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ORIGINAL ARTICLE

Increasing Burden of Hepatic Encephalopathy Among Hospitalized Adults: An Analysis of the 2010–2014 National Inpatient Sample

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Abstract

Background Hepatic encephalopathy (HE) is associated with substantial morbidity and mortality, contributing significant burden on healthcare systems.

Aim We aim to evaluate trends in clinical and economic burden of HE among hospitalized adults in the USA.

Methods Using the 2010–2014 National Inpatient Sample, we identified adults hospitalized with HE using ICD-9-CM codes. Annual trends in hospitalizations with HE, in-hospital mortality, and hospital charges were stratified by the presence of acute liver failure (ALF) or cirrhosis. Adjusted multivariable regression models were evaluated for predictors of in-hospital mortality and hospitalization charges.

Results Among 142,860 hospitalizations with HE (mean age 59.3 years, 57.8% male), 67.7% had cirrhosis and 3.9% ALF. From 2010 to 2014, total number of hospitalizations with HE increased by 24.4% (25,059 in 2010 to 31,182 in 2014, $p < 0.001$). Similar increases were seen when stratified by ALF (29.7% increase) and cirrhosis (29.7% increase). Overall in-hospital mortality decreased from 13.4% (2010) to 12.3% (2014) ($p = 0.001$), with similar decreases observed in ALF and cirrhosis. Total inpatient charges increased by 46.0% ($8.15 billion, 2010 to $11.9 billion, 2014). On multivariable analyses, ALF was associated with significantly higher odds of in-hospital mortality (OR 5.37; 95% CI 4.97–5.80; $p < 0.001$) as well as higher mean inpatient charges (122.6% higher; 95% CI + 115.0–130.3%; $p < 0.001$) compared to cirrhosis. The presence of ascites, hepatocellular carcinoma, and hepatorenal syndrome was associated with increased mortality.

Conclusions The clinical and economic burden of hospitalizations with HE in the USA continues to rise. In 2014, estimated national economic burden of hospitalizations with HE reached $11.9 billion.

Keywords Hepatic encephalopathy · Cirrhosis · Acute liver failure · Burden · Mortality · Charges · Liver disease

Abbreviations

ALD	Alcoholic liver disease
ALF	Acute liver failure
EV	Esophageal varices
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCUP	Healthcare Cost and Utilization Project
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
NAFLD	Nonalcoholic fatty liver disease
NIS	National (Nationwide) Inpatient Sample
USD	US dollar

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Introduction

Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers [1, 2]. It is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations, known as minimal HE, to hepatic coma [1]. HE has been classified according to four factors: the type of underlying disease, the severity of manifestations, its time course, and the existence of precipitating factors [3].

Development of HE is associated with a poor prognosis [4, 5]. In the presence of chronic liver disease, HE typically heralds hepatic decompensation, and its development is usually associated with high mortality, indicating the need for liver transplantation [4, 6–8]. Overt HE occurs in approximately 30–45% of patients with cirrhosis, while minimal HE may affect up to 60% of patients with chronic liver disease and up to 80% with cirrhosis [9–13]. HE is also the most common, possibly preventable, cause for readmission [14–16]. Cirrhosis and cirrhosis-related complications contribute to significant healthcare resource utilization, with a majority of this attributed to inpatient hospitalization [4, 17, 18]. Better understanding trends and predictors of HE-related outcomes can help target quality improvement programs to improve management of patients and to reduce healthcare resource utilization among this high-risk population [16].

HE is subdivided into three types: Type A is due to acute liver failure (ALF), type B is due to portosystemic bypass or shunting without intrinsic liver disease, and type C is due to cirrhosis [3]. While the clinical manifestations of types B and C are similar, type A has distinct features and may be associated with increased intracranial pressure and a risk of cerebral herniation [1, 19]. Due to differences in clinical manifestations, the burden associated with each type could vary significantly. Previous studies analyzing the burden of HE in the USA have not accounted for the differences in clinical manifestations based on etiology and associated complications [4, 17, 20]. In this study, we used the National Inpatient Sample (NIS), a large, nationally representative, inpatient database, to analyze recent trends in HE hospitalizations and to estimate the national burden of HE in the USA, with a focus on HE patients with ALF and cirrhosis.

Methods

Data Sources

The NIS is the largest all-payer inpatient database of hospital discharges in the USA maintained as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality [21]. The NIS contains de-identified information regarding each hospitalization including patient demographics, admission status, discharge diagnoses, procedures, comorbid conditions, outcomes, and hospital charges. Participating hospitals are sampled based on characteristics such as size, location (rural/urban), geographic region, ownership, and teaching status.

Our study evaluated 2010–2014 NIS data. Between 2010 and 2011, the NIS comprised all inpatient discharges (100%) from a random 20% sample of acute-care hospitals in the USA. Starting in 2012, NIS modified its method of data acquisition to include a systematic sampling of 20% of discharges from all (100%) hospitals stratified by hospital, census division, ownership status, urban versus rural location, teaching status, and bed size, as well as patient diagnosis-related group and admission month [22, 23].

