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Sociodemographic disparities in documented nonadherence to medication for hepatic encephalopathy: a National Inpatient Sample analysis

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Abstract

Background Medication nonadherence is often cited as a precipitant of hepatic encephalopathy. However, the underlying reasons and clinical implications of medication nonadherence in this population are understudied.

Methods This was a retrospective cross-sectional analysis of hospitalization for hepatic encephalopathy within the National Inpatient Sample from 2016-2022. Multivariate logistic regression analysis was used to assess for patient factors associated with documented nonadherence; results were presented as adjusted odds ratios (aOR) and 95% confidence intervals (CI). Additionally, analysis was performed to assess for associations between documented nonadherence and clinical outcomes.

Results Medication nonadherence was documented in 44,685 of the 250,755 (17.8%) hospitalizations for hepatic encephalopathy. Nonadherence was documented more in Black (aOR 1.35, 95%CI 1.24-1.47; P<0.001) and Hispanic (aOR 1.20, 95%CI 1.12-1.28; P<0.001) patients compared to White patients. Substance use diagnoses (aOR 1.36, 95%CI 1.29-1.43; P<0.001) and housing insecurity (aOR 2.47, 95%CI 2.11-2.90; P<0.001) were both associated with documented nonadherence. Discharge against medical advice was more frequent in patients with documented nonadherence (33.8% vs. 18.8%, P<0.001), whereas mortality, need for mechanical ventilation, cost, and length of stay were all less.

Conclusions Marginalized populations have higher rates of documented medication nonadherence in cases of hospitalization for hepatic encephalopathy. Structural barriers and provider bias could both be contributing to the documented medication nonadherence in this population.

Keywords Medication adherence, patient discharge, retrospective studies, socioeconomic disparities in health

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Introduction

Hepatic encephalopathy (HE) is a complication of advanced liver disease that affects approximately 30-45% of patients with cirrhosis [1,2]. In 2018, it was estimated to impact around 202,000 individuals in the United States [3]. HE manifests a range of cognitive and behavioral disturbances, from subtle neuropsychological changes to deep coma, significantly impairing both quality of life, and prognosis [3,4]. A variety of conditions can precipitate HE in patients with cirrhosis, including infection, dehydration, bleeding, and constipation [5,6].

Current management strategies for HE focus on supportive care, identifying and treating precipitating factors, and reducing serum toxin levels, including ammonia [7]. Standard pharmacologic therapies include lactulose and rifaximin, which reduce ammonia-producing gut bacteria by acidifying the colon and causing a decrease in urease-

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producing bacteria (lactulose), or by direct antimicrobial effects (rifaximin) [8-10]. Lactulose and rifaximin are not only important in the treatment of HE, but also play crucial roles in preventing its recurrence [11,12]. Medication nonadherence is frequently cited by providers as a precipitant of HE; however, the underlying precipitating factors leading to decreased adherence have not been thoroughly explored [13]. Barriers such as drug cost, side-effects and cognitive dysfunction could be driving poor medication adherence, and could lead to recurrent episodes of HE if not addressed [14-18]. The practice of labeling patients as "noncompliant" or "nonadherent" itself has come into question in recent years. Studies have shown that providers can be inaccurate in their assessments of patient adherence, and that providers are more likely to view Black and poorer patients as nonadherent based on subjective perception, even if objective evidence of nonadherence is lacking [19-21].

While patient-reported barriers to lactulose and rifaximin use have previously been assessed, there has been no large-scale, generalizable analysis of documented nonadherence in HE [22]. In order to explore disparities in the diagnosis of medication nonadherence and the potential underlying barriers to consistent medication use in HE, we performed a national analysis of HE admissions using the National Inpatient Sample (NIS). We hypothesized that nonadherence would be more frequently documented in marginalized populations, as a result of systemic barriers and provider bias. Additionally, we compared clinical outcomes in those with and without documented nonadherence to explore the interactions between documented nonadherence and clinical outcomes.

Materials and methods

Study design and database description

This was a cross-sectional retrospective study, conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research. All adult hospitalizations within the NIS with a primary diagnosis of HE from 2016-2022 were included. Patients with documented medication nonadherence were compared to those without documented medication nonadherence. Both HE and medication nonadherence were defined by International Classification of Diseases, 10th Revision (ICD-10) diagnostic codes (Supplementary Table 1). In the case of nonadherence, the relevant ICD-10 diagnostic codes indicate that a patient was nonadherent to their medications at the time of admission, but the codes do not specify the precise medication or the duration of nonadherence.

