CLINICAL RESEARCH STUDY

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History of Depression is Associated With Higher Prevalence of Hepatic Encephalopathy in Patients With Advanced Liver Disease

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ABSTRACT

BACKGROUND: Depression and hepatic encephalopathy are common in patients with advanced liver disease. Although these are distinct entities, they share several clinical features. In this analysis, we evaluated whether having a history of depression was associated with developing hepatic encephalopathy in patients with advanced liver disease.

METHODS: We performed a retrospective cohort study of patients with cirrhosis referred for liver transplant. Patients were categorized into 1 of 2 groups: "history of depression" or "no history of depression." Multivariable logistic regression was used to evaluate history of depression as a potential independent predictor of hepatic encephalopathy.

RESULTS: A total of 447 patients were included, of which 158 (35%) had a history of depression and 233 (52%) had experienced hepatic encephalopathy. Hepatic encephalopathy was more common in patients with a history of depression (63% vs 46%, $P < .01$). On multivariate analyses, depression history was independently associated with hepatic encephalopathy (aOR 2.3, 95% CI 1.4-3.6), along with alcohol associated cirrhosis (aOR 2.0, 95% CI 1.3-3.2), history of ascites (aOR 3.5, 95% CI 2.1-5.9) and presence of a trans-jugular intra-hepatic shunt (aOR 9.2, 95% CI 2.6-32.6). The relationship between history of depression and hepatic encephalopathy remained significant in a subgroup of patients with alcohol associated liver disease ($P = .04$). Among those with a history of depression, SNRI prescription was more common in the hepatic encephalopathy group (14% vs 3%), and SNRI prescription was as an independent predictor of hepatic encephalopathy in the multivariable model (OR 4.8, 95% CI 1.0-24.6)

CONCLUSIONS: Patients with a history of depression were significantly more likely to experience hepatic encephalopathy. Patients with cirrhosis who have a history of depression should be closely monitored for the development of hepatic encephalopathy. Further research is needed to understand the nuances of this relationship and whether the use of certain psychiatric medications may modify the relationship between depression and hepatic encephalopathy.

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INTRODUCTION

The global burden of chronic liver disease is steadily increasing. In the United States, rising rates of obesity and alcohol use disorder are expected to perpetuate this trend over the next 2 decades.[1] Thus, it is crucial for clinicians to be familiar with common disease manifestations and comorbidities in patients with cirrhosis. Hepatic encephalopathy is one of the most common hepatic decompensations and is the leading cause of hospital readmission in patients with cirrhosis.[2] Broadly defined, hepatic encephalopathy is a neurological syndrome caused by portosystemic shunting in advanced liver disease[3] and up to 70% of patients experience hepatic encephalopathy at least once after cirrhosis diagnosis.[3-5] Hepatic encephalopathy exists along a spectrum but is often categorized as either "covert" or "overt." Covert hepatic encephalopathy is characterized by subtle cognitive and neurologic dysfunction in the absence of obvious clinical signs. Overt hepatic encephalopathy is characterized by readily identifiable cognitive and neurologic abnormalities, such as asterixis.[3] In extreme cases, hepatic encephalopathy can lead to cerebral edema and coma.

CLINICAL SIGNIFICANCE

- Depression and hepatic encephalopathy have a clinically significant relationship in patients with advanced liver disease.
- Depression may increase the risk of developing hepatic encephalopathy, independent of disease severity, etiology and patient age, sex, and race.
- Type of antidepressant therapy may modulate the risk of hepatic encephalopathy in patients with a history depression.

Depression is a mood disorder characterized by persistent (≥ 2 weeks) feelings of sadness, anhedonia, and other symptoms including changes in appetite, sleep, and energy.[6] Depressive symptoms can occur in the absence of depressive disorders, and this frequently occurs in patients with chronic disease. Up to 50% of patients with cirrhosis experience depressive symptoms, but only 20%-25% have a depressive disorder.[6,7] Both depression and depressive symptoms contribute to a reduced quality of life and increased morbidity in patients with cirrhosis.[8] Interestingly, there are several shared features between covert hepatic encephalopathy and depression, including fatigue, altered sleep cycles, and cognitive impairment. This has prompted the question of whether an underlying relationship between the 2 syndromes exists.[9,10] Indeed, multiple studies evaluating the quality of life in cirrhosis patients have reported a higher frequency of depressive symptoms in those with hepatic encephalopathy.[9] A small study of 43 patients with chronic hepatitis C found that depressive symptoms were related to hepatic encephalopathy and noted that increased depressive symptoms were associated with more severe hepatic encephalopathy.[11]

While it is established that depressive *symptoms* and hepatic encephalopathy frequently coexist in patients with chronic liver disease, whether pre-existing depression influences the risk of developing hepatic encephalopathy has yet to be explored. Further, few studies use real world clinical evaluations when assessing the relationship between hepatic encephalopathy and depression. Our primary objective was to assess whether a history of depression was associated with an increased odds of hepatic encephalopathy in patients with advanced liver disease.