Study Population and Variables

In this study, we used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify all hospitalized adults (age $\geq$ 18 years) between the years of 2010 and 2014 with HE listed as a diagnosis (ICD-9-CM code 572.2) at the time of discharge from the hospital [4]. HE patients were further categorized based on the type of underlying disease: only ALF (ALF–HE), only cirrhosis (cirrhosis–HE), both ALF and cirrhosis (ALF + cirrhosis), and other or unknown causes. Our analyses specifically focused on ALF–HE and cirrhosis–HE hospitalizations. Demographic characteristics included age, sex, race, and primary payer status. Other patient-level data included a comprehensive list of etiologies identified using ICD-9-CM codes (Supplementary Table 1) [24, 25]. Elixhauser comorbidities, number of chronic conditions, diagnoses, and procedures as provided by NIS were also evaluated [26, 27]. Hospital-level data included hospital size, location and teaching status, and region of the hospital. Outcomes analyzed in this study were in-hospital mortality, defined as death prior to hospital discharge, and inpatient charges. Inpatient charges were inflation adjusted to 2014 US dollars (USD) using the consumer price index maintained by the US Department of Labor [28].

Statistical Analysis

National estimates were obtained for the total number of hospitalizations with HE and total resource utilization parameters by calendar year using individual discharge sampling weights, and sampling strata (used in the NIS to sample hospitals based on geographic region, control, location/teaching status, and bed size) were accounted for the survey design effects using Taylor series linearization. Secular trends were

Table 1 Patient- and hospital-level characteristics of HE-related hospitalizations, 2010–2014 NIS Data ($N = 142,860$)

Characteristic	*N*	Mean or % (SE)
Age, years		59.3 (0.06)
Male sex	82,517	57.8 (0.17)
Race		
White	90,947	68.3 (0.50)
Black	12,704	9.51 (0.21)
Hispanic	21,206	16.0 (0.45)
Asian or Pacific Islander	2128	1.61 (0.07)
Native American	2395	1.84 (0.12)
Other	3819	2.84 (0.14)
Insurance		
Medicare	67,018	47.0 (0.23)
Medicaid	28,433	20.0 (0.23)
Private (including HMO)	32,288	22.6 (0.27)
Self-pay	8579	6.03 (0.12)
No charge	814	0.58 (0.06)
Other	5383	3.77 (0.12)
Hospital bed size		
Small	18,376	12.6 (0.28)
Medium	35,445	25.1 (0.45)
Large	88,253	62.3 (0.54)
Hospital location/teaching status		
Rural	14,378	10.1 (0.26)
Urban non-teaching	52,859	36.8 (0.58)
Urban teaching	74,837	53.1 (0.62)
Hospital region		
Northeast	25,055	17.5 (0.50)
Midwest	29,341	20.4 (0.57)
South	55,290	38.8 (0.63)
West	33,174	23.3 (0.52)
Primary predictor		
Cirrhosis	96,629	67.7 (0.24)
ALF	5532	3.88 (0.07)
ALF + cirrhosis	3903	2.74 (0.05)
Other/unknown	36,796	25.7 (0.23)
Etiologies		
Alcoholic liver disease	64,472	45.2 (0.26)
Biliary cholangitis	1896	1.33 (0.04)
Hepatitis B	484	0.34 (0.02)
Hepatitis C	8709	6.10 (0.18)
Nonalcoholic fatty liver disease	10,111	7.10 (0.12)
Cirrhosis-related complications		
Ascites	54,247	38.0 (0.25)
Esophageal varices	27,401	19.2 (0.19)
Hepatocellular carcinoma	5062	3.56 (0.07)
Hepatorenal syndrome	12,006	8.41 (0.12)
Portal hypertension	38,270	26.8 (0.29)
Number of chronic conditions		6.78 (0.02)
Number of diagnoses		15.6 (0.06)
Number of procedures		2.30 (0.03)
Primary diagnosis of hepatic encephalopathy	52,730	37.0 (0.20)
Comorbidities		
AIDS	453	0.32 (0.02)
Alcohol abuse	57,093	40.0 (0.26)
Deficiency anemias	48,972	34.3 (0.23)
Rheumatoid arthritis/collagen vascular diseases	2673	1.88 (0.05)
Chronic blood loss anemia	4146	2.90 (0.05)
Congestive heart failure	17,430	12.2 (0.13)
Chronic pulmonary disease	24,479	17.1 (0.15)
Coagulopathy	61,187	42.9 (0.25)
Depression	18,612	13.0 (0.15)
Diabetes, uncomplicated	41,213	28.9 (0.18)
Diabetes with chronic complications	9064	6.36 (0.10)
Drug abuse	7919	5.57 (0.09)
Hypertension, uncomplicated and complicated	64,754	45.4 (0.22)
Hypothyroidism	17,832	12.5 (0.12)
Lymphoma	949	0.66 (0.02)
Fluid and electrolyte disorders	80,311	56.3 (0.25)
Metastatic cancer	5013	3.51 (0.07)
Other neurological disorders	16,536	11.6 (0.12)
Obesity	16,721	11.8 (0.13)
Paralysis	2265	1.57 (0.04)
Peripheral vascular disorders	5498	3.85 (0.07)
Psychoses	9728	6.81 (0.10)
Pulmonary circulation disorders	5067	3.52 (0.07)
Renal failure	30,318	21.2 (0.17)
Solid tumor without metastasis	5520	3.87 (0.07)
Peptic ulcer disease excluding bleeding	98	0.07 (0.01)
Valvular disease	5167	3.62 (0.06)
Weight loss	24,582	17.1 (0.24)

assessed using standard orthogonal contrasts in the effect estimates after regressing all the available socioeconomic and clinical outcomes on year, modeled as a categorical predictor. Multivariable logistic regression was used to identify factors associated with in-hospital deaths. Similarly, factors that impacted hospital charges were assessed using multiple linear regression after logarithmic transformation of the outcome. Coefficients from these linear models were exponentiated to yield a percentage change in the outcome associated with each predictor. To avoid over-fitting, variables included in the multivariable models were identified a priori based on what we hypothesized to be clinically relevant in affecting in-hospital mortality and in-hospital charges. All multivariable models were adjusted for patient-level characteristics (age, sex, race, primary payer), hospital-level characteristics (size, location and teaching status, region),

and comorbidities. p values ≤ 0.05 were considered statistically significant. All statistical analyses were performed on survey-weighted data and utilized Stata version 14.0 (StataCorp, College Station, TX). This study was granted exempt status by the Alameda Health System Institutional Review Board.