The NIS is the largest all-payer inpatient database in the United States, and was developed for the Healthcare Cost and Utilization Project (HCUP). It provides data on approximately 7 million annual hospitalizations, which are selected by a stratified systematic sampling design. HCUP provides standardized weighting procedures to allow the provided data to be converted to national estimates. All results presented in this study are weighted and intended to approximate the United States inpatient HE population from 2016-2022.

The NIS includes patient demographic and clinical information, along with clinical and healthcare utilization outcomes. A single primary diagnosis is provided for each hospitalization, and this is considered the diagnosis chiefly responsible for the admission. Secondary diagnoses encompass chronic conditions, acute concurrent conditions and complications. The secondary diagnoses used in this study were defined by relevant ICD-10 codes. The NIS is a publicly available de-identified database and Institutional Review Board approval was waived.

Objectives

The primary objective of this study was to determine what patient factors are associated with documented medication nonadherence in hospitalizations for HE. The following patient factors were assessed: sex, race, insurance status, the presence of a substance use-related diagnosis, hepatitis C virus (HCV), the presence of a mental health diagnosis, and housing insecurity. Substance use-related diagnosis was defined as the presence of a secondary diagnosis related to any of the following: alcohol, opioids, stimulants or sedatives. Mental health diagnoses were defined as the presence of a secondary diagnosis related to any of the following: post-traumatic stress disorder, schizophrenia, major depressive disorder, bipolar disorder or generalized anxiety disorder. The secondary objective of this study was to determine whether clinical outcomes were different in those with documented medication nonadherence. The following clinical outcomes were assessed: in-hospital death, mechanical ventilation, discharge against medical advice (AMA), length of stay (LOS) in days, and total hospital cost in United States dollars.

Statistical analysis

Means were compared using Student's *t*-test, while categorical variables were compared using the chi-square test. Multivariate logistic regression was used to assess for factors associated with medication nonadherence. Multivariate logistic regression was also used in the assessment of the following clinical outcomes: in-hospital mortality, mechanical ventilation and AMA discharge, with results presented as adjusted odds ratios (aOR) and absolute risk differences (ARD). A negative binomial regression analysis was used to assess for factors associated with LOS, while a generalized linear model was to assess for factors associated with cost. Both LOS and cost analysis results are presented as rate ratios (RR). Patients who did not have LOS or cost information available were excluded from those respective assessments. For each multivariate analysis, a univariate screen was used to determine which variables would be included in the analysis, namely those with a P-value <0.20 (Supplementary Tables 2-6). The following were the candidate variables and were assessed

separately for each multivariate analysis: age, sex, race, hospital region, hospital bed size, primary payer, Charlson Comorbidity Index, housing insecurity, substance use, and a mental health diagnosis. All statistical computations were performed using STATA, version 17.0.

Results

Sociodemographic and clinical characteristics

A total of 250,755 hospitalizations for HE were identified, of which 44,685 (17.8%) included documentation of medication nonadherence. Patients with documented medication nonadherence tended to be younger (mean 59.8 vs. 62.0 years, P<0.001), male (57.6% vs. 54.7%, P<0.001), and were more likely to be of non-White race (39.1% vs. 33.8%, P<0.001) (Table 1). Alcohol use and HCV were more common in those with documented nonadherence, while autoimmune liver disease was more common in those without. A substance-use diagnosis was present in 36.0% of hospitalizations, and was more common in patients with documented medication nonadherence (45.1% vs. 34.1%, P<0.001). A mental health diagnosis was present in 25.5% of hospitalizations, and was also more common in patients with documented medication nonadherence (27.4% vs. 25.1%, P<0.001). Those with documented medication nonadherence had lower rates of identifiable HE inciting factors, with 5.9% having a secondary diagnosis of infection or gastrointestinal bleeding, compared to 9.0% of patients without a diagnosis of medication nonadherence (P<0.001).