METHODS

Patient Selection and Data Collection

We conducted a single-center retrospective analysis of patients with cirrhosis undergoing liver transplant evaluation at a large academic, tertiary care and liver transplant center between October 2017 and June 2021. Patients with fulminant liver failure, prior liver transplantation, and those requiring inpatient liver transplant evaluation were excluded. Patients who completed routine transplant evaluation met initial inclusion criteria for the study (Figure 1).

Patients were categorized into 1 of 2 groups: "history of depression" or "no history of depression" based on several factors. We reviewed the psychosocial and psychiatric assessment performed by an experienced psychiatrist during the liver transplant evaluation to obtain each patient's complete psychiatric history. This data was used in conjunction with ICD-10 codes and medication prescriptions to identify patients with depression that was diagnosed prior to their diagnosis of liver disease. Patients who were diagnosed with depression concurrently with or after being diagnosed with liver disease were excluded from analyses (n = 16). In those with longstanding depression, diagnoses were typically included in the patient's medical history as soon as they were enrolled in our electronic medical record and the transplant psychiatric evaluation was used to ascertain details of this timeline.

All data were extracted from the electronic health record. Demographic data included age, biological sex, race, ethnicity, primary language, and tobacco use history. Clinical data included medical conditions, liver disease etiology, height, weight, body mass index (BMI), substance use, and prescribed medications. Liver disease etiology was dichotomized into alcohol associated cirrhosis and nonalcohol associated cirrhosis. Malnutrition diagnoses were collected from the nutrition portion of the transplant evaluation; nutrition evaluations were performed by a registered dietician and diagnoses were made based on the A.S.P.E.N criteria.[12] The queried psychiatric medications included selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA), antidopaminergic medications (anti-Da), and mood-stabilizers. Laboratory data included platelet count, thyroid stimulating hormone (TSH), serum

