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## Retrospective Study

# Racial and gender-based disparities and trends in common psychiatric conditions in liver cirrhosis hospitalizations: A ten-year United States study

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## Abstract

### BACKGROUND

Chronic liver disease is associated with various neuropsychiatric conditions. There are currently no large studies assessing and comparing the prevalence of psychiatric illnesses based on patient profiles and the etiology of cirrhosis.

### AIM

To examine the trends of hospitalizations among psychiatric conditions in cirrhosis.

### METHODS

We used the National Inpatient Sample database 2009-2019 for the primary diagnosis of liver cirrhosis. The outcomes included the prevalence, trends, and

associations of psychiatric diagnoses in these hospitalizations. Chi-square for categorical variables and the Wilcoxon rank test for continuous variables were utilized.

## RESULTS

The prevalence of generalized anxiety disorder (GAD) in liver cirrhosis hospitalizations increased from 0.17% in 2009 to 0.92% in 2019 ( $P < 0.001$ ). The prevalence of depression increased from 7% in 2009 to 12% in 2019 ( $P < 0.001$ ). Attention deficit hyperactivity disorder (ADHD) prevalence increased from 0.06% to 0.24%. The prevalence of schizophrenia increased from 0.59% to 0.87% ( $P < 0.001$ ). Schizoaffective disorder prevalence increased from 0.10% to 0.35% ( $P < 0.001$ ). Post-traumatic stress disorder (PTSD) prevalence displayed increasing trends from 0.36% in 2009 to 0.93% in 2019 ( $P < 0.001$ ). The prevalence of suicidal ideation increased from 0.23% to 0.56% in 2019. Cirrhosis related to alcoholic liver disease [adjusted odds ratios (aOR) 1.18, 95% CI 1.08-1.29,  $P < 0.001$ ] and non-alcoholic fatty liver disease (NAFLD) (aOR 1.14, 95% CI 1.01-1.28,  $P = 0.025$ ) was associated with depression more than other causes. Alcohol- and NAFLD-associated cirrhosis had a stronger link to psychiatric disorders. Females had a higher association with GAD (aOR 2.56, 95% CI 2.14-3.06,  $P < 0.001$ ), depression (aOR 1.78, 95% CI 1.71-1.84,  $P < 0.001$ ), bipolar disorder (aOR 1.64, 95% CI 1.52-1.77,  $P < 0.001$ ) and chronic fatigue (aOR 2.31, 95% CI 1.31-4.07,  $P < 0.001$ ) when compared to males. Blacks, Hispanics, and Asian/Native Americans had a significantly lower association with GAD, depression, bipolar disorder, PTSD, and ADHD when compared to the white race.

## CONCLUSION

The prevalence of psychiatric comorbidities in liver cirrhosis hospitalizations has increased over the last decade. Females had a higher association with psychiatric disorders compared to males. Blacks, Hispanics, and Asian/Native Americans had lower associations with psychiatric comorbidities compared to the white race.

**Key Words:** Liver cirrhosis hospitalizations; Psychiatric conditions; Racial and gender disparities

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**Core Tip:** Currently, large studies assessing and comparing the prevalence of psychiatric conditions based on patient profiles and the etiology of cirrhosis are lacking in the published literature. In this National Inpatient Sample-based retrospective study, we aimed to assess the trends of hospitalizations among psychiatric conditions in cirrhosis. Our findings highlight the disparities in the diagnoses of certain psychiatric conditions in cirrhotics between gender and race. It is pertinent to recognize these disparities, as doing so may expedite management and improve overall outcomes. Therefore, all patients with cirrhosis should be provided with a referral to a mental health professional at the time of diagnosis.

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## INTRODUCTION

Chronic liver disease is associated with a wide variety of neuropsychiatric conditions, ranging from depression and sleep disturbances to coma. The etiology of these illnesses can be either medical or psychiatric, and at times it can be difficult to distinguish. Neuropsychiatric symptoms in chronic liver disease can be partially explained by aberrations in the liver's critical role in filtering neurotoxins such as ammonia and manganese from the blood[1]. This results in a buildup of these neurotoxins, which are implicated in mental status changes and alterations in consciousness. Additionally, liver disease has been shown to increase circulating inflammatory cytokines such as tumor necrosis factor, interleukin-1 $\beta$ , and interleukin-6, which can lead to neuroinflammation[1]. The combination of these factors is thought to lead to the development of hepatic encephalopathy (HE) in patients with cirrhosis.

HE is a relatively common neuropsychiatric manifestation of cirrhosis, and as such, it would not be overlooked by a hepatologist or gastroenterologist. Although the neuropsychiatric signs and symptoms of confusion, asterixis, and sleep disturbances seen in HE can be directly attributed to the cirrhosis itself

via the aforementioned mechanisms, other psychiatric symptoms such as apathy, psychomotor retardation, and low energy are nonspecific. These manifestations of psychiatric disorders may be missed due, in part, to the stigma surrounding mental illness and addiction, along with the lack of systematic screening in specialist offices. Left untreated, mental illness can interfere with treatment compliance for other medical conditions, increase disease burden, and lower quality of life[2,3]. While there is significant data in regard to the pathophysiology and management of HE as well as psychiatric conditions in cirrhosis, the disparities among these conditions are not well studied.