Patient factors associated with diagnosed medication nonadherence

Documented nonadherence was more common in males (18.6% vs. 16.9%, P<0.001); however, after adjusting for confounding variables with multivariate analysis, male sex was not significantly associated with documented nonadherence (Table 2). Nonadherence was documented more frequently in Black patients (22.1%) and Hispanic patients (19.6%) compared to White patients (16.6%), and these differences remained significant after adjusting for confounding variables (P<0.001). Non-private insurance was also significantly associated with documented medication nonadherence after confounding adjustment (aOR 1.32, 95%CI 1.24-1.41; P<0.001).

Patients with a secondary diagnosis of substance use had documented medication nonadherence in 22.3% of hospitalizations, and this was significantly greater compared to patients with no documented substance use (aOR 1.36, 95%CI 1.29-1.43; P<0.001). The presence of a mental health diagnosis was associated with documented medication nonadherence, although the magnitude of the association was small (aOR 1.06, 95%CI 1.01-1.12). Patients with housing insecurity had documented medication nonadherence in

Table 1 Characteristics of hospitalizations for patients with hepatic encephalopathy 2016-2022 stratified by documented medication nonadherence

Variable	Medication nonadherence	No medication nonadherence	P-value
Sample size	44,685	206,070	
Mean age, years	59.8	62.0	<0.001
Female, %	42.4	45.3	<0.001
Race, %			
White	60.9	66.2	<0.001
Black	10.3	7.9	<0.001
Hispanic	22.0	19.6	<0.001
Asian	1.4	2.0	<0.001
Other	5.5	4.4	<0.001
Hospital region, %			
Northeast	18.1	15.4	<0.001
Midwest	20.9	19.4	0.002*
South	37.6	42.5	<0.001
West	23.4	22.7	0.160
Primary payer, %			
Medicare	49.4	54.6	<0.001
Medicaid	31.0	22.2	<0.001
Private	15.4	19.5	<0.001
Self-pay	4.2	3.7	0.051
Alcohol use secondary diagnosis, %	40.8	31.5	<0.001
Hepatitis C virus, %	27.5	19.2	<0.001
Hepatitis B virus, %	2.3	2.1	0.148
Autoimmune liver disease, %	2.6	3.7	<0.001
Diabetes, %	19.3	19.7	0.352
Obesity, %	16.2	16.6	0.288
Ascites, %	37.6	42.9	<0.001
Mean Charlson Comorbidity Index	5.0	5.2	<0.001
HIV, %	1.3	0.7	<0.001
PTSD, %	1.3	1.2	0.438
Schizophrenia, %	2.7	2.0	<0.001
Major depressive disorder, %	16.6	15.1	<0.001
Bipolar disorder, %	4.3	3.3	<0.001
Generalized anxiety disorder	11.8	11.6	0.607
Opioid use disorder, %	4.8	3.2	<0.001
Sedative use, %	0.3	0.3	0.724
Stimulant use, %	5.1	2.1	<0.001
Tobacco use, %	23.9	15.8	<0.001
Housing insecurity, %	3.4	1.1	<0.001

(*Contd...*)

Table 1 (*Continued*)

Variable	Medication nonadherence	No medication nonadherence	P-value
Incarceration, %	0.3	0.2	0.011*
Secondary diagnosis of gastrointestinal bleeding	2.9	4.4	<0.001
Secondary diagnosis of spontaneous bacterial peritonitis	1.9	2.6	<0.001
Secondary diagnosis of sepsis	1.6	2.9	<0.001

*P < 0.05

HIV, human immunodeficiency virus; PTSD, post-traumatic stress disorder

40.2% of hospitalizations, and this association remained after adjustment for confounders (aOR 2.47, 95%CI 2.11-2.90; P<0.001).

Outcomes in patients with documented medication nonadherence

Mortality for all HE hospitalizations was 4.3%, and was significantly lower in hospitalizations with documented medication nonadherence on multivariate analysis (ARD 31.5:1000, aOR 0.35, 95%CI 0.29-0.42; P<0.001). Mechanical ventilation was required in 4.7% of hospitalizations, and was also less common in patients with documented medication nonadherence (3.3% vs. 5.0%, ARD 17.2:1,000) (Table 3). Patients with documented medication nonadherence were more likely to discharge AMA (ARD 15.0:1000).