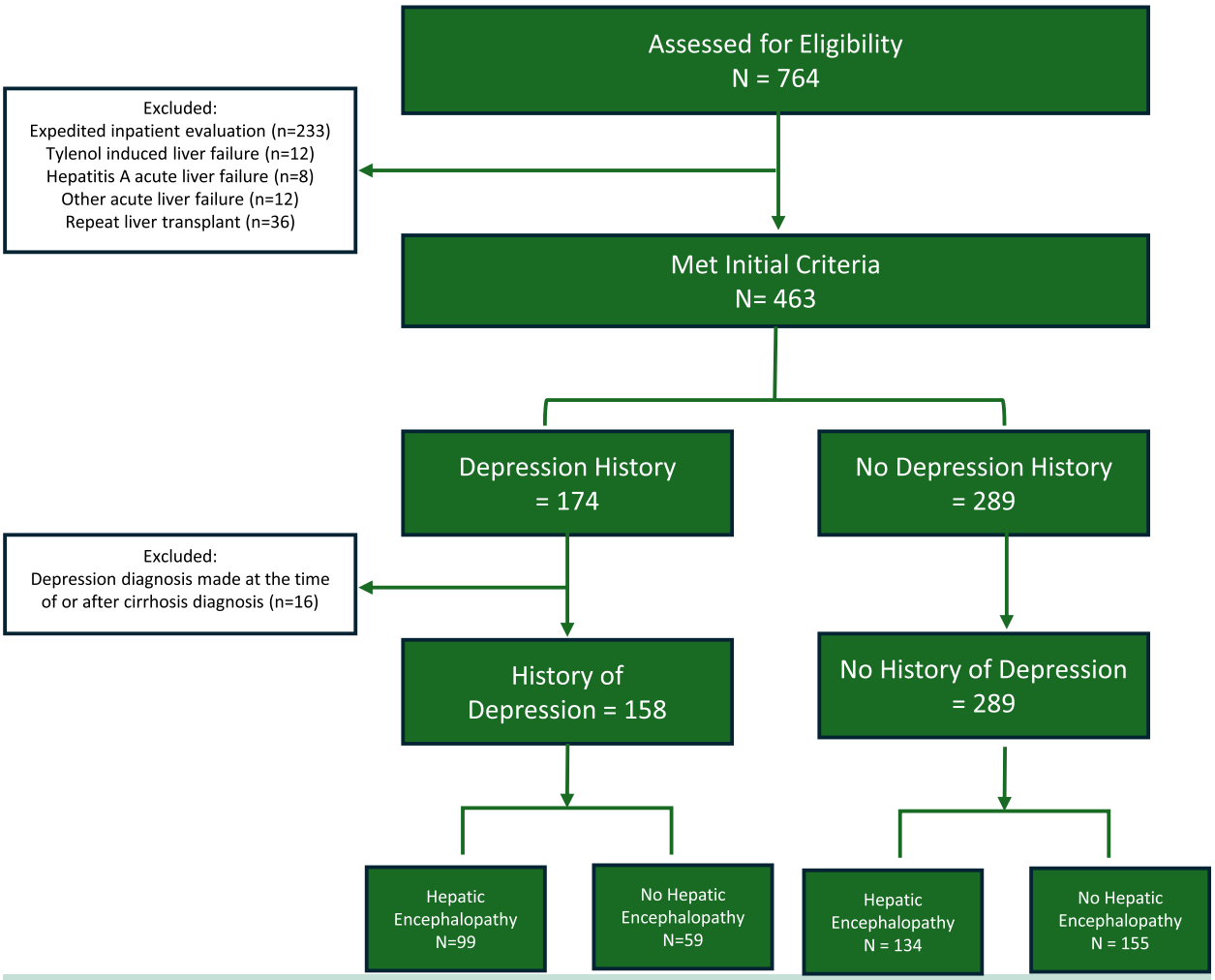

Figure 1 Patient inclusion chart.

albumin, and those relevant to the Model for End Stage Disease- Sodium (MELD-Na) score. Clinical events (decompensations, hospitalizations) were evaluated at the time of transplant evaluation; these data were available in the intake history of the transplant evaluation and were confirmed through querying the electronic health record. Potential decompensations included ascites, jaundice, variceal bleeding, and hepatic encephalopathy. The total number of decompensations refers to the types of decompensations experienced and ranged from 0 to 4.

Study Endpoints and Analysis

The primary objective was to evaluate whether a history of depression was associated with higher odds of developing hepatic encephalopathy. Univariable logistic regression was used to evaluate associations between hepatic encephalopathy and each variable. The primary predictor assessed was history of depression and potential covariates were selected *a priori* based on clinical relevance. Multivariable logistic regression was performed using the covariates identified as significant on univariate analyses to assess history of depression as an independent predictor of hepatic encephalopathy. We evaluated for interactions and conducted subgroup analyses by liver disease etiology (alcohol associated cirrhosis vs nonalcohol associated cirrhosis) and by patient sex (male vs female), due to their relationships with hepatic encephalopathy and depression, respectively.

We further explored patients with a history of depression with hepatic encephalopathy compared to those without hepatic encephalopathy. Univariable and multivariable logistic regression were performed as above to identify potential risk factors for hepatic encephalopathy among patients with a history of depression.

Strength of associations were reported as odds ratios with 95% confidence intervals (95% CI); univariable analyses were reported as crude OR (cOR) and multivariable analyses were reported as adjusted OR (aOR). Data were managed using REDCap electronic data capture tools at our institution.[13,14] Statistical analyses were performed in SPSS 29. This study was reviewed and approved with a waiver of informed consent by the institutional review board at the University of Massachusetts Chan Medical School.

RESULTS

A total of 447 patients were included in the study. Most patients were male, white, and non-Hispanic. The most common etiology of liver disease was alcohol associated cirrhosis, followed by metabolic dysfunction associated steatotic liver disease (MASLD) and chronic hepatitis C (Table 1). A total of 158 patients (35%) had a history of depression and 233 patients (52%) had hepatic encephalopathy.

Table 1 Baseline Characteristics

	No Depression (n = 289)	Depression (n = 158)	*P*
Demographic and Social			
Age, years	58 ± 10	54 ± 11	<.01
Female sex, n *(%)*	79 (27.3)	76 (48.1)	<.01
White race, n *(%)*	240 (83.0)	137 (86.7)	.31
Hispanic ethnicity, n *(%)*	33 (11.4)	18 (11.4)	.76
Alcohol associated cirrhosis, n *(%)*	130 (45.0)	89 (56.3)	.02
≤ High school education, n *(%)*	145 (50.2)	86 (54.4)	.39
Non-English 1st language, n *(%)*	35 (12.1)	15 (9.5)	.41
Liver Disease History			
MELD-Na, points	13 ± 6	12 ± 6	.07
Admissions, median [IQR]	1 [1-1]	1 [1-1]	.62
Prior TIPS, n *(%)*	17 (5.9)	12 (7.6)	.48
Hospitalizations, median [IQR]			
Decompensations[a], median [IQR]	2 [1-3]	2.5 [1-3]	.59
Ascites, n *(%)*	206 (71.3)	112 (70.9)	.93
Hepatic encephalopathy, n *(%)*	134 (46.3)	99 (62.7)	<.01
Variceal bleed, n *(%)*	77 (26.7)	53 (33.5)	.13
Jaundice, n *(%)*	90 (31.3)	45 (28.5)	.54
Clinical and Laboratory			
Malnutrition, n *(%)*	20 (6.9)	19 (12.0)	.07
Levothyroxine, n *(%)*	35 (12.1)	33 (20.9)	.01
Never smoker, n *(%)*	131 (45.3)	46 (29.1)	<.01
Prior opioid use, n *(%)*	29 (10.0)	34 (22.4)	<.01
Body Mass Index, kg/m2	29.5 ± 7	29.6 ± 7	.92
Height, cm	172 ± 10	169 ± 10	<.01
Weight, kg	88 ± 22	85 ± 24	.19
MELD-Na, points	13 ± 6	12 ± 6	.07
Serum albumin, mg/dl	3.4 ± 0.7	3.6 ± 0.7	.22
Platelet count, x109/L	132 ± 78	124 ± 76	.26
Serum TSH, (mIU/L)	3.1 ± 5.4	4.5 ± 16.4	.19
Transplant Outcomes			
Denied for waitlisting, n *(%)*	35 (12.1)	18 (11.4)	.82
Expired on waitlist, n *(%)*	44 (15.2)	22 (13.9)	.71
Removed from waitlist, n *(%)*	26 (9.0)	22 (13.9)	.11
Received liver transplant, n *(%)*	77 (26.6)	30 (19.0)	.07