The psychological stress that patients with cirrhosis experience plays a negative role in their mental health. Previous research has shown a correlation between psychiatric conditions and liver disease, in particular anxiety and depression[4-6]. Prior studies have also focused on liver disease associated with substance use disorders, such as alcohol-related liver disease and viral hepatitis related to intravenous drug use, but data on psychiatric conditions in other etiologies of chronic liver disease has only recently gained preeminence. Among other etiologies of liver disease, nonalcoholic fatty liver disease (NAFLD) and autoimmune liver disease comprise a significant component. NAFLD and metabolic syndrome have been associated with increased rates of psychiatric illnesses[7-9]. It is also well understood that patients with autoimmune diseases of any etiology suffer more commonly from psychiatric conditions[10-13]. However, the data on psychiatric conditions in autoimmune liver disease is not as robust[14,15]. There are currently no large studies assessing and comparing the prevalence of psychiatric conditions based on patient profiles and the etiology of cirrhosis. We aim to examine the trends of hospitalizations among common psychiatric conditions in cirrhosis based on gender, race, and the etiology of liver disease over an 11-year period in the United States.

## MATERIALS AND METHODS

### *Design and data source*

The National Inpatient Sample (NIS), designed by the Agency for Healthcare Research and Quality (AHRQ), was used. The design of this particular database is to approximate a 20% stratified sample of hospitals along with sampling weights to calculate national estimates[16]. Data in NIS is provided using the International Classification of Diseases (ICD) 9 (before September 2015) and 10 (after October 2015) coding systems. The present study utilized the NIS database to identify patients with a primary diagnosis of liver cirrhosis from January 2009 to December 2019[16]. All patients below the age of 18 were excluded. Additionally, patients with primary biliary cirrhosis were excluded, as these are misnomers. Based on the etiology, cirrhosis was divided into NAFLD cirrhosis, alcoholic cirrhosis, and other causes (viral, autoimmune, or non-specified). The exact codes utilized in this study for each variable can be found in [Supplementary Table 1](#). Additional information on the design and sampling methods of the NIS is available at: <https://www.hcup-us.ahrq.gov>.

### *Outcome measures*

Primary outcomes included the prevalence of common psychiatric conditions that included GAD, major depressive disorder (MDD), bipolar disorder (BD), attention deficit/hyperactivity disorder (ADHD), schizophrenia, schizoaffective disorder, post-traumatic stress disorder (PTSD), chronic fatigue, and suicidal ideation (SI). Secondary outcomes included associations of gender and race among liver cirrhosis hospitalizations with the aforementioned psychiatric conditions. We also reported trends in liver cirrhosis hospitalizations over the study period with demographics. A trend analysis for the respective outcomes was also reported in order to identify any time-based shifts.

### *Statistical analysis*

Multivariate logistic regression was conducted to assess the relationship between gender, race, and psychiatric conditions among liver cirrhosis hospitalizations; outcomes were reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI) and a *P* value. The analysis used 0.05 as the threshold for statistical significance, and all *P* values were 2-sided. Bivariate analysis was conducted using a chi-square test for categorical variables and an independent-samples *t*-test or Wilcoxon rank test for continuous variables. Categorical variables were presented as frequency (N) and percentage (%), and continuous variables were reported as mean with standard deviation (SD) as appropriate. For outcomes like the length of stay (LOS) and mean inpatient charges (MIC) given in [Supplementary Table 2](#), a hierarchical multivariate linear regression analysis was conducted to adjust the patient- or hospital-level factors as in prior studies[17-19]. For prevalence, the trend over time was evaluated using the score test with the "tabodds" command; for this, 2009 was used as the reference category. The score test compares the odds of cases occurring consecutively every year[20,21]. Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to generate figures[22,23]. Statistical Software for Data Science (STATA) version 16.0 software (StataCorp LLC, Station, TX, United States) was used for statistical analysis.

**Ethical considerations**

The NIS contains de-identified information, protecting the privacy of patients, physicians, and hospitals. Therefore, it was deemed exempt from the institutional review board (IRB). As each hospitalization was stripped of any patient identifiers, patient consent was waived.

**RESULTS****Demographic characteristics of the study sample**

There was a total of 724612 hospitalizations with a primary diagnosis of liver cirrhosis for the study period. Of these hospitalizations, 14.04% were due to NAFLD cirrhosis, 42.89% were following alcoholic cirrhosis, and 43.0% were secondary to other causes (viral, autoimmune, or non-specified). Total liver cirrhosis hospitalizations decreased from 78728 (208 per 100,000 total NIS hospitalizations) in 2009 to 52139 (147 per 100,000 total NIS hospitalizations) in 2019 ( $P < 0.001$ ) (Supplementary Figure 1). Liver cirrhosis hospitalizations were more common in males compared to females (62% vs 38%) ( $P < 0.001$ ). Most patients belonged to the age group 50-64 years (49%), followed by 65-79 years (21%) ( $P < 0.001$ ). There was white race predominance (70%), followed by Hispanics (20%) and blacks (9%) without significance ( $P = 0.16$ ). Most patients had a Charlson comorbidity index (CCI) score of  $CCI \geq 3$  (77%) ( $P < 0.001$ ). Urban teaching hospitals had the highest frequency of liver cirrhosis hospitalizations (61%), followed by Urban non-teaching (32%) and rural (7%) hospitals ( $P < 0.001$ ). Medicare remained the primary payer for 39% of hospitalizations for liver cirrhosis, followed by Medicaid (27%), and private insurers (24%;  $P < 0.001$ ). Inpatient mortality significantly decreased from 7% in 2009 to 4% in 2019 ( $P < 0.001$ ). Additional demographic characteristics over the study period are described in Supplementary Table 2. Adjusted linear regression revealed a declining trend in LOS for liver cirrhosis patients from  $6.10 \pm 0.22$  d in 2009 to  $5.18 \pm 0.08$  d in 2019 ( $P < 0.001$ ); and an increasing trend in MIC from  $\$59266 \pm 4111$  in 2009 to  $\$69882 \pm 23608$  in 2019 ( $P = 0.001$ ) (Supplementary Figure 2). The associations of common psychiatric conditions with liver cirrhosis hospitalizations are also described in Supplementary Table 3.