The mean LOS for all HE hospitalizations was 5.1 days. Mean LOS was significantly shorter in patients with documented medication nonadherence (4.3 vs. 5.2 days, P<0.001), and the difference remained significant after adjustment for confounders. The mean cost of hospitalization was $13,099, and was also lower in patients with documented medication nonadherence ($9,468 vs. $13,855, P<0.001).

Discussion

We found higher rates of documented nonadherence in patients who were younger, non-White, on non-private insurance, experiencing housing insecurity, and with secondary diagnoses of substance use, HCV infection or mental health conditions. Additionally, medication nonadherence was associated with higher rates of discharge AMA, but shorter hospital stays, lower rates of mechanical ventilation, lower mortality and lower hospitalization costs.

Prior data have shown that non-White populations have more frequent readmissions related to complications from cirrhosis [23]. Of patients hospitalized with cirrhosis and HE between 2009 and 2013, Hispanic and Black populations made up the second and third highest racial groups [24]. Hispanic populations are at particularly high risk for liver disease-related complications, as chronic liver disease is the sixth most common cause of death in this group [17]. For these populations, there exist many additional institutional barriers in the United States that may impact healthcare and make medication adherence more difficult. Black patients have a lower median income, as well as the highest mean total hospital admissions and mean number of 30-day readmissions compared to all other racial groups [18]. Hispanic persons in the United States have a similar socioeconomic status profile compared to Black persons [25]. In HE, evidence has already suggested that cost is a considerable barrier to medication: one previous study found that a greater cost of rifaximin was associated with worse adherence [26].

Housing insecurity was associated with nonadherence in our study, providing further evidence that socioeconomic status significantly impacts documented nonadherence. While we do suspect that socioeconomic barriers lead to patients not taking medication and subsequently being documented for nonadherence, it is also certainly possible that provider bias is leading to certain groups of patients being more likely to be labeled as "nonadherent". Prior studies have shown that race, economic status and insurance status are associated with documented nonadherence [19-21]. These associations have been noted even independently of clinical markers [19-21]. For example, Black patients with diabetes are more likely to be labeled as nonadherent compared to White patients, regardless of hemoglobin A1c results [19]. The NIS lacks the granular data to fully explore potential provider bias in documenting nonadherence, so it is unclear what role it may have played in our results. We would advocate caution in declaring that a patient is nonadherent, and would also note the importance of exploring the underlying reasons, such as cost or side-effects, when nonadherence is suspected.

For patients with concurrent mental health diagnoses, significantly higher rates of medication nonadherence were documented for conditions such as schizophrenia, major depressive disorder and bipolar disorder. Even before development of HE, patients with psychiatric conditions have higher rates of developing liver disease [27]. The self-titration and multidrug nature of HE treatment can be difficult for patients at baseline. We suspect that this difficulty with self-titrating, keeping appointments and refilling medications in a timely matter is exacerbated in the setting of decompensated psychiatric illness. Similarly, substance use was associated with nonadherence, and we suspect that active substance use probably causes difficulty with consistent medication use.

Patients with documented medication nonadherence were found to have higher rates of discharge AMA. Our study reflected prior results that revealed higher rates of self-discharge in patients hospitalized with cirrhosis who had underlying psychiatric disorders, substance abuse, lower socioeconomic status and less severe liver disease [28]. The association between AMA discharge and documented nonadherence could be the result of concerns over hospital cost or missed work for lower socioeconomic patients, as demonstrated in prior

Table 2 Logistic regression assessing factors associated with documented medication nonadherence in hospitalizations for hepatic encephalopathy

Patient characteristic	Odds ratio (95%CI)	P-value	Adjusted[a] odds ratio	P-value
Male sex	1.12 (1.07-1.18)	<0.001	1.03 (0.98-1.09)	0.201
Race				
White	Ref.	-		
Black	1.42 (1.31-1.54)	<0.001	1.35 (1.24-1.47)	<0.001
Hispanic	1.22 (1.15-1.30)	<0.001	1.20 (1.12-1.28)	<0.001
Asian	0.77 (0.63-0.94)	0.012*	0.83 (0.68-1.02)	0.080
Other	1.36 (1.22-1.51)	<0.001	1.26 (1.12-1.41)	<0.001
Non-private insurance	1.28 (1.20-1.36)	<0.001	1.32 (1.24-1.41)	<0.001
Substance use-related diagnosis	1.59 (1.51-1.66)	<0.001	1.36 (1.29-1.43)	<0.001
Hepatitis C virus	1.59 (1.51-1.68)	<0.001	1.41 (1.33-1.50)	<0.001
Mental health diagnosis	1.13 (1.07-1.19)	<0.001	1.06 (1.01-1.12)	0.031*
Housing insecurity	3.17 (2.74-3.68)	<0.001	2.47 (2.11-2.90)	<0.001