[a]Decompensations refers to the number of the hepatic decompensations the patient had experienced at the time of transplant evaluation out of the four potential envents: ascites, hepatic encephalopathy, variceal bleed, and jaundice.

Patients with a history of depression were more likely to be under of the age of 50, to be female and to have alcohol associated cirrhosis than patients without a history of depression (Table 1). Approximately 25% of patients were diagnosed with depression 1-5 years prior to their cirrhosis diagnosis, 29% of patients were diagnosed 10-15 years prior to their cirrhosis diagnosis, 16% of patients were diagnosed 11-15 years prior to their cirrhosis diagnosis and 30% of patients had longstanding depression that they reported started in adolescence or childhood. Sixty-six percent of patients with a history of depression (n = 104) were on a psychotropic medication at the time of liver transplant evaluation including SSRI (n = 56), SNRI (n = 16), and mood stabilizers or other second line medications (n = 23).

A total of 99 out of 158 (62%) patients with history of depression had experienced hepatic encephalopathy as a decompensation compared to 134 of 289 (46%) patients without a history of depression ($P < .01$). Most patients with hepatic encephalopathy (91%) were receiving treatment including lactulose (55%), rifaximin (6%) or combination therapy (39%). Twenty-six percent of patients with hepatic encephalopathy had at least 1 hospital admission for hepatic encephalopathy including 28% of the patients with a history of depression and 26% of the patients with no history of depression. The other hepatic decompensations including ascites, variceal bleeding, and jaundice occurred at similar rates between groups.

Evaluating Depression as a Predictor of Hepatic Encephalopathy

There were no differences in baseline race, ethnicity, sex, education, tobacco use, or BMI between patients with and without hepatic encephalopathy (Table 2). Patients with hepatic encephalopathy had higher MELD-Na scores ($P < .01$) and were more likely to have alcohol associated cirrhosis ($P < .01$) and a trans-jugular intrahepatic portosystemic shunt (12% vs 1%, $P = .01$). Prevalence of comorbid psychiatric conditions including anxiety ($P = .12$), bipolar disorder ($P = 1.00$), and trauma ($P = .90$) was similar in patients with and without hepatic encephalopathy (*data not shown*). A history of depression was significantly more common in the hepatic encephalopathy group compared to the no hepatic encephalopathy group (41% vs 27%, $P < .01$). On multivariable logistic regression, depression history was associated with 2-fold higher odds of hepatic encephalopathy (aOR:2.3, 95% CI: 1.4-3.6, $P < .01$) (Table 2).

Subgroup Analyses

Alcohol: Patients with alcohol associated cirrhosis (n = 220) were more likely to have a history of depression (41% vs 30%, $P = .02$) and to have experienced hepatic encephalopathy (65% vs 40%, $P < .01$) compared to patients with other forms of liver disease. Among patients with alcohol associated cirrhosis, depression was associated with 2-fold higher odds of hepatic encephalopathy (cOR 1.9, 95% CI 1.1-3.4,