To deal with missing data, we implemented a sensitivity analysis using reweighted estimating equations [29, 30]. In this analysis, the probability of having all covariates observed was calculated using ancillary logistic models using all non-missing variables, including the outcomes (in-hospital mortality and inpatient charges), as predictors. Each observation with complete data is weighted by the inverse of the probability of having no missing data. In this reweighted sensitivity analysis, results did not differ meaningfully from the primary complete-case analyses.

Results

Hospitalization Trends

From 2010 to 2014, a total of 142,860 hospitalizations with HE met the inclusion criteria, which translates to a national estimate of 698,077 hospitalizations with HE. From 2010 to 2014, the total number of hospitalizations with HE increased by 24.4% (25,059 in 2010 to 31,182 in 2014, $p < 0.001$),

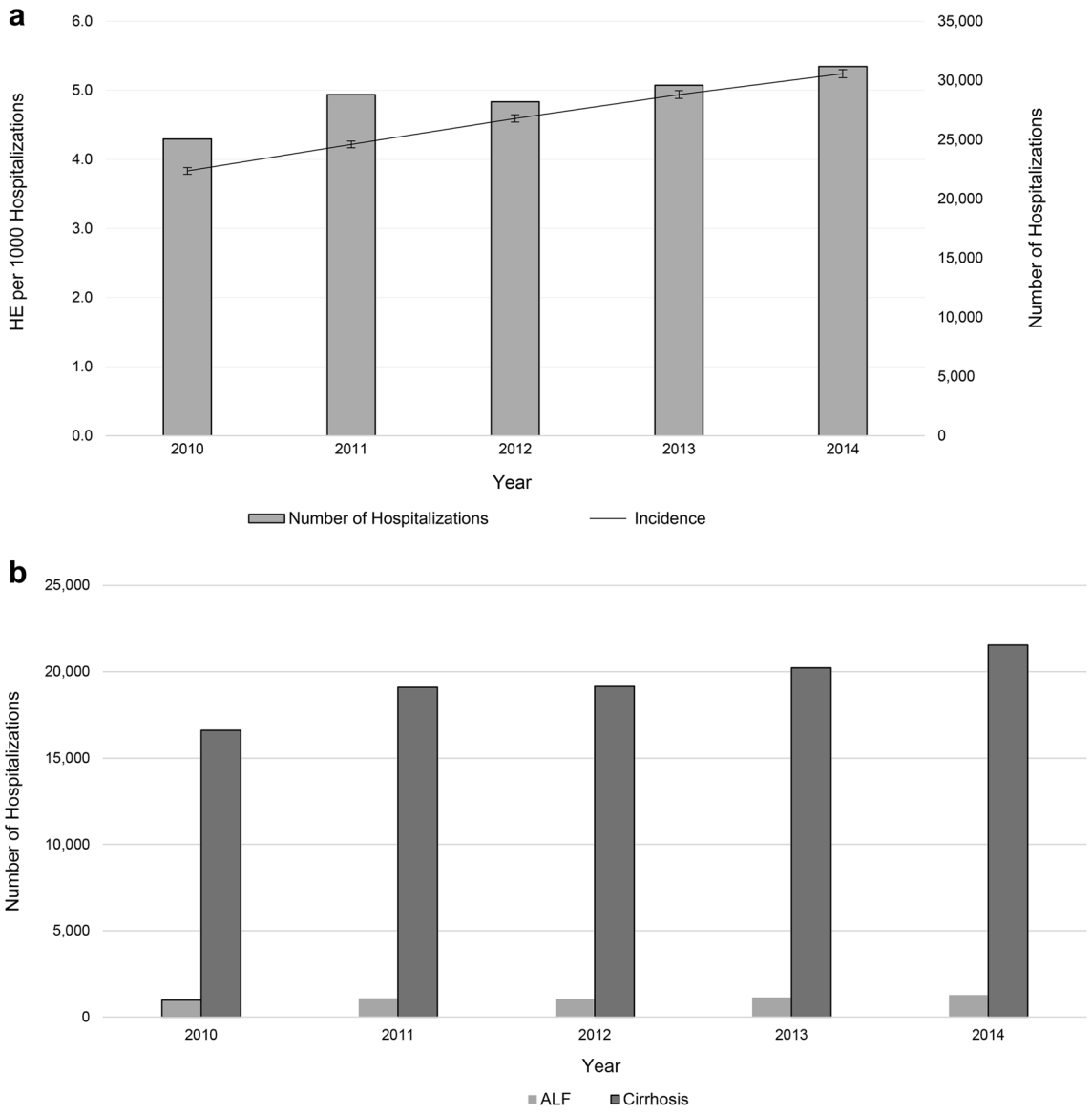

Fig. 1 **a** Incidence of HE per 1000 hospitalizations and the number of total hospitalizations with HE. Error bars represent 95% CI. **b** Number of ALF- and cirrhosis-related hospitalizations among HE patients

and the incidence of HE hospitalizations increased by 36.7% (3.83 per 1000 in 2010 to 5.24 per 1000 in 2014, $p < 0.001$) (Fig. 1a). During this same period, the total number of ALF–HE hospitalizations increased by 29.7% (985 in 2010 to 1278 in 2014, $p = 0.48$) and cirrhosis–HE hospitalizations also increased by 29.7% (16,612 in 2010 to 21,542 in 2014, $p = 0.0001$) (Fig. 1b).