*P < 0.05

[a]Each multivariate model included the following variables: age, sex, hospital region, Charlson Comorbidity Index, primary payer, substance use diagnosis, mental health diagnosis, housing insecurity

Table 3 Multivariate regression assessing associations between documented medication nonadherence and outcomes in hospitalizations for hepatic encephalopathy

Variable	Medication nonadherence	No medication nonadherence	Adjusted odds ratio (95%CI)	P-value
Clinical outcomes	Rate per 1000 hospitalizations	Rate per 1000 hospitalizations		
Death[a]	16.7	48.2	0.35 (0.29-0.42)	<0.001
Mechanical ventilation[a,b]	32.9	50.1	0.60 (0.52-0.68)	<0.001
Discharge against medical advice[a]	33.8	18.8	1.47 (1.28-1.70)	<0.001
Utilization outcomes	Mean	Mean	Adjusted[a] rate ratio (95%CI)	P-value
Length of stay (days)[a,b]	4.3	5.2	0.82 (0.80-0.84)	<0.001
Cost (US dollars)[d]	$9,468	$13,885	0.70 (0.68-0.72)	<0.001

[a]Adjusted for sex, race, hospital region, hospital bed size, primary payer, Charlson Comorbidity Index, presence of housing insecurity, presence of substance use, and the presence of a mental health diagnosis; [b]adjusted for age; [c]adjusted for age, sex, race, hospital region, primary payer, Charlson Comorbidity Index, presence of housing insecurity, presence of substance use, and the presence of a mental health diagnosis; [d]adjusted for age, sex, race, hospital region, hospital bed size, primary payer, Charlson Comorbidity Index, presence of substance use, and the presence of a mental health diagnosis
CI, confidence interval

studies [29,30]. It is also possible that patients who generally distrust the medical system are more likely to be labeled as nonadherent, and more likely to discharge AMA. Indeed, prior studies have shown distrust of the medical system as a frequent cause of AMA discharge [31,32].

Patients with medication nonadherence were found to have lower rates of mechanical ventilation and death in our study. There are several likely explanations for this finding. Patients without documented adherence had a slightly but statistically significantly higher level of comorbid illness, as measured by the Charlson Comorbidity Index. Additionally, they appeared to have worse baseline liver disease, with higher rates of ascites compared to those with documented nonadherence. Higher rates of secondary diagnoses of both infection and gastrointestinal bleeding were found in those without documented nonadherence. Taken together, these findings suggest that patients without documented nonadherence were sicker at baseline, and that it was more likely to be an acute condition, rather than medication nonadherence, that triggered their HE. This is a reasonable explanation for the worse outcomes in those without documented medication nonadherence.

This study was limited by its reliance on ICD-10 coding, which does not account for the severity of underlying liver conditions or HE. Documentation of nonadherence is provider-dependent and is not validated. The codes do not identify the exact medication to which the nonadherence applies. Additionally, the codes do not allow us to distinguish whether nonadherence is chronic or intermittent. We also cannot determine the underlying reason for nonadherence,

and whether the patient's nonadherence is self-reported, or an assumption made by the provider, which could reflect provider bias as opposed to patient behavior. Confounding etiologies of encephalopathy could also have affected the data in this study. A strength of this study is the large data set from the NIS during 2016-2022 which was analyzed. The reliability and relevance of these findings are enhanced by the large sample size and recent data in this study.

In summary, in our large retrospective cross-sectional study, higher rates of documented medication nonadherence were seen in patients admitted with HE who were younger, non-white, and experiencing housing insecurity. Nonadherence was associated with higher rates of discharge AMA. Investigating the underlying reasons for medication nonadherence, and the potential for bias in the documentation of nonadherence, will both be important for our understanding of how medication nonadherence can contribute to HE.