Table 2 Logistic Regression for Independent Predictors of Hepatic Encephalopathy

	Univariable Analyses			Multivariable Analyses		
Variable	No Hepatic Encephalopathy (n = 214)	Hepatic Encephalopathy (n = 233)	*P* Value	Coeff	aOR (95% CI)	*P*
History of depression	59 (27.6)	99 (42.5)	.0011	0.823	2.28 (1.44, 3.59)	.0004
Sex: female	71 (33.2)	84 (36.1)	.5237	-	-	-
Ethnicity: Non-Hispanic	188 (87.9)	207 (88.8)	.7442	-	-	-
Race: White/Caucasian	180 (84.1)	197 (84.5)	.8989	-	-	-
Age: years	57.5 ± 11	55.7 ± 10	.0763	-	-	-
Cirrhosis etiology: alcohol	77 (36.0)	143 (61.4)	<.0001	0.710	2.03 (1.31, 3.15)	.0010
BMI: mg/kg^2	29.3 ± 6	29.8 ± 7	.3860	-	-	-
Height (cm)	171.2 ± 10	171.1 ± 9	.9686	-	-	-
Weight (kg)	86.1 ± 22	87.7 ± 24	.4207	-	-	-
Malnutrition: present	15 (7.0)	24 (10.3)	.2207	-	-	-
Platelet count (x109/L)	139.9 ± 84	126.5 ±125	.2080	-	-	-
Serum albumin (mg.dl)	3.61 ± 0.7	3.37 ± 0.7	.0002	- 0.273	0.76 (0.52, 1.11)	.1539
Serum TSH (mIU/L)	4.17 ± 14	3.09 ±5	.3389	-	-	-
MELD-Na (points)	11.8 ±6	14.3 ±6	<.0001	0.040	1.04 (1.00, 1.09)	.0681
History of ascites: present	117 (54.7)	201 (86.3)	<.0001	1.253	3.50 (2.07, 5.91)	<.0001
Levothyroxine use: present	31 (14.5)	37 (15.9)	.6820	-	-	-
Opioids use history: present	25 (11.7)	38 (16.3)	.1619	-	-	-
Education: ≤ Highschool	112 (52.3)	129 (55.4)	.8600	-	-	-
Prior TIPS: Yes	3 (1.4)	26 (11.2)	.0004	2.214	9.15 (2.57, 32.57)	.0010
Smoking: Never smoker	125 (58.4)	145 (62.2)	.4095	-	-	-
Non-English 1st language	24 (11.2)	25 (10.8)	.8697	-	-	-
Anxiety: present	46 (21.5)	68 (29.2)	.0632	-	-	-

P = .03). This relationship persisted when controlling for age, sex, race, ascites, and MELD-Na (aOR 2.3, 95% CI 1.2-4.4, *P* = .02) (Supplementary Table 1, available online). Results were similar in patients with other etiologies of cirrhosis (aOR 2.1, 95% CI 1.1-4.0, *P* = .03). Importantly, interaction testing revealed no significant interaction between disease etiology and history of depression with respect to hepatic encephalopathy (*P* = .78) (Supplementary Table 4, available online).

Sex: Females were more likely to have a history of depression than males (49% vs 28%, *P* < .01), but a similar proportion of males and females had experienced hepatic encephalopathy (54% vs 51%, *P* = .52). Among those with a history of depression, a similar proportion of females (n = 48, 64%) and males (n = 51, 62%) had experienced hepatic encephalopathy (*P* = .90) On univariate analyses, history of depression was associated with about a 2-fold higher odds of hepatic encephalopathy in both males (cOR 1.8, 95% CI 1.1-3.1, *P* = .02) and females (cOR 2.1, 95% CI 1.1-3.9, *P* = .03). When controlling for age, race, etiology, ascites, and MELD-Na, this relationship persisted for males (aOR 1.8, 95% CI 1.0-3.2, *P* = .04) and trended toward association in females (aOR 1.9, 95% CI 1.0-4.0, *P* = .07) (Supplementary Table 2, available online). Interaction testing revealed no significant interaction between patient sex and history of depression with respect to association with hepatic encephalopathy (*P* = .84) (Supplementary Table 4, available online).

Hepatic Encephalopathy in Patients with History of Depression

Among patients with history of depression, those with hepatic encephalopathy were younger in age (52 vs 56, *P* = .03) and had a higher MELD-Na score (14 vs 11, *P* < .01). The percentage of patients prescribed a psychotropic medication did not differ between those with and without hepatic encephalopathy (70% vs 59%, *P* = .18) (Table 3). Interestingly, SNRI prescription was significantly more common in patients with hepatic encephalopathy (14% vs 3%, *P* = .03) and SNRI was associated with higher odds of hepatic encephalopathy when compared to SSRI (*P* = .05) (Supplementary Table 3, available online). Figure 2 demonstrates the percentage of patients diagnosed with hepatic encephalopathy by each medication class. Ultimately, alcohol associated cirrhosis (aOR 2.1, 95% CI 1.0-4.5) and the presence of ascites (aOR 2.8, 95% CI 1.2- 6.5) were associated with hepatic encephalopathy amongst patients with a history of depression (Table 4). When SNRI was added as a covariable, it was significantly associated with hepatic encephalopathy in the multivariable model (aOR 4.8, 95% CI 1.0- 24.6).

DISCUSSION

The findings of our study reveal a substantive and statistically significant link between a history of depression and hepatic encephalopathy in patients with cirrhosis who are

Table 3 Rates of Prescribed Psychotropic Medications in Patients with a History of Depression With Compared to Without Hepatic Encephalopathy