**Prevalence and trends of common psychiatric conditions in liver cirrhosis population**

The prevalence of GAD in liver cirrhosis hospitalizations increased from 0.17% in 2009 (1.76 per 1000 hospitalizations) to 0.92% in 2019 (9.21 per 1000 hospitalizations) ( $P < 0.001$ ). The prevalence of MDD increased from 7% in 2009 (71.7 per 1000 hospitalizations) to 12% in 2019 (120.1 per 1000 hospitalizations) ( $P < 0.001$ ). ADHD prevalence increased from 0.06% in 2009 (0.61 per 1000 hospitalizations) to 0.24% in 2019 (2.49 per 1000 hospitalizations). The prevalence of schizophrenia increased from 0.59% in 2009 (5.93 per 1000 hospitalizations) to 0.87% in 2019 (8.72 per 1000 hospitalizations) ( $P < 0.001$ ). Schizoaffective disorder prevalence increased from 0.10% in 2009 (1.90 per 1000 hospitalizations) to 0.35% in 2019 (3.54 per 1000 hospitalizations) ( $P < 0.001$ ). PTSD prevalence displayed increasing trends from 0.36% in 2009 (3.69 per 1000 hospitalizations) to 0.93% in 2019 (9.39 per 1000 hospitalizations) ( $P < 0.001$ ). The prevalence of SI increased from 0.23% in 2009 (2.38 per 1000 hospitalizations) to 0.56% in 2019 (5.65 per 1000 hospitalizations) ( $P < 0.001$ ) (Table 1) (Figure 1).

**Associations of common psychiatric conditions based on liver cirrhosis etiology**

The associations based on etiologies were compared against other causes of liver cirrhosis (viral, autoimmune, or unspecified) as they had the highest weights to ensure the best statistical accuracy. Patients with alcoholic liver cirrhosis had a higher association with GAD compared to other causes (aOR 1.79, 95%CI 1.29-2.47,  $P < 0.001$ ). At the same time, no difference existed between NAFLD cirrhosis and other causes ( $P = 0.69$ ). Both alcohol (aOR 1.18, 95%CI 1.08-1.29,  $P < 0.001$ ) and NAFLD cirrhosis (aOR 1.14, 95%CI 1.01-1.28,  $P = 0.025$ ) had a higher association with MDD compared to other causes. Alcohol cirrhosis (aOR 1.62, 95%CI 1.34-1.96,  $P < 0.001$ ) and NAFLD cirrhosis (aOR 1.37, 95%CI 1.04-1.79,  $P = 0.021$ ) had a stronger association with bipolar disorder than other causes. No difference existed between liver cirrhosis etiologies for association with ADHD, schizophrenia, or schizoaffective disorder. Alcoholic liver cirrhosis had a higher association with PTSD (aOR 1.57, 95%CI 1.15-2.13,  $P = 0.004$ ) and SI (aOR 2.01, 95%CI 1.33-3.04,  $P = 0.001$ ) compared to other causes. There was no difference in PTSD and SI between NAFLD cirrhosis and other causes (Table 2).

**Gender-based disparities of common psychiatric conditions in liver cirrhosis population**

Among liver cirrhosis hospitalizations, females had a higher association with GAD (aOR 2.56, 95%CI 2.14-3.06,  $P < 0.001$ ), MDD (aOR 1.78, 95%CI 1.71-1.84,  $P < 0.001$ ), bipolar disorder (aOR 1.64, 95%CI 1.52-1.77,  $P < 0.001$ ) and chronic fatigue (aOR 2.31, 95%CI 1.31-4.07,  $P < 0.001$ ), when compared to males. There was no significant association between ADHD, SI, schizophrenia, and schizoaffective disorders among females compared to males in liver cirrhosis hospitalizations (Table 3).