Patient Characteristics

Table 1 summarizes patient demographics for hospitalizations with HE from 2010 to 2014. The mean age was 59.3 years, 57.8% were male, and 68.3% were non-Hispanic whites. Nearly half of the patients were on Medicare (47.0%), whereas 20.0% had Medicaid and 22.6% had private insurance. When evaluating the etiology of HE, the majority of HE patients had cirrhosis (67.7%), whereas 3.88% had ALF and 2.74% had ALF + cirrhosis. The most common etiology was alcoholic liver disease (ALD) (45.2%), followed by nonalcoholic fatty liver disease (NAFLD) (7.1%) and hepatitis C virus (HCV) infection (6.1%). Among cirrhosis-related complications, ascites was the most common complication (38.0%), followed by portal hypertension (26.8%) and esophageal varices (EV) (19.2%). As expected, alcohol abuse, anemia, coagulopathy, diabetes, hypertension, fluid and electrolyte disorders, and renal failure were among some of the more frequent comorbid conditions (Table 1).

Among all hospitalizations with HE, the proportion of hospitalizations with a primary diagnosis of HE showed a decreasing trend (38.5% in 2007 to 35.6% in 2014, $p = 0.0037$) (Table 2). The mean age at the time of discharge increased slightly, and the proportion of hospitalizations among women also increased (Table 2). From 2010 to 2014, the prevalence of HCV infection among hospitalizations with HE decreased from 7.81 to 5.18% ($p < 0.0001$), whereas the prevalence of NAFLD increased from 5.21 to 8.60% ($p < 0.0001$). When evaluating the prevalence of cirrhosis-related complications, ascites, EV, hepatorenal syndrome (HRS), and portal hypertension all increased significantly from 2010 to 2014 (Table 2). When evaluating the subset of ALF–HE and cirrhosis–HE hospitalizations, similar trends were observed (Supplementary Tables 2 and 3).

In-Hospital Mortality

Over the 5-year period, in-hospital mortality for hospitalizations with HE decreased by 8.21% (13.4% in 2010 to 12.3% in 2014, $p = 0.0009$) (Fig. 2). Among HE hospitalizations, in-hospital mortality among those with a primary diagnosis of HE also showed a decline (decreased by 18.6%, 6.67% in 2007 to 5.43% in 2014, $p = 0.0005$). In-hospital mortality among the ALF–HE subset of patients decreased by 10.8% (44.8% in 2010 to 40.0% in 2014, $p = 0.011$) and cirrhosis–HE patients decreased by 5.86% (9.38% in 2010 to 8.83% in 2014, $p = 0.095$) (Fig. 2).

Table 2 Overall trends in clinical characteristics of patients with HE

Outcome/year	2010	2011	2012	2013	2014	*p* value
Age, years, mean (SE)	58.9 (0.19)	59.3 (0.18)	59.3 (0.10)	59.5 (0.10)	59.5 (0.10)	0.0037
Male sex, % (SE)	58.9 (0.45)	57.4 (0.47)	58.3 (0.35)	57.4 (0.33)	57.1 (0.32)	0.0039
Etiologies, % (SE)						
Alcoholic liver disease	45.7 (0.80)	45.6 (0.75)	45.5 (0.43)	44.7 (0.41)	44.6 (0.41)	0.1319
Biliary cholangitis	1.31 (0.12)	1.34 (0.12)	1.26 (0.08)	1.28 (0.08)	1.45 (0.08)	0.5270
Hepatitis B	0.44 (0.07)	0.30 (0.05)	0.37 (0.04)	0.31 (0.04)	0.32 (0.04)	0.1916
Hepatitis C	7.81 (0.62)	6.24 (0.57)	6.19 (0.27)	5.49 (0.25)	5.18 (0.23)	< 0.0001
Nonalcoholic fatty liver disease	5.21 (0.28)	6.22 (0.32)	7.25 (0.23)	7.71 (0.23)	8.60 (0.25)	< 0.0001
Cirrhosis complications, % (SE)						
Ascites	36.6 (0.70)	36.7 (0.67)	37.4 (0.47)	38.4 (0.48)	40.5 (0.49)	< 0.0001
Esophageal varices	18.1 (0.44)	18.5 (0.61)	19.0 (0.35)	19.6 (0.35)	20.6 (0.35)	< 0.0001
Hepatocellular carcinoma	3.48 (0.23)	3.43 (0.19)	3.57 (0.14)	3.57 (0.13)	3.71 (0.13)	0.3115
Hepatorenal syndrome	8.37 (0.37)	7.70 (0.31)	8.30 (0.22)	8.51 (0.23)	9.06 (0.22)	0.0223
Portal hypertension	23.6 (0.84)	26.2 (0.89)	26.9 (0.44)	27.6 (0.47)	29.0 (0.51)	< 0.0001
LOS, d, mean (SE)	8.14 (0.16)	8.09 (0.17)	7.99 (0.10)	7.81 (0.10)	7.99 (0.10)	0.1710
Number of chronic conditions, mean (SE)	6.20 (0.08)	6.72 (0.07)	6.87 (0.03)	7.01 (0.03)	6.99 (0.04)	< 0.0001
Number of diagnoses, mean (SE)	13.9 (0.19)	15.3 (0.17)	15.7 (0.09)	16.0 (0.09)	16.9 (0.09)	< 0.0001
Number of procedures, mean (SE)	2.35 (0.08)	2.29 (0.08)	2.31 (0.04)	2.26 (0.03)	2.31 (0.04)	0.6122
Primary diagnosis of hepatic encephalopathy, %(SE)	38.5 (0.55)	36.4 (0.64)	37.4 (0.35)	37.4 (0.35)	35.6 (0.34)	0.0037