	No Hepatic Encephalopathy (n = 59)	Hepatic Encephalopathy (n = 99)	*P* Value
No medications, n (%)	24 (40.7)	30 (30.3)	.18
Any medication, n (%)	35 (59.3)	69 (69.7)	
No SSRI, n (%)	36 (61.0)	66 (66.7)	.47
SSRI, n (%)	23 (39.0)	33 (33.3)	
No SNRI, n (%)	57 (96.6)	85 (85.9)	.03
SNRI, n (%)	2 (3.4)	14 (14.1)	
No TCA, n (%)	55 (93.2)	87 (87.9)	.26
TCA, n (%)	4 (6.8)	12 (12.1)	
No bupropion, n (%)	52 (88.1)	92 (92.9)	.31
Bupropion, n (%)	7 (11.9)	7 (7.1)	
No mood stabilizer, n (%)	57 (96.6)	96 (97.0)	.90
Mood stabilizer, n (%)	2 (3.4)	3 (3.0)	

evaluated for liver transplant. This relationship retained significance when considering key patient-related factors that can obscure the diagnosis of either condition, including opioid use, hypothyroidism, and education level; a history of depression was predictive of hepatic encephalopathy across multiple statistical models. While previous studies have shown that hepatic encephalopathy is associated with development of depression,[9-11] our study distinctively explores the inverse question: Does pre-existing depression alter the odds of hepatic encephalopathy in patients diagnosed with cirrhosis?

We observed alcohol associated liver disease both to be more common in patients with a history of depression and to be a strong predictor of hepatic encephalopathy. Indeed, other studies have shown that alcohol use increases the odds of developing hepatic encephalopathy and it is possible that episodes of encephalopathy occurred when candidates were actively using alcohol in this group.[15] However, we found that the relationship between a history of depression and hepatic encephalopathy was generally the same in both patients with and without alcohol associated liver disease. Further, interaction testing between alcohol associated liver disease and history of depression with respect to hepatic encephalopathy was not statistically significant. Thus, while alcohol may modulate the risk of both hepatic encephalopathy and depression, our analysis demonstrates that alcohol is unable to fully account for the relationship between history of depression and hepatic encephalopathy.

Due to the robust relationship between patient sex and having a history of depression, we explored the interplay between sex, depression, and hepatic encephalopathy. While some studies have shown hepatic encephalopathy to be more common in males,[15,16] we observed similar rates of hepatic encephalopathy in each sex. We initially thought that the difference in observation may reflect an interaction between sex and history of depression with respect to hepatic encephalopathy. However, patient sex was not associated with hepatic encephalopathy on univariable analyses and the strength of association between history of

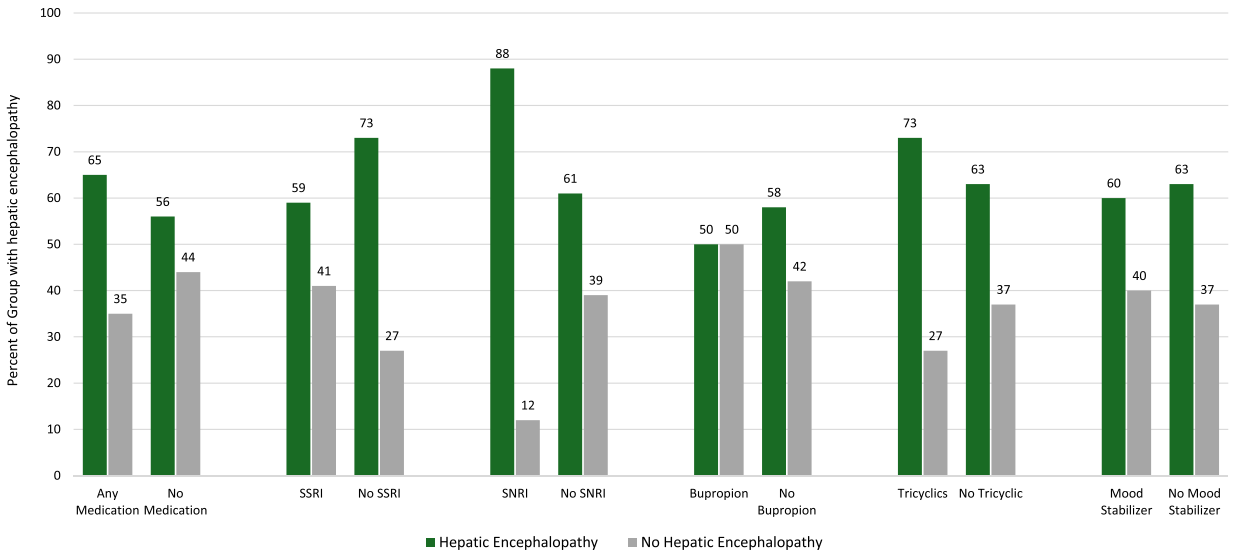

Figure 2 Rate of hepatic encephalopathy in patients with a history of depression across by psychotropic medication class. The occurrence of hepatic encephalopathy was similar in patients prescribed and not prescribed a psychotropic medication ($P = 0.23$). There was significant difference in the rate of hepatic encephalopathy in patients prescribed an SNRI compared to patients who were not prescribed an SNRI ($P = .02$). The rate of hepatic encephalopathy in patients on an SSRI was >20% lower than the rate of hepatic encephalopathy in patients on SNRI. SSRI = selective serotonin reuptake inhibitors; SNRI = selective norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants.

