HE. Although consistent with increased mortality due to cirrhosis in the south and west as well as among white persons, potentially reflecting a greater burden of severe disease,[14] the higher incidence of HE in the southern United States requires further study to elucidate the mechanism, particularly with respect to the role of access to care, diet, and specific comorbidities.

MEDICATIONS AND THE RISK OF HE

Medication use records can refine risk stratification for incident HE in administrative data. First, we showed that medications associated with more advanced liver disease, namely diuretics and nonselective beta blockers, can be used to identify high-risk patients and inform risk models for and clinical assessments of HE risk. Second, we demonstrated that despite the uniformly increased risk of incident HE diagnoses among patients exposed to medications such as opioids, PPIs, GABAergics, and benzodiazepines, only benzodiazepines are associated with an increased risk of hospitalization with HE. Further research is needed to determine whether these relationships may indicate either increased severity of HE or confounding by indication associated with benzodiazepines. Whether correlation or causation, these medication records refine and improve our ability to identify persons at risk for HE when using administrative data.[42] Third, we showed that each class is more frequently prescribed over time. We confirmed concerning trends observed in the Veterans Affairs study demonstrating increased opioid and benzodiazepine prescription over time among patients with cirrhosis.[43] We extended those findings by showing that these medication classes are associated with incident HE. PPIs also appear to present a similar pitfall given their frequency of use and association with HE. Although our data cannot determine appropriateness of use, it is likely these medications are overused.

To validate our findings, a prospective study is needed. The only safe method to discern whether these medication classes are truly linked with the risk of HE is a trial of deprescribing or substituting alternatives for benzodiazepines, opiates, GABAergics, and PPIs in patients with cirrhosis. This is likely to be feasible. Patients with Medicare coverage are open to trials of decreasing polypharmacy.[44] Furthermore, deprescribing psychoactive medications has been undertaken without significant adverse effects at the population level.[45]

THE ROLE OF SUBSPECIALTY CONSULTATION

The risk of HE was lowest among patients who received gastroenterology/hepatology consultation at baseline. Although this is consistent with the lower mortality associated with subspecialty consultation seen in other studies of cirrhosis,[46,47] we also found that when treated as a time-varying covariate, gastroenterology consultation is positively associated with incident HE. At a minimum, this temporal association shows that GI consultants are most likely to diagnose HE and that patients who receive frequent follow-up are more likely to be diagnosed. The reduced risk of HE associated with baseline GI consultation (adjusted for the time-varying covariate) may represent lead-time bias but could represent the effect of an intervention. Referred patients may be more likely to receive disease-modifying therapy for their underlying liver disease, such as antiviral therapy for HBV. Indeed, we found that patients with HBV were less likely to develop HE over time, possibly due to antiviral therapy. Similarly, referred patients may be less likely to continue alcohol use. It will be important to evaluate whether interventions initiated in subspecialty clinics could modify the risk of incident HE.

CONTEXTUAL FACTORS

Our findings must be interpreted in the context of the study design. First, although we used ICD codes and medication use as surrogates of liver disease severity, laboratory results were not available to calculate Model for End-Stage Liver Disease scores and we could not determine which patients with hepatitis C were viremic. Second, some triggers for HE, such as continued alcohol abuse, although challenging to determine even in prospective studies using granular data, are not available in this data set. Third, indications for medications could not be captured. Thus, despite an extensive multivariable adjustment, including the use of other medications (i.e., antidepressants and antipsychotics) as surrogates for neuropsychiatric disturbances, residual confounding by indication may be present. The symptoms of mild HE include poor sleep, depression, and irritability[48] and are often managed using benzodiazepines, GABAergics, and opiates. Patients receiving these medications could have mild HE at enrollment and are therefore at greater risk of incident HE. PPIs are frequently linked with adverse events, such as pneumonia and *Clostridium difficile* infection, in retrospective studies, but few such associations have been validated in prospective studies. Fourth, further research is needed to elucidate the mechanism for the impact of baseline gastroenterology consultation on the risk of HE, focusing on the effect of disease-specific interventions, such as HCV therapy and alcohol abstinence, and whether such consults decrease psychoactive medication use. Fifth, we could not distinguish covert from overt HE on the basis of these data. Furthermore, even though it can be challenging to adjudicate the accuracy of a given clinician's diagnosis of HE in a prospective study,[49] the clinical decision to bill for HE or initiate ≥90 days of therapy for HE cannot be interrogated further using these data. Finally, these data reflect the experience of Medicare-enrolled persons who are either >65 years old or eligible as a result of disability or specific comorbidities (e.g., dialysis).

Conclusion

Incident HE is frequent in a cohort of Medicare-enrolled patients with cirrhosis. These data provide novel data regarding the risk of HE in a cohort of predominantly older contemporary patients with NAFLD and comorbidities. We demonstrated associations between the risk of HE and certain classes that can be potentially discontinued, justifying prospective trials of deprescribing. Given the adverse consequences of HE and the economic costs of managing HE, preventative efforts are warranted for high-risk subsets.

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Supporting Information

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