Summary Box

What is already known:

- Hepatic encephalopathy (HE) is a frequent cause of hospitalization among patients with cirrhosis, and contributes substantially to morbidity, mortality and healthcare costs
- Adherence to HE therapy, particularly lactulose and rifaximin, is critical for preventing recurrent episodes and optimizing outcomes
- Nonadherence is often multifactorial, reflecting both patient-level and systemic factors, such as cost, complexity of treatment and social determinants of health
- Prior studies evaluating nonadherence have been limited to small, single-center cohorts or pharmacy-based data, with limited insight into real-world inpatient outcomes at a national level

What the new findings are:

- Nonadherence was more frequently documented among younger, female, uninsured and lower-income patients, suggesting underlying socioeconomic and structural disparities
- Hospitalizations attributed to nonadherence were associated with more frequent discharges against medical advice, but lower in-hospital mortality, a shorter length of stay, and lower costs compared to other HE admissions
- These findings highlight the need to address systemic barriers and improve access and education rather than attributing recurrent HE solely to patient-level noncompliance

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Supplementary material

Supplementary Table 1 ICD-10 codes used to assess substance use-related hospitalizations for patients with a history of liver transplantation

Disorders	ICD-10 codes
Alcohol use	K70.0, K70.10, K70.30, K70.9
Anxiety disorder	F41*
Autoimmune liver disease	K75.4, K74.3, K74.5, K83.0
Bipolar disorder	F31*
Diabetes	E10, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E10.9, E11, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E11.9
Gastrointestinal bleeding	I85.01, I85.11, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K2101, K2091, K2211, K920, K55.21, K50.111, K50.811, K50.911, K51.011, K51.211, K51.311, K51.411, K51.511, K51.811, K51911, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K5791, K5793, K625, K63.81, K94.01
HBV	B16.2, B16.9, B18.1, B19.1, B19.10. B19.11
HCV	B17.10, B17.11, B181.2, B19.20, B19.21, Z22.52
Hepatic encephalopathy	K72.91, K72.01, K72.11, K72.90
History of incarceration	Z65.1
HIV	B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21.0. B21.1, B21.2, B21.3, B21.7, B21.8, B21.9, B22.0, B22.1, B22.2, B22.7, B23.0, B23.1, B23.2, B23.8, B20, B24, Z21
Housing insecurity	Z59.0, Z59, Z59.1, Z59.2, Z59.3, Z598.1
Major depressive disorder	F32*, F33*
Mechanical ventilation	0BH17EZ, 0BH18EZ, 5A1935Z, 5A1945Z, 5A1955Z
Medication non-compliance	Z9112*, Z9113*, Z9114*, Z9119*, Z91A1*, Z91A2*, Z91A3*, Z91A4*
Obesity	Z68.3, Z68.4, E66.0, E66.01, E66.09, E66.1, E66.2, E66.3, E66.8, E66.9
Opioid use	F11*, T400, T401, T402, T403, T404
Post-traumatic stress disorder	F431*
Schizophrenia	F200, F201, F202, F203, F205, F2081, F2089, F209, F22, F23, F250, F251, F258, F259, F28, F29
Sedative use	F13*, T424*, T423*, T426*, T427*
Sepsis	A40*, A41*
Spontaneous bacterial peritonitis	K65.2
Stimulant use	F15*, F14*, T4368
Tobacco use	F17*
Vasopressor use	3E030XZ, 3E033XZ, 3E040XZ, 3E043XZ, 3E050XZ, 3E053XZ, 3E060XZ, 3E063XZ

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus

Supplementary Table 2 Univariate screening analysis assessing for factors associated with medication noncompliance in hepatic encephalopathy hospitalizations