Table 3 Predictors of in-hospital mortality in patients with HE

	In-hospital mortality			
	OR	LL 95% CI	UL 95% CI	*p*
Age, years	1.02	1.01	1.02	< 0.001
Sex				
Male	1.00	Ref.	Ref.	Ref.
Female	1.03	0.99	1.07	0.156
Race				
White	1.00	Ref.	Ref.	Ref.
Black	1.21	1.14	1.29	< 0.001
Hispanic	0.96	0.91	1.02	0.145
Asian or Pacific Islander	1.13	0.99	1.29	0.081
Native American	0.92	0.79	1.05	0.219
Other	0.93	0.83	1.04	0.187
Insurance				
Medicare	1.00	Ref.	Ref.	Ref.
Medicaid	1.26	1.19	1.34	< 0.001
Private (including HMO)	1.22	1.16	1.28	< 0.001
Self-pay	1.63	1.50	1.76	< 0.001
No charge	1.49	1.18	1.87	0.001
Other	1.68	1.50	1.87	< 0.001
Hospital bed size				
Small	1.00	Ref.	Ref.	Ref.
Medium	1.14	1.06	1.23	0.001
Large	1.20	1.12	1.28	< 0.001
Hospital location/teaching status				
Rural	1.00	Ref.	Ref.	Ref.
Urban non-teaching	1.09	1.01	1.17	0.033
Urban teaching	1.22	1.13	1.31	< 0.001
Hospital region				
Northeast	1.00	Ref.	Ref.	Ref.
Midwest	0.83	0.77	0.89	< 0.001
South	0.92	0.86	0.97	0.005
West	0.96	0.90	1.03	0.254
Primary predictor				
Cirrhosis	1.00	Ref.	Ref.	Ref.
ALF	5.37	4.97	5.80	< 0.001
Etiologies[a]				
Alcoholic liver disease	0.99	0.94	1.05	0.840
Biliary cholangitis	0.52	0.44	0.62	< 0.001
Hepatitis C	0.81	0.74	0.89	< 0.001
Nonalcoholic fatty liver disease	0.54	0.49	0.60	< 0.001
Cirrhosis complications[a]				
Ascites	1.21	1.16	1.26	< 0.001
Esophageal varices	0.97	0.92	1.02	0.252
Hepatocellular carcinoma	1.16	1.03	1.31	0.014
Hepatorenal syndrome	3.38	3.20	3.57	< 0.001
Portal hypertension	0.79	0.76	0.83	< 0.001

Adjusted for Elixhauser comorbidities

[a]Compared to not having the disease (referent group OR 1)

On adjusted multivariable analyses, among patients hospitalized with HE, the presence of ALF was associated with significantly higher odds of in-hospital mortality (OR 5.37; 95% CI 4.97–5.80; $p < 0.001$) compared to cirrhosis (Table 3). The presence of ascites (OR 1.21; 95% CI 1.16–1.26; $p < 0.001$), hepatocellular carcinoma (HCC) (OR 1.16; 95% CI 1.03–1.31; $p = 0.014$), and HRS (OR 3.38; 95% CI 3.20–3.57; $p < 0.001$) was associated with higher odds of in-hospital mortality (Table 3). Additionally, increasing age, being female (vs. male), and being black (vs. non-Hispanic White) were all associated with higher odds of in-hospital mortality (Table 3). With respect to hospital settings, being admitted to a larger, urban, teaching hospital in the Northeast region of the USA was associated with higher odds of in-hospital mortality.

Resource Utilization

From 2010 to 2014, total inpatient charges associated with HE hospitalizations increased by 46.0% (8.15 billion USD to 11.9 billion USD) (Fig. 3a). Among HE hospitalizations, total charges among those with a primary diagnosis of HE also showed an increase (increased by 28.7%, 1.81 billion USD in 2007 to 2.33 billion USD in 2014). Total charges for the subset of ALF–HE increased by 44.7% (0.76 billion USD in 2010 to 1.1 billion USD in 2014) and cirrhosis–HE increased by 49.8% (4.58 billion USD in 2010 to 6.86 billion USD in 2014) (Fig. 3a). Mean inpatient charges increased by 12.4% ($p = 0.004$) overall for HE patients, 8.36% for those with a primary diagnosis of HE ($p = 0.015$), 8.81% ($p = 0.82$) for ALF–HE patients, and 10.9% ($p = 0.003$) for cirrhosis–HE patients (Fig. 3b).