Table 4 Multivariable Logistic Regression for Predictors of Hepatic Encephalopathy in Patients with History of Depression

Variable	(a) No SNRI B	(a) No SNRI aOR (95% CI)	(a) No SNRI *P* Value	(b) SNRI B	(b) SNRI aOR (95% CI)	(b) SNRI *P* Value
Age	−0.030	0.97 (0.94, 1.00)	.0783	−0.0259	0.97 (0.94, 1.00)	.1366
Alcohol	0.7556	2.13 (1.02, 4.46)	.0451	0.7497	2.12 (1.02, 4.46)	.0500
Albumin	−0.3844	0.68 (0.36, 1.28)	.2337	−0.4027	0.67 (0.36, 1.28)	.2133
MELD-NA	0.0279	1.03 (0.95, 1.11)	.4863	0.0296	1.03 (0.95, 1.11)	.4696
Ascites	1.0333	2.81 (1.21, 6.51)	.0159	1.0482	2.85 (1.21, 6.51)	.0165
SNRI	-	-	-	1.5709	4.81 (1.04, 24.6)	.0493

depression and hepatic encephalopathy was similar on sex-stratified analyses. Further, interaction testing between history of depression and sex did not reveal statistical significance, indicating that having a history of depression affects the odds of hepatic encephalopathy consistently across patient sex. These findings underscore the relevance of depression as a risk factor for hepatic encephalopathy, transcending sex distinctions. However, as the sample size of these subgroups was small, this relationship should be further investigated prospectively or in larger sample size studies.

Beyond shared risk factors, there are several pathophysiologic pathways that could connect depression and hepatic encephalopathy including hypoperfusion of specific frontal gyri, microglial activation, and particularly, astrocyte dysfunction.[7,17] Reduced hepatic clearance of ammonia and portosystemic shunting result in hyperammonemia and increased movement of ammonia across the blood brain barrier in patients with cirrhosis.[18] Cerebral astrocytes take up and metabolize ammonia to glutamine which can cause astrocyte swelling and degeneration when in excess. The breakdown of cerebral ammonia and resultant glutamate-mediate astrocyte swelling is central to the pathogenesis of hepatic encephalopathy.[19] Emerging preclinical evidence suggests that astrocyte dysfunction is involved in the pathogenesis of depressive disorders as well.[20] Thus, it is plausible that astrocyte dysfunction in patients with depression predisposes for the development of hepatic encephalopathy, though this theory is beyond the scope of this study. There is also data supporting that systemic inflammation is crucial in linking depression and hepatic encephalopathy. Interestingly, systemic inflammatory markers have been shown to decrease significantly in patients with clinical response to SSRIs, the first-line pharmacotherapy for depression.[21,22] Although hepatic encephalopathy was slightly less common in patients on SSRI, this relationship was not statistically significant. In contrast, being prescribed an SNRI medication appeared to worsen the odds of developing hepatic encephalopathy, which is interesting in light of preclinical models showing increased brain noradrenergic activity to be associated with hepatic encephalopathy.[23]

It is important to recognize that there are several limitations to our study. First, the study was retrospective and relied on ICD-10 code based and clinical diagnoses of depression. Second, we were not able to account for the severity of patient depression over time. We were also unable to obtain detailed information on depression treatment prior to the transition to the electronic medical record. This information may have further informed whether certain depression treatments mitigate the odds of hepatic encephalopathy. Similarly, while we reported hospital admissions for hepatic encephalopathy as a marker for severity, we did not have neuropsychiatric testing to objectively assess hepatic encephalopathy grade. Lastly, because the exact dates of diagnoses were not consistently available, we were unable to perform time dependent analyses such as Cox hazard regression. However, we were able to extract granular patient level data and the results of this study inform multiple areas of future clinical practice and research in patients with chronic liver disease and depression.

In conclusion, pre-existing depression may increase the odds of developing hepatic encephalopathy in patients with advanced liver disease, independent of age, sex, and disease etiology. Additional research is needed to identify which patients with depression are at the highest for developing this outcome. Future studies should also assess whether specific antidepressant medication classes are more beneficial than others in patients with cirrhosis. For example, SSRI monotherapy may be preferred in patients with controlled depressive symptoms. Additionally, incorporating routine depression and hepatic encephalopathy screening into multidisciplinary care models should be considered, particularly in patients with alcohol associated liver disease who are at high risk for both conditions.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2024.04.036.