Variable	Odds ratio (95%CI)	P-value
Age	0.98 (0.98-0.98)	<0.001
Female sex	0.89 (0.85-0.93)	<0.001
Race		
White	Ref.	-
Black	1.42 (1.31-1.54)	<0.001
Hispanic	1.22 (1.15-1.30)	<0.001
Asian or Pacific Islander	0.77 (0.633-0.94)	0.012
Other	1.36 (1.22-1.51)	<0.001
Charlson Comorbidity Index	0.95 (0.94-0.96)	<0.001
Hospital region, %		
Northeast	Ref.	-
Midwest	0.92 (0.85-1.00)	0.048
South	0.76 (0.70-0.81)	<0.001
West	0.88 (0.81-0.96)	0.003
Primary payer, %		
Private	Ref.	-
Medicare	1.54 (1.46-1.63)	<0.001
Medicaid	0.88 (0.82-0.94)	<0.001
Self-pay	1.25 (1.10-1.41)	0.001
Hospital size		
Small	Ref.	-
Medium	0.96 (0.90-1.04)	0.319
Large	1.02 (0.96-1.09)	0.464
Substance use diagnosis	1.59 (1.51-1.66)	<0.001
Mental health diagnosis	1.13 (1.07-1.19)	<0.001
Housing insecurity	3.17 (2.74-3.68)	<0.001

CI, confidence interval

Supplementary Table 3 Univariate screening analysis assessing for factors associated with in-hospital mortality in hepatic encephalopathy hospitalizations

Variable	Odds ratio (95%CI)	P-value
Medication noncompliance	0.34 (0.28-0.40)	<0.001
Age	1.00 (1.00-1.00)	0.933
Female sex	0.90 (0.83-0.99)	0.022
Race		
White	Ref.	-
Black	1.14 (0.98-1.34)	0.088
Hispanic	0.79 (0.70-0.89)	<0.001
Asian or Pacific Islander	1.45 (1.09-1.92)	0.010
Other	1.06 (0.86-1.30)	0.590
Charlson Comorbidity Index	1.03 (1.01-1.05)	0.016
Hospital region, %		
Northeast	Ref.	-
Midwest	1.03 (0.89-1.20)	0.688
South	0.88 (0.77-1.00)	0.052
West	1.12 (0.98-1.29)	0.105
Primary payer, %		
Private	Ref.	-
Medicare	1.19 (1.07-1.33)	0.002
Medicaid	1.36 (1.21-1.53)	<0.001
Self-pay	1.95 (1.60-2.38)	<0.001
Hospital size		
Small	Ref.	-
Medium	1.08 (0.94-1.22)	0.278
Large	1.14 (1.01-1.28)	0.034
Substance use diagnosis	1.09 (1.00-1.19)	0.057
Mental health diagnosis	0.68 (0.60-0.75)	<0.001
Housing insecurity	0.46 (0.27-0.77)	0.003

CI, confidence interval

Supplementary Table 4 Univariate screening analysis assessing for factors associated with mechanical ventilation in hepatic encephalopathy hospitalizations

Variable	Odds ratio (95%CI)	P-value
Medication noncompliance	0.64 (0.57-0.73)	<0.001
Age	0.97 (0.97-0.98)	<0.001
Female sex	0.91 (0.84-0.99)	0.033
Race		
White	Ref.	-
Black	1.36 (1.18-1.56)	<0.001
Hispanic	0.93 (0.83-1.05)	0.241
Asian or Pacific Islander	1.42 (1.09-1.86)	0.011
Other	1.10 (0.91-1.34)	0.327
Charlson Comorbidity Index	0.96 (0.94-0.98)	<0.001
Hospital region, %		
Northeast	Ref.	-
Midwest	1.22 (1.06-1.42)	0.007
South	1.07 (0.94-1.22)	0.304
West	0.96 (0.83-1.11)	0.558
Primary payer, %		
Private	Ref.	-
Medicare	1.68 (1.52-1.86)	<0.001
Medicaid	1.51 (1.35-1.69)	<0.001
Self-pay	1.99 (1.65-2.40)	<0.001
Hospital size		
Small	Ref.	-
Medium	1.27 (1.11-1.46)	<0.001
Large	1.49 (1.32-1.69)	<0.001
Substance use diagnosis	1.31 (1.20-1.42)	<0.001
Mental health diagnosis	0.76 (0.69-0.84)	<0.001
Housing insecurity	0.58 (0.38-0.90)	0.015

CI, confidence interval

Supplementary Table 5 Univariate screening analysis assessing for factors associated with discharge against medical advice in hepatic encephalopathy hospitalizations