On adjusted multivariable analyses, among patients hospitalized with HE, the presence of ALF was associated with significantly higher mean inpatient charges compared to cirrhosis (122.6% higher; 95% CI + 115.0–130.3%; $p < 0.001$) (Table 4). The presence of ascites (21.4% higher; 95% CI + 19.8–23.0%; $p < 0.001$), EV (18.3%; 95% CI + 16.4–20.2%; $p < 0.001$), HRS (38.9% higher; 95% CI + 34.8–43.1%; $p < 0.001$), and portal hypertension (14.4% higher; 95% CI + 12.5–16.4%; $p < 0.001$) was associated with significantly higher mean inpatient charges (Table 4). Increasing age, being female (vs. male), and being black, Hispanic, or Asian Pacific Islander (vs. non-Hispanic White) were all associated with higher mean inpatient charges (Table 4). Additionally, being admitted to a larger, urban, teaching hospital in the Western region of the USA was associated with higher mean inpatient charges.

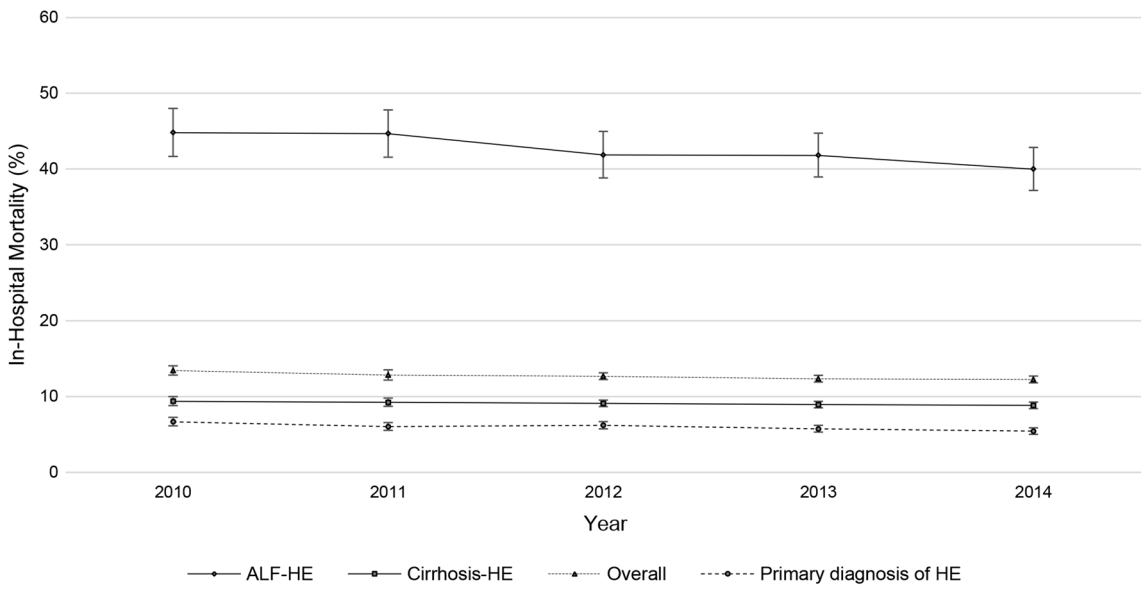

Fig. 2 Overall in-hospital mortality among all patients with HE and among subgroups of patients with a primary diagnosis of HE, ALF–HE, and cirrhosis–HE. Error bars represent 95% CI

Discussion

Previous studies evaluating HE hospitalization trends through 2009 reported on the rising burden of hospitalizations and healthcare resource utilization [4, 17]. Our current study encompassing the 5-year period from 2010 to 2014 demonstrated a concerning observation: the incidence of hospitalizations with HE in the USA continued to rise, driving a steady increase in healthcare resource utilization such that estimated national inpatient charges for hospitalizations among patients with HE reached $11.9 billion USD in 2014. While the proportion of patients hospitalized with a primary diagnosis of HE seemed to decrease, the overall economic burden due to HE is still on the rise.

The rising clinical and economic burden of HE is a reflection of the increasing burden of chronic liver disease in the USA [31, 32]. Previous studies have reported on the significant burden of chronic HCV and ALD, both leading causes of HCC and end-stage liver disease requiring liver transplantation [33]. The increasing burden of NAFLD is also recognized [34], and while disease progression to cirrhosis and HCC among NAFLD patients may be slower than viral hepatitis, the overwhelming number of individuals at risk for NAFLD and the current lack of effective therapies may contribute to a large emerging cohort of aging NAFLD patients with advanced liver disease. While success with antiviral therapies has significantly altered the epidemiology and outcomes of individuals with chronic hepatitis B virus (HBV) and chronic HCV [33, 35], the sparse therapeutic landscape for ALD and NAFLD is concerning, but offers many opportunities. The development and implementation of therapies early in disease progression to prevent cirrhosis and cirrhosis-related complications will have the greatest impact on healthcare resource utilization and overall mortality among chronic liver disease patients.