SUPPLEMENTAL MATERIAL

Supplementary Table 1 Multivariable Logistic Regression for Predictors of Hepatic Encephalopathy in Patients With Alcohol Associated Cirrhosis (Left, Panel a) and No Alcohol Associated Cirrhosis (Right, Panel b)

	(a) Alcohol			(b) No Alcohol		
Variable	Coef	OR (95% CI)	*P*	Coef	OR (95% CI)	*P*
Depression	0.815	2.26 (0.17, 4.38)	.016	0.720	2.05 (1.06, 3.99)	.033
Age (Years)	−0.030	1.00 (0.97, 1.03)	.853	0.008	1.01 (0.98, 1.04)	.571
Race (White)	−0.775	0.46 (0.15, 1.39)	.169	0.175	1.19 (0.56, 2.52)	.647
Sex (Male)	−0.099	0.91 (0.46, 1.78)	.773	0.156	1.17 (0.64, 2.16)	.617
MELD-Na (Points)	0.019	1.02 (0.97, 1.07)	.476	−0.085	0.92 (0.87, 0.97)	.003
Ascites (Present)	1.419	4.13 (1.67, 9.69)	.001	1.407	4.08 (2.12, 7.85)	.791

Multivariable regression evaluating history of depression as a predictor for hepatic encephalopathy with covariates selected a priori based on clinical relevance and statistical relationships identified in the total cohort.

Alcohol = alcohol associated cirrhosis; MELD-Na = model for end stage liver disease sodium.

Supplementary Table 2 Multivariable Logistic Regression for Predictors of Hepatic Encephalopathy in Male Patients (Left, Panel a) and Female Patients (Right, Panel b)

	(a) Males			(b) Females		
Variable	B	OR (95% CI)	*P*	Coef	OR (95% CI)	*P*
Depression	0.693	2.00 (1.10, 3.64)	.023	0.696	2.01 (0.94, 4.27)	.071
Age (years)	−0.004	1.00 (0.97, 1.02)	.750	0.004	1.00 (0.97, 1.04)	.842
Race (White)	−1.144	0.32 (0.14, 0.70)	.005	1.157	3.18 (1.04, 9.69)	.042
ALD (+)	0.741	2.10 (1.22, 3.60)	.007	−0.586	0.56 (0.25, 1.22)	.143
MELD-Na (points)	0.053	1.06 (1.01, 1.11)	.031	−0.057	0.94 (0.88, 1.01)	.089
Ascites (present)	1.662	5.27 (2.68, 10.38)	<.001	1.124	3.08 (1.34, 7.08)	.008

Multivariable regression evaluating history of depression as a predictor for hepatic encephalopathy with covariates selected a priori based on clinical relevance and statistical relationships identified in the total cohort.

Alcohol = alcohol associated cirrhosis; MELD-Na = model for end stage liver disease sodium.

Supplementary Table 3 Univariable Logistic Regression for Predictors of Hepatic Encephalopathy in Patients with a History of Depression

Variable	cOR (95% CI)	*P*
Sex: Female	0.96 (0.50, 1.83)	.9005
Ethnicity: Non-Hispanic	1.40 (0.52, 3.76)	.5095
Race: White/Caucasian	0.63 (0.23, 1.74)	.3752
Age: years	0.96 (0.93, 1.00)	.0276
Cirrhosis etiology: Alcohol	2.92 (1.50, 5.68)	.0016
BMI: mg/kg^2	1.04 (0.99, 1.09)	.1502
Height (cm)	0.99 (0.96, 1.03)	.7369
Weight (kg)	1.01 (1.00, 1.02)	.1956
Malnutrition: Present	0.80 (0.30, 2.11)	.6477
Platelet Count (x109/L)	1.00 (1.00, 1.01)	.7147
Albumin (mg.dl)	0.50 (0.30, 0.83)	.0074
TSH (mIU/L)	0.99 (0.96, 1.01)	.3571
MELD-Na (point)	1.10 (1.03, 1.17)	.0044
History of ascites: Present	4.66 (2.25, 9.68)	.0000
Levothyroxine use: Present	0.56 (0.26, 1.21)	.1396
Opioids use history: Present	1.88 (0.81, 4.36)	.1428
Education: ≤ Highschool	0.94 (0.49, 1.78)	.8382
Prior TIPS: Yes	3.20 (0.68, 15.15)	.1422
Smoking: Never smoker	1.11 (0.55, 2.26)	.7658
English 2nd language	1.21 (0.39, 3.74)	.7361
Anxiety: Present	1.31 (0.69, 2.50)	.4113
SNRI	4.69 (1.03, 21.44)	.0460

Variables significant on univariable analyses were included in multivariable analyses in Table 4 of the main text.

BMI = body mass index; TIPS = transjugular intrahepatic shunt; MELD-Na = model for end stage liver disease sodium; TSH = thyroid stimulating hormone; SNRI = selective norepinephrine reuptake inhibitor.

Supplementary Table 4 Interaction Testing

Interaction Variable	Coefficient	*P* Value
Depression * sex	−0.085	.840
Depression * ALD	−0.115	.783
Depression * age	−0.039	.062
Depression * ascites	0.285	.561
Depression * psychotropics	−0.468	.394
Depression * tips	−1.875	.151
Depression * education	−0.105	.796
Depression * anxiety	0.301	.539

Interactions of pertinent clinical variables and history of depression with respect to odds of having hepatic encephalopathy. Interactions were evaluated using interaction variables on logistic regression analyses.

ALD = alcoholic liver disease.