Variable	Odds ratio (95%CI)	P-value
Medication noncompliance	1.83 (1.60-2.10)	<0.001
Age	0.94 (0.94-0.95)	<0.001
Female sex	0.60 (0.53-0.69)	<0.001
Race	Ref.	-
White	1.29 (1.04-1.59)	0.019
Black	1.27 (1.09-1.47)	0.002
Hispanic	0.59 (0.31-1.13)	0.114
Asian or Pacific Islander	0.83 (0.60-1.15)	0.268
Other		
Charlson Comorbidity Index	0.83 (0.79-0.86)	<0.001
Hospital region, %		
Northeast	Ref.	-
Midwest	0.67 (0.54-0.83)	<0.001
South	0.93 (0.78-1.11)	0.414
West	1.10 (0.91-1.34)	0.328
Primary payer, %		
Private	Ref.	-
Medicare	3.26 (2.83-3.75)	<0.001
Medicaid	0.96 (0.77-1.18)	0.688
Self-pay	3.30 (2.56-4.27)	<0.001
Hospital size		
Small	Ref.	-
Medium	1.00 (0.83-1.20)	0.982
Large	0.93 (0.79-1.11)	0.418
Substance use diagnosis	2.27 (2.01-2.56)	<0.001
Mental health diagnosis	1.10 (0.96-1.26)	0.177
Housing insecurity	4.57 (3.52-5.94)	<0.001

CI, confidence interval

Supplementary Table 6 Univariate screening analysis assessing for factors associated with length of stay in hepatic encephalopathy hospitalizations

Variable	Rate ratio (95%CI)	P-value
Medication noncompliance	0.83 (0.81-0.85)	<0.001
Age	1.00 (1.00-1.00)	0.047
Female sex	1.03 (1.00-1.05)	0.017
Race		
White	Ref.	-
Black	1.17 (1.11-1.22)	<0.001
Hispanic	0.90 (0.87-0.92)	<0.001
Asian or Pacific Islander	1.02 (0.93-1.12)	0.666
Other	1.00 (0.94-1.05)	0.878
Charlson Comorbidity Index	1.02 (1.02-1.03)	<0.001
Hospital region, %		
Northeast	Ref.	-
Midwest	0.91 (0.87-0.95)	<0.001
South	0.89 (0.86-0.92)	<0.001
West	0.82 (0.79-0.85)	<0.001
Primary payer, %		
Private	Ref.	-
Medicare	1.06 (1.03-1.09)	<0.001
Medicaid	1.08 (1.05-1.11)	<0.001
Self-pay	1.02 (0.96-1.08)	0.536
Hospital size		
Small	Ref.	-
Medium	1.06 (1.02-1.09)	0.001
Large	1.19 (1.15-1.23)	<0.001
Substance use diagnosis	1.03 (1.01-1.05)	0.011
Mental health diagnosis	1.09 (1.06-1.11)	<0.001
Housing insecurity	1.22 (1.09-1.36)	<0.001

CI, confidence interval

Supplementary Table 7 Univariate screening analysis assessing for factors associated with cost in hepatic encephalopathy hospitalizations

Variable	Rate ratio (95%CI)	P-value
Medication noncompliance	0.68 (0.66-0.71)	<0.001
Age	0.99 (0.99-0.99)	<0.001
Female sex	0.95 (0.93-0.98)	0.001
Race		
White	Ref.	-
Black	1.07 (1.02-1.13)	0.010
Hispanic	0.98 (0.94-1.03)	0.474
Asian or Pacific Islander	1.46 (1.23-1.73)	<0.001
Other	1.04 (0.97-1.12)	0.257
Charlson Comorbidity Index	1.01 (1.00-1.02)	0.001
Hospital region, %		
Northeast	Ref.	-
Midwest	0.91 (0.84-0.99)	0.024
South	0.78 (0.72-0.83)	<0.001
West	0.99 (0.92-1.06)	0.787
Primary payer, %		
Private	Ref.	-
Medicare	1.12 (1.08-1.17)	<0.001
Medicaid	1.42 (1.35-1.49)	<0.001
Self-pay	0.93 (0.87-1.00)	0.061
Hospital size		
Small	Ref.	-
Medium	1.10 (1.04-1.16)	<0.001
Large	1.45 (1.39-1.52)	<0.001
Substance use diagnosis	0.93 (0.90-0.96)	<0.001
Mental health diagnosis	0.95 (0.92-0.99)	0.007
Housing insecurity	0.97 (0.88-1.08)	0.583

CI, confidence interval