Our study is unique in attempting to separate out patients with HE due to ALF and those with HE due to cirrhosis. The rationale for this stratification is that ALF patients and cirrhosis patients are inherently different, and while a combined analysis does offer the advantage of a big picture view, a stratified analysis offers more granular insight into mortality and healthcare resource utilization among these groups. Although the incidence of HE hospitalizations increased overall, among both cirrhosis and ALF groups, the vast majority of HE burden is driven by cirrhosis patients (Fig. 1a, b). When evaluating healthcare resource utilization, we observed that majority of hospitalization charges were driven by cirrhosis patients (Fig. 3a); however, mean hospitalization charges for ALF patients were significantly higher than charges for cirrhosis patients (Fig. 3b), suggesting that while sicker and requiring more complex care, ALF patients with HE are less common and thereby contribute less to the overall HE burden. Along the same lines, ALF patients had significantly greater in-hospital mortality compared to cirrhosis patients (Fig. 2). Furthermore, given differences in disease pathogenesis between ALF and cirrhosis, implementing therapies aimed at delaying or halting disease progression to prevent HE is clinically more effective in cirrhosis patients than ALF patients. Thus, future studies assessing HE epidemiology and outcomes should ensure a separate analyses of ALF patients.

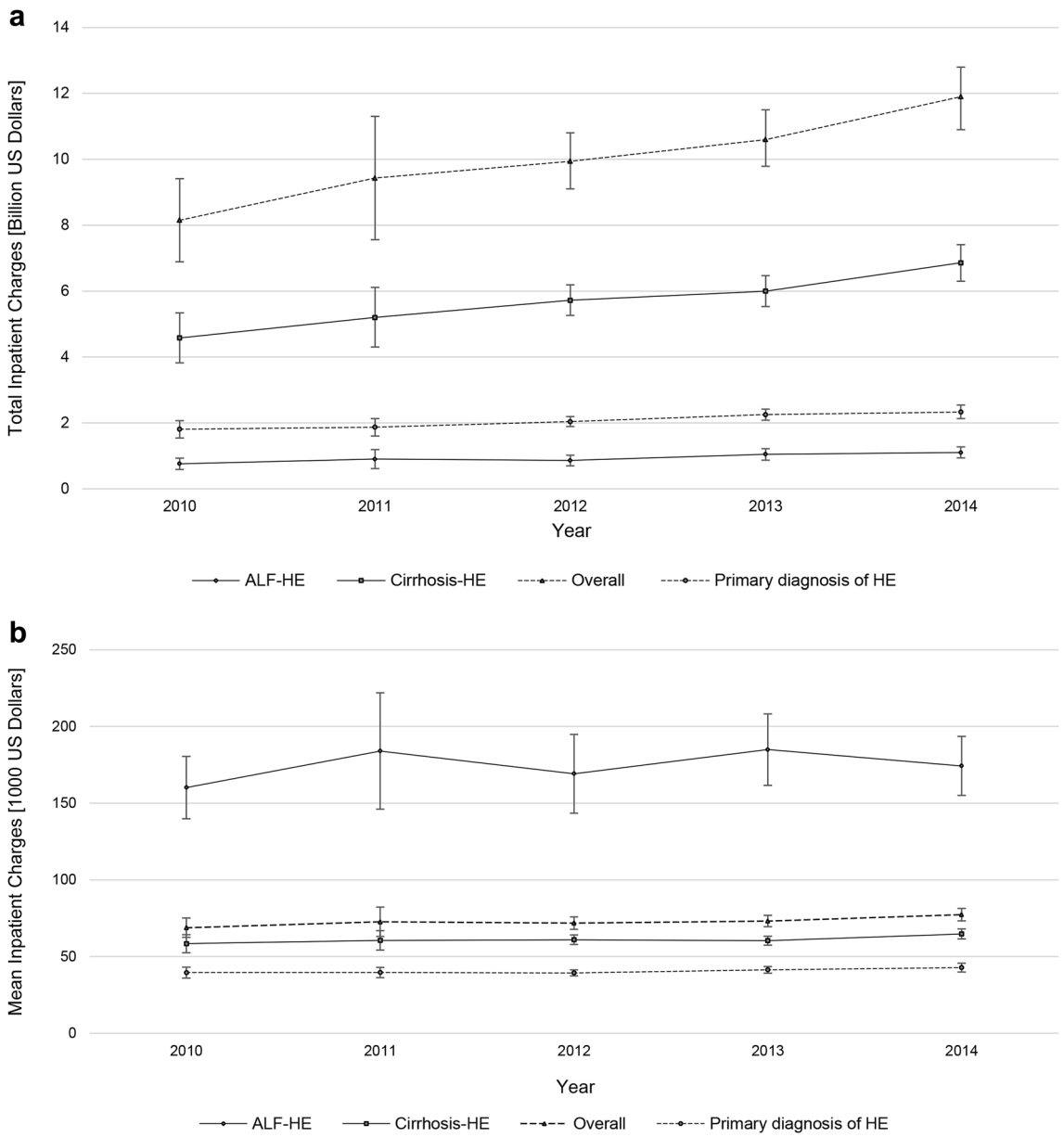

Fig. 3 **a** Total inpatient charges among all patients with HE and among subgroups of patients with a primary diagnosis of HE, ALF–HE, and cirrhosis-HE. Error bars represent 95% CI. **b** Mean inpatient charges among all patients with HE, and among subgroups of patients with a primary diagnosis of HE, ALF–HE, and cirrhosis–HE. Error bars represent 95% CI