**Table 1 Trends of psychiatric comorbidities in patients hospitalized with primary diagnosis of liver cirrhosis in the national inpatient database from 2009 to 2019, n (%)**

Variables	Years											P value
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
GAD	139 (0.17)	97 (0.12)	158 (0.20)	295 (0.38)	225 (0.29)	275 (0.34)	270 (0.42)	245 (0.55)	285 (0.60)	360 (0.71)	480 (0.92)	$P < 0.001$
Depression	5652 (7)	5835 (8)	6828 (9)	7770 (10)	8599 (11)	9345 (12)	7395 (12)	4885 (11)	5710 (12)	6165 (12)	6264 (12)	$P < 0.001$
Bipolar disorder	1331(1.69)	1552 (2)	1689 (2)	1630 (2)	1730 (2)	1785 (2)	1575 (3)	1085 (2)	1065 (2)	1210 (2)	1390 (3)	$P < 0.001$
ADHD	48 (0.06)	78 (0.10)	151 (0.19)	165 (0.21)	130 (0.16)	235 (0.29)	210 (0.33)	75 (0.17)	85 (0.17)	110 (0.21)	130 (0.24)	$P < 0.001$
Schizophrenia	467 (0.59)	613 (0.79)	491 (0.64)	465 (0.60)	545 (0.70)	535 (0.66)	465 (0.74)	305 (0.69)	400 (0.84)	445 (0.87)	455 (0.87)	$P < 0.001$
Schizoaffective disorder	150 (0.19)	145 (0.18)	170 (0.22)	205 (0.26)	130 (0.16)	210 (0.26)	215 (0.34)	150 (0.34)	165 (0.34)	200 (0.39)	185 (0.35)	$P < 0.001$
PTSD	291 (0.36)	230 (0.30)	300 (0.39)	350 (0.45)	440 (0.56)	555 (0.68)	525 (0.83)	350 (0.79)	410 (0.86)	485 (0.95)	490 (0.93)	$P < 0.001$
Chronic Fatigue	19 (0.02)	28 (0.03)	18 (0.02)	20 (0.03)	25 (0.032)	25 (0.031)	5 (0.007)	40 (0.091)	5 (0.01)	20 (0.039)	45 (0.08)	$P < 0.001$
Suicidal Ideation	188 (0.23)	235 (0.33)	188 (0.24)	265 (0.34)	235 (0.30)	305 (0.37)	215 (0.34)	105 (0.23)	160 (0.33)	250 (0.48)	295 (0.56)	$P < 0.001$

GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder.

### ***Race-based disparities of common psychiatric conditions in liver cirrhosis population***

The Black, Hispanic, and Asian/Native American races had a significantly lower association with GAD, MDD, bipolar disorder, PTSD, and ADHD when compared to the white race among liver cirrhosis hospitalizations. Blacks had a higher association with schizophrenia (aOR 3.10, 95%CI 2.60-3.66,  $P < 0.001$ ) and schizoaffective disorder (aOR 2.03, 95%CI 1.50-2.73,  $P < 0.001$ ) when compared to the white race with liver cirrhosis. The black race also had a higher association with schizoaffective disorder (aOR 2.03, 95%CI 1.50-2.73,  $P < 0.001$ ) compared to the white race with liver cirrhosis. There was no significant difference in the association of other races compared to the white race for schizophrenia or schizoaffective disorder. The black race had a lower association with PTSD than whites (aOR 0.70, 95%CI 0.52-0.94,  $P = 0.019$ ). Blacks (aOR 0.64, 95%CI 0.45-0.92,  $P = 0.018$ ) and Hispanics (aOR 0.72, 95%CI 0.56-0.92,  $P = 0.009$ ) had a lower association with SI than whites (Table 4).

## **DISCUSSION**

Our study revealed a significant increase in the prevalence of GAD, MDD, PTSD, ADHD, schizophrenia, schizoaffective disorder, and SI in hospitalized patients with cirrhosis from 2009 to 2019. According to the World Health Organization (WHO), the worldwide diagnoses of all mental illnesses increased by 13% from 2007 to 2017[24]. While this represents a significant increase, the rise of psychiatric diagnoses in cirrhosis hospitalizations was even more staggering in our study. Over the 11-

**Table 2 Associations of common psychiatric conditions based on liver cirrhosis etiology compared against “other” causes of cirrhosis (viral, autoimmune and non-specified)**

Variables	Adjusted odds ratio with 95% confidence interval	P value
<b>GAD</b>		
Alcoholic liver cirrhosis	1.79 [1.29-2.47]	<i>P</i> < 0.001
NAFLD cirrhosis	1.09 [0.69-1.73]	<i>P</i> = 0.690
<b>Depression</b>		
Alcoholic liver cirrhosis	1.18 [1.08-1.29]	<i>P</i> < 0.001
NAFLD cirrhosis	1.14 [1.01-1.28]	<i>P</i> = 0.025
<b>Bipolar disorder</b>		
Alcoholic liver cirrhosis	1.62 [1.34-1.96]	<i>P</i> < 0.001
NAFLD cirrhosis	1.37 [1.04-1.79]	<i>P</i> = 0.021
<b>ADHD</b>		
Alcoholic liver cirrhosis	1.02 [0.55-1.87]	<i>P</i> = 0.94
NAFLD cirrhosis	1.49 [0.65-3.41]	<i>P</i> = 0.34
<b>Schizophrenia</b>		
Alcoholic liver cirrhosis	1.09 [0.76-1.57]	<i>P</i> = 0.60
NAFLD cirrhosis	0.82 [0.45-1.47]	<i>P</i> = 0.51
<b>Schizoaffective disorder</b>		
Alcoholic liver cirrhosis	1.18 [0.71-1.94]	<i>P</i> = 0.50
NAFLD cirrhosis	0.41 [0.15-1.13]	<i>P</i> = 0.08
<b>PTSD</b>		
Alcoholic liver cirrhosis	1.57 [1.15-2.13]	<i>P</i> = 0.004
NAFLD cirrhosis	1.05 [0.65-1.69]	<i>P</i> = 0.81
<b>Chronic Fatigue</b>		
Alcoholic liver cirrhosis	0.16 [0.03-0.73]	<i>P</i> = 0.019
NAFLD cirrhosis	0.73 [0.24-2.20]	<i>P</i> = 0.58
<b>Suicidal ideations</b>		
Alcoholic liver cirrhosis	2.01 [1.33-3.04]	<i>P</i> = 0.001
NAFLD cirrhosis	0.51 [0.19-1.32]	<i>P</i> = 0.16

NAFLD: Non-alcoholic fatty liver disease; GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder.

year study period, rates of GAD and MDD in hospitalized patients with cirrhosis increased by approximately 400% and 70%, respectively. Additionally, the occurrences of PTSD, ADHD, schizophrenia, schizoaffective disorder, and SI increased at greater rates than the worldwide average. Therefore, our study indicates a significantly increased prevalence of mental illness in patients with cirrhosis. This can have a negative impact on quality of life, increase the burden on the healthcare system, and decrease compliance with medical treatment. The results of our study highlight the importance of evaluating patients with cirrhosis for concomitant psychiatric conditions. It could be argued that all patients with cirrhosis should be referred for evaluation by psychiatry and/or psychology at the time of diagnosis. This could lead to improved psychiatric outcomes and have positive downstream effects for the cirrhotic patients, leading to improved clinical outcomes.

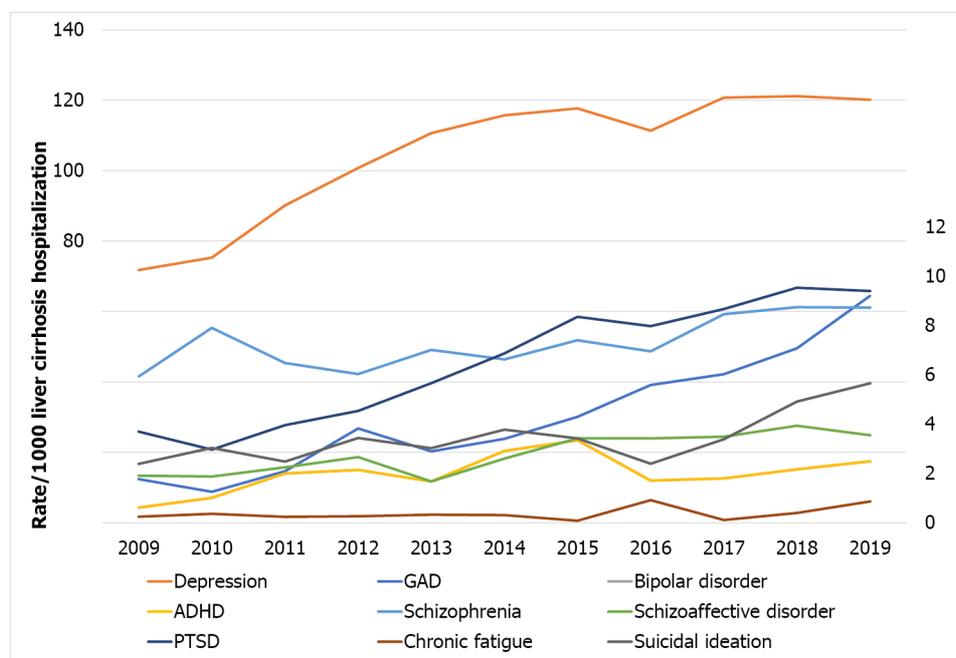
#### **Psychiatric conditions based on etiology of cirrhosis**

A number of studies have assessed the prevalence of psychiatric disorders in alcohol-related liver disease. However, there are no large studies assessing rates of comorbid psychiatric conditions in cirrhotics based on the etiology of liver disease. Our study compared associated psychiatric diseases by dividing the etiology of cirrhosis into alcohol, NAFLD and other etiologies (viral, autoimmune, or

**Table 3 Gender disparities with common psychiatric conditions in inflammatory bowel disease hospitalizations (Females compared against males)**

Variables	Adjusted odds ratio with 95% confidence interval	P value
GAD	2.56 [2.14-3.06]	$P < 0.001$
Depression	1.78 [1.71-1.84]	$P < 0.001$
Bipolar disorder	1.64 [1.52-1.77]	$P < 0.001$
ADHD	1.07 [0.82-1.39]	$P = 0.610$
Schizophrenia	0.90 [0.79-1.04]	$P = 0.170$
Schizoaffective disorder	0.90 [0.73-1.13]	$P = 0.390$
PTSD	0.83 [0.72-0.97]	$P = 0.021$
Chronic Fatigue	2.31 [1.31-4.07]	$P = 0.004$
Suicidal ideation	0.86 [0.71-1.04]	$P = 0.120$

GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder.



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**Figure 1 Rate of common psychiatric conditions in liver cirrhosis hospitalizations.** The colored lines represent rates of different psychiatric diagnoses per 1000 liver cirrhosis hospitalizations for the study period (2009-2019). GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder.

unspecified). Our data revealed a significantly higher rate of GAD (aOR 1.79) in alcohol cirrhosis compared to other etiologies of cirrhosis. This association was not statistically significant when comparing the NAFLD cohort to the other etiologies of cirrhosis ( $P = 0.69$ ). As numerous studies have shown, there is a significant association between alcohol use disorder and anxiety[25-28]. It is possible that self-treatment of anxiety with alcohol predisposes these patients to develop alcohol-induced cirrhosis, thus explaining the findings of our study. Interestingly, while Santos *et al*[29] revealed a high prevalence of anxiety in patients with alcoholic cirrhosis listed for transplant, they found patients with cirrhosis related to autoimmune hepatitis to have the most severe anxiety symptoms.