While our study provides important epidemiological trends using the largest all-payer database of hospital discharges in the USA, limitations inherent in cross-sectional and claims-based studies should be acknowledged. The use of data collected from administrative claims is potentially limited by errors in coding leading to misclassification biases [36]. However, we used a thorough process to identify ICD-9 codes to ensure comprehensive capture, and particularly for our definition of HE, we used similar codes from previously published manuscripts to ensure consistency of comparisons and trends analyses [4, 24, 25]. In addition, while we utilized a thorough review of ICD-9 codes to identify HE, given the cross-sectional nature of the study, it was difficult to determine whether HE was present at diagnosis or developed as a complication during the hospitalization. In our analysis of liver disease etiology, HCV, ALD, and NAFLD only accounted for 58% of all hospitalizations with HE. Clinically, we would have expected these three leading

Table 4 Predictors of mean inpatient charges in patients with HE

	%Δ	Lower %	Upper %	*p*
Age, years	−0.20%	−0.30%	−0.10%	<0.001
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	+2.25%	+0.99%	+3.53%	<0.001
Race				
White	Ref.	Ref.	Ref.	Ref.
Black	+5.36%	+2.18%	+8.64%	0.001
Hispanic	+12.7%	+9.25%	+16.2%	<0.001
Asian or Pacific Islander	+13.5%	+6.83%	+20.5%	<0.001
Native American	−16.3%	−20.8%	−11.5%	<0.001
Other	+6.77%	+1.33%	+12.5%	0.014
Insurance				
Medicare	Ref.	Ref.	Ref.	Ref.
Medicaid	−0.98%	−2.90%	+1.00%	0.326
Private (including HMO)	+1.28%	−0.60%	+3.20%	0.183
Self-pay	+0.35%	−2.90%	+3.70%	0.833
No charge	+9.56%	+0.80%	+19.1%	0.032
Other	−11.0%	−14.8%	−7.10%	<0.001
Hospital bed size				
Small	Ref.	Ref.	Ref.	Ref.
Medium	+11.6%	+7.01%	+16.3%	<0.001
Large	+36.9%	+31.5%	+42.5%	<0.001
Hospital location/teaching status				
Rural	Ref.	Ref.	Ref.	Ref.
Urban non-teaching	+64.5%	+57.4%	+71.9%	<0.001
Urban teaching	+92.4%	+83.9%	+101.3%	<0.001
Hospital region				
Northeast	Ref.	Ref.	Ref.	Ref.
Midwest	−23.5%	−28.3%	−18.3%	<0.001
South	−13.4%	−18.4%	−8.03%	<0.001
West	+20.8%	+13.1%	+29.0%	<0.001
Primary predictor				
Cirrhosis	Ref.	Ref.	Ref.	Ref.
ALF	+122.6%	+115.0%	+130.3%	<0.001
Etiologies[a]				
Alcoholic liver disease	−2.10%	−3.80%	−0.20%	0.029
Biliary cholangitis	−23.0%	−27.2%	−18.5%	<0.001
Hepatitis C	−7.70%	−11.0%	−4.30%	<0.001
Nonalcoholic fatty liver disease	−17.4%	−19.3%	−15.5%	<0.001
Cirrhosis complications[a]				
Ascites	+21.4%	+19.8%	+23.0%	<0.001
Esophageal varices	+18.3%	+16.4%	+20.2%	<0.001
Hepatorenal syndrome	+38.9%	+34.8%	+43.1%	<0.001
Portal hypertension	+14.4%	+12.5%	+16.4%	<0.001

Adjusted for Elixhauser comorbidities

[a]Compared to not having the disease (referent group %Δ = 0%)

etiologies to account for a larger proportion of hospitalizations. Thus, given the potential of misclassification as it relates to disease etiology, we did not focus on etiology-specific trends and instead focused on overall trends. As previously mentioned, we further attempted to limit bias by strictly focusing on those with either ALF or cirrhosis. Thus, it is likely that our findings provide a conservative estimate of the true clinical and economic burden of HE among hospitalized patients. As our dataset is focused on in-hospital care, outpatient resource utilization and mortality was not captured. Future studies will need to more accurately capture the cohort of ALF patients with HE who die prior to gaining access to clinical care as well as individuals with undiagnosed cirrhosis with early signs of HE who are not linked to the healthcare system. Furthermore, patients with ALF and chronic cirrhosis not referred for liver transplant evaluation and hepatology care may experience delays with accessing appropriate health care, precluding capture by existing datasets despite significant clinical and economic burden to healthcare systems. As such, our findings are only the tip of the iceberg in understanding the magnitude of clinical and economic burden of HE.

In conclusion, the current analysis of the largest all-payer database of hospital discharge data in the USA from 2010 to 2014 demonstrated a worrisome continued rising incidence and burden of HE hospitalizations. While this rising trend was seen among both ALF patients with HE and cirrhosis patients with HE, cirrhosis patients by far were the major contributors to the clinical and economic burden. In 2014, the estimated national economic burden of hospitalizations among patients with HE reached $11.9 billion USD, which is a very conservative estimate given the limitations of the current database.

Author's contribution GH and RJW were involved in study concept and design. GH and RJW were involved in acquisition of data. GH, EV, and RJW were involved in analysis and interpretation of data and statistical analysis. GH and RJW drafted the manuscript. GH, EV, RJW critically revised the manuscript for important intellectual content. RJW was involved in study supervision. RJW had full access to all the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest RJW receives research funding from Gilead Sciences and Abbvie, has served as a consultant and member of the advisory board for Gilead Sciences, and serves on the speaker's bureau for Gilead Sciences, Salix, and Bayer. RJW is also funded by an AASLD Foundational Clinical and Translational Research Award in Liver Diseases. GH receives funding from Gilead Sciences. EV reports no conflicts of interest.

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