Alcohol use is a commonly associated comorbidity with both PTSD and SI[30-33]. The results of our study mirror these findings, with PTSD (aOR 1.57) and SI (aOR 2.01) significantly associated with alcohol cirrhosis compared to NAFLD and other etiologies of cirrhosis. Disinhibition and executive dysfunction from alcohol intoxication, coupled with stressors from living with a chronic medical condition, potentially play a role in the increased frequency of SI in alcohol cirrhosis. A survey-based study by Le Strat *et al*[34] noted an increased rate of SI among patients with liver disease but did not

**Table 4 Race disparities with common psychiatric conditions in inflammatory bowel disease hospitalizations (compared against white race)**

Variables	Adjusted odds ratio with 95% confidence interval	P value
<b>GAD</b>		
Black	0.33 [0.21-0.53]	<i>P</i> < 0.001
Hispanic	0.43 [0.33-0.57]	<i>P</i> < 0.001
Asian/Native American	0.08 [0.01-0.60]	<i>P</i> = 0.014
<b>Depression</b>		
Black	0.54 [0.50-0.59]	<i>P</i> < 0.001
Hispanic	0.58 [0.54-0.61]	<i>P</i> < 0.001
Asian/Native American	0.36 [0.30-0.43]	<i>P</i> < 0.001
<b>Bipolar disorder</b>		
Black	0.79 [0.69-0.90]	<i>P</i> = 0.001
Hispanic	0.48 [0.43-0.55]	<i>P</i> < 0.001
Asian/Native American	0.16 [0.08-0.29]	<i>P</i> < 0.001
<b>ADHD</b>		
Black	0.14 [0.06-0.34]	<i>P</i> < 0.001
Hispanic	0.22 [0.13-0.37]	<i>P</i> < 0.001
Asian/Native American	0.16 [0.02-1.14]	<i>P</i> = 0.068
<b>Schizophrenia</b>		
Black	3.10 [2.6-3.66]	<i>P</i> < 0.001
Hispanic	1.05 [0.88-1.26]	<i>P</i> = 0.540
Asian/Native American	0.72 [0.39-1.32]	<i>P</i> = 0.290
<b>Schizoaffective disorder</b>		
Black	2.03 [1.50-2.73]	<i>P</i> < 0.001
Hispanic	1.05 [0.79-1.39]	<i>P</i> = 0.710
Asian/Native American	0.66 [0.24-1.79]	<i>P</i> = 0.420
<b>PTSD</b>		
Black	0.70 [0.52-0.94]	<i>P</i> = 0.019
Hispanic	0.46 [0.37-0.58]	<i>P</i> < 0.001
Asian/Native American	0.69 [0.39-1.22]	<i>P</i> = 0.210
<b>Chronic Fatigue</b>		
Black	0.18 [0.02-0.139]	<i>P</i> = 0.100
Hispanic	0.50 [0.20-1.19]	<i>P</i> = 0.110
Asian/Native American	-	-
<b>Suicidal ideations</b>		
Black	0.64 [0.45-0.92]	<i>P</i> = 0.018
Hispanic	0.72 [0.56-0.92]	<i>P</i> = 0.009
Asian/Native American	0.43 [0.16-1.16]	<i>P</i> = 0.097

NAFLD: Non-alcoholic fatty liver disease; GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; ADHD: Attention deficit hyperactivity disorder.

differentiate based on the etiology of liver disease. It is possible that the high prevalence of alcohol-related liver disease impacted the findings of their study.

Our study also revealed that the prevalence of MDD was significantly higher in the alcoholic cirrhosis (aOR 1.18) and NAFLD cirrhosis (aOR 1.14) cohorts when compared to other etiologies of cirrhosis. Similarly, bipolar disorder had a higher prevalence in alcoholic cirrhosis (aOR 1.62) and NAFLD cirrhosis (aOR 1.37) when compared to other etiologies of cirrhosis.

There was no statistically significant difference in the rates of schizophrenia, schizoaffective disorder, and ADHD among the different etiologies of cirrhosis in our study. This could be due, in part, to the fact that ADHD is considered a neurodevelopmental disorder per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and symptoms of ADHD must be present before the age of 12 years old, which would likely predate the onset of cirrhosis for the vast majority of patients, regardless of the etiology of cirrhosis. Similarly, psychotic disorders such as schizophrenia and schizoaffective disorder are typically diagnosed in late adolescence or early adulthood, again predating a liver cirrhosis diagnosis for most patients. In our results, it does not seem as though having a psychotic disorder would predispose the patient to a certain etiology of liver cirrhosis. It is possible that the neuropsychiatric pathways for the development of these disorders are not as affected by the effects of chronic liver disease when compared to GAD, MDD, SI, and bipolar disorder. Notably, this is a complex pathway that requires greater understanding prior to developing causality related to liver disease.

### **Psychiatric conditions in cirrhosis based on gender disparities**

When comparing the rates of psychiatric conditions between genders, our study revealed a significantly increased rate of GAD (aOR 2.56), MDD (aOR 1.78), bipolar disorder (aOR 1.64) and chronic fatigue (aOR 2.31) among females compared to males with cirrhosis. Similarly, a large United States survey-based study by Vesga-López *et al*[35] revealed a lifetime prevalence of GAD of 5.3% in women and 2.8% in men. Prior studies have shown an approximate 1.6-1.7 fold greater incidence of MDD in females compared to males[36-38]. Our study revealed a slightly higher rate of MDD in female patients with cirrhosis compared to males. These findings are mirrored in studies by Lee *et al*[39] (male gender OR = 0.45, 95%CI: 0.37-0.55) and Rivera-Matos *et al*[40] (12-mo prevalence of MDD: 7% males *vs* 13% females). It is unclear if the higher rates of MDD in females with cirrhosis are significant; however, none of the above-referenced studies included 11 years of data. These findings highlight the importance of screening for MDD, particularly in female patients with cirrhosis.

The data for gender-based differences in bipolar disorder in the general population remains unclear. While some studies suggest an equal distribution of bipolar disorder between males and females, other studies suggest a greater prevalence in females. One large analysis consisting of more than 47000 patients with bipolar disorder revealed that approximately 55%-65% of patients were female[41]. Patel *et al*[42] found that females made up 54.8% of bipolar disorder admissions from 2010 to 2014 using NIS data. On the other hand, a survey-based study involving approximately 13000 patients in New Zealand revealed similar rates of bipolar disorder among males and females[43]. Vega *et al*[44] suggested similar rates of bipolar I disorder between both sexes and a female predominance in bipolar II disorder. Further classification between the two types of bipolar disorder was not available, but females had a greater association with overall bipolar disorder (aOR 1.64) than males among cirrhotics in our study. Pertinently, this is a stronger association compared to the findings of other studies.

It is generally accepted that chronic fatigue syndrome (CFS) is more prevalent in females. A cohort study involving patients with chronic fatigue performed by Faro *et al*[45] revealed an approximate 10:1 ratio between females and males. Another survey-based study from Iceland showed that 78% of respondents with chronic fatigue were female[46]. However, the significant variation between genders with a diagnosis of CFS seen in the general population was not replicated in the cirrhotic patients in our study (F > M, aOR 2.31). This is at least partly explained by the fact that fatigue is a very common somatic symptom in patients with chronic liver disease. Swain *et al*[47] revealed that chronic fatigue may be seen in up to 50% of patients with chronic liver disease. Patients with cirrhosis should be screened for symptoms of fatigue as it may play a role in the development of sarcopenia, which could present a barrier to future liver transplantation[48].

### **Psychiatric conditions in cirrhosis based on racial disparities**

We found that among patients with cirrhosis, Caucasians have a greater association with GAD, MDD, bipolar disorder, PTSD, ADHD, chronic fatigue, and SI when compared to other races. These findings are in line with many previous studies involving the general population, including a 16-year cohort study by Manseau *et al*[49]. Of note, the study by Manseau *et al*[49] did not evaluate rates of psychiatric conditions in Asian and Native Americans. Interestingly, in our study, the Asian/Native American cohort had a significantly lower association with GAD (aOR 0.08), depression (aOR 0.36), and bipolar disorder (aOR 0.16) compared to Caucasians. It is possible that the differences in psychiatric diagnoses among minorities are in part explained by the underutilization of mental health services by minorities. Abe-Kim *et al*[50] showed that Asian Americans had lower rates of utilization of mental health services than the general population. A survey-based study by Dobalian *et al*[51] revealed that African Americans and Hispanics were less likely to have visited a mental health professional than whites. Lipson *et al*[52] found that people of color had more unmet mental health needs than whites in a study

involving over 40000 college students. They also found that Asian Americans had the lowest utilization of mental health services compared to other races[52]. While our study revealed a higher prevalence of mental illnesses among Caucasians, diligence should be taken in assessing mental health conditions in all patients with cirrhosis. Possible explanations for the lower utilization of mental health services by racial minorities may be due to the stigmatization of mental illness, especially in communities of color, the lack of access to psychiatric care, particularly in rural areas, the lack of trust in mental health due to past racist medical practices, and possibly poor rapport due to cultural differences. Normalizing mental illness, developing rapport with the patient, incorporating the patient's own belief system into the treatment plan, and using language interpreters may assist with the proper management of mental health conditions in minority patients with cirrhosis.

According to the DSM-5, schizophrenia falls under the category of psychotic disorders. Other conditions in this category include schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to another medical condition, substance- or medication-induced psychotic disorder, unspecified schizophrenia spectrum disorder, and other psychotic disorders[53]. Our study revealed a significantly higher rate of schizophrenia (aOR 3.10) and schizoaffective disorder (aOR 2.03) among African Americans compared to other races, including Caucasians. These findings are in accordance with the findings of many previous studies assessing racial differences in the diagnosis of schizophrenia in the general population. Several studies have found that African Americans are approximately 3-5 times more likely to be diagnosed with schizophrenia than Caucasians[54-56]. However, these findings have raised concern about the role of bias in the diagnosis of schizophrenia in African Americans[57]. Additionally, some have postulated that the underdiagnosis of other psychiatric conditions in African Americans has led to an overdiagnosis of schizophrenia[58]. Garb argued that African Americans and Hispanics may receive diagnoses of schizophrenia even when they are not justified using proper diagnostic methods[59]. Cohen *et al*[60] found that African Americans and Hispanics had a higher prevalence of lifetime psychotic symptoms compared to Caucasians and Asians. However, the differences were less significant than in our study. Cirrhosis is a chronic medical condition that not only places psychosocial stress on the patient but also can result in neuropsychiatric symptoms such as HE. As a result, accurate psychiatric diagnoses in these patients are critical. It is plausible that patients with cirrhosis may be misdiagnosed with schizophrenia when their underlying medical condition is contributing to their symptoms. Unbiased examination and optimization of neurologic symptoms such as HE is needed prior to diagnosing psychiatric conditions such as schizophrenia.

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## LIMITATIONS

While we included a large population of cirrhotics over an 11-year study period, there are a few limitations to our study. The NIS database comprises approximately 20% of the hospitals in the United States. The final data is a national estimate calculated using sampling weights for extrapolation of national numbers. Furthermore, entry into the NIS database represents a single hospitalization. A single patient could potentially have multiple entries in the database through readmissions and hospital transfers. Another limitation is that our study only used ICD coding for psychiatric diagnoses. The DSM-5 classification may be more commonly used among psychiatric professionals, and thus, psychiatric diagnoses may be missed or incorrect. As all psychiatric illnesses are multifactorial, it is impossible to relate them to one specific cause. The exact etiology of the psychiatric illnesses reported here is unknown and likely multifactorial. Therefore, the authors only reported associations (ORs) and not relative risks. Moreover, we only reported prevalence, not incidence, as this is a retrospective database. Finally, data entry for race may have some limitations in that many patients are misclassified or may not have documentation for race during their hospitalization.

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## CONCLUSION

As mental health conditions continue to become less stigmatized over time, more patients are becoming open to mental health evaluation and treatment. For reasons that are not completely understood, there is a continued rise in the diagnosis of psychiatric conditions in the general population. Our study revealed that the remarkably increasing rate of psychiatric diagnoses in cirrhotics is alarming. Our findings highlight the disparities in the diagnoses of certain psychiatric conditions in cirrhotics between gender as well as race. As a medical professional, it is important to understand and recognize these disparities as they may expedite management and improve overall outcomes. It is not uncommon for neuropsychiatric symptoms in cirrhotics to be ignored or misdiagnosed due to the role that liver disease plays in neurologic function. Although transplant psychiatrists and psychologists play an integral role in the management of all patients evaluated for liver transplantation, this resource is not available for all patients with cirrhosis despite the fact that many patients who are not liver transplant candidates may be suffering from concomitant mental illness. The findings in our study suggest that all cirrhotics should

be provided with a referral to a mental health professional at the time of diagnosis.

## ARTICLE HIGHLIGHTS

### **Research background**

Chronic liver disease is associated with various neuropsychiatric conditions, such as generalized anxiety disorder (GAD) and major depression. The psychological stress experienced by patients with cirrhosis can negatively affect their mental health.

### **Research motivation**

There is limited data assessing and comparing the prevalence of psychiatric conditions based on patient profiles and the etiology of cirrhosis.

### **Research objectives**

To examine the trends of hospitalizations among common psychiatric conditions in cirrhosis based on gender, race, and the etiology of liver disease over 11 years in the United States by dividing the etiology of cirrhosis into alcohol, non-alcoholic fatty liver disease, and other causes (viral, autoimmune, or unspecified) using the National Inpatient Sample (NIS) 2009-2019.

### **Research methods**

The present study utilized the NIS database to identify patients with a primary diagnosis of liver cirrhosis from January 2009 to December 2019 and assess the prevalence of common psychiatric conditions that included GAD, major depressive disorder, bipolar disorder, attention-deficit/hyperactivity disorder, schizophrenia, schizoaffective disorder, post-traumatic stress disorder, chronic fatigue, and suicidal ideation.

### **Research results**

Our study showed an uptrend in psychiatric comorbidities over the last decade, with racial and gender disparities.

### **Research conclusions**

The findings of this study revealed a remarkably increasing rate of psychiatric diagnoses in cirrhotics. Therefore, it is imperative for clinicians to understand and recognize associated disparities based on gender and race.

### **Research perspectives**

Our study suggests that all liver cirrhosis patients should be provided a referral to a mental health professional at the time of diagnosis, and more studies are needed to look into the etiology of these diagnoses.

## FOOTNOTES

**Author contributions:** Patel P, Ali H, Inayat F, Pamarthy R, and Giammarino A contributed to conceptualization, methodology, software, data curation, validation, writing, and original draft preparation; Ilyas F and Smith-Martinez LA contributed to writing, reviewing, editing, and supervision; Satapathy SK project administration, supervision, and critical revision of the manuscript; all authors had access to the study data and reviewed and approved the final manuscript.

**Institutional review board statement:** Patients' data was not acquired by any specific institution but rather open-access United States National Inpatient Sample (NIS) data. The NIS contains de-identified information, protecting the privacy of patients, physicians, and hospitals. Therefore, it was deemed exempt from the institutional review board (IRB).

**Informed consent statement:** Participants were not required to give informed consent for this retrospective study since the analysis of baseline characteristics used anonymized clinical data.

**Conflict-of-interest statement:** There is no conflict of interest associated with publication of this manuscript.

**Data sharing statement:** No additional data are available.

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