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Concomitant psychiatric and non-alcohol related substance use disorders among hospitalized patients with alcoholic liver disease in the United States

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Abbreviations:

ALD: Alcoholic liver disease

CI: Confidence interval

HCUP: Healthcare Cost and utilization project

ICD-9CM: International Classification of Diseases-Ninth Revision, Clinical Modification

NIS: National inpatient sample

OR: Odds ratio

ABSTRACT

Background: Despite that the epidemiological studies on the comorbidity of alcohol misuse and psychiatric disorders have been studied, less is known about the magnitude of these disorders among patients with alcoholic liver disease (ALD). Our aim was to determine the prevalence of psychiatric and substance use disorders among hospitalized ALD patients in the US.

Methods: We utilized a single level clinical classification software to identify patients with ALD and psychiatric/substance use disorders from the 2011 National Inpatient Sample data. The primary outcome was the prevalence of these disorders among hospitalized patients with ALD (n=74,972) compared to those with chronic liver diseases not caused by alcohol (n=350,140) and those without underlying liver diseases (n=1,447,063).

Results: The prevalence of adjustment disorder, anxiety disorder, post-traumatic stress disorder and depression was significantly higher among hospitalized patients with ALD when compared to those with chronic liver diseases not caused by alcohol (all with p values <0.05).

Younger age, female gender, and White race were the independent predictors of psychiatric/substance use disorders among hospitalized patients with ALD.

Conclusions: Hospitalized patients with ALD have significantly high prevalence of concomitant psychiatric and substance abuse disorders when compared to those with chronic liver diseases not caused by alcohol and those without underlying liver diseases. Screening and appropriate intervention should be implemented as part of routine clinical care for these patients.

INTRODUCTION

Excessive alcohol consumption can cause diseases with significant economic and social burdens (Basra and Anand, 2011; Rehm et al., 2013). Recent data showed that approximately 6% of all global deaths were attributed to alcohol consumption (World Health Organization, 2015). Alcoholic liver disease (ALD) is a main cause of alcohol-related morbidity accounting for 48% of all deaths from cirrhosis (Rehm et al., 2013). It consists of a spectrum of disorders ranging from alcohol-induced fatty liver to alcoholic hepatitis and cirrhosis. Alcoholic steatosis, once considered benign, is now recognized as a condition that may lead to advanced liver disease or cirrhosis (Teli et al., 1995). At present, there are no specific pharmacotherapies for patients with ALD. In those with advanced and decompensated liver disease, liver transplantation has been shown to improve the overall outcomes and survival (Mathurin and Bataller, 2015; Varma et al., 2011). Abstaining from alcohol is the cornerstone in the management of ALD. A French study showed the improvement in Child-Pugh scores in 66% of subjects with ALD who became abstinent (Veldt et al., 2002).

One of the major problems in the management of patients with ALD is the relapse to harmful drinking after abstinence (Cuadrado et al., 2005; Egawa et al., 2014). Alcohol use relapse is a risk factor for hepatic decompensation and recurrent alcoholic hepatitis (Potts et al., 2013). In post liver transplant patients, it can lead to poor compliance to medical care, graft loss, and impaired long-term survival (Cuadrado et al., 2005; Egawa et al., 2014; Hartl et al.,

2011; Pfitzmann et al., 2007). Several factors predicting relapse include a family history of alcohol abuse/dependence, lack of self-perception of having an alcohol drinking problem, a poor social support system, the duration of abstinence before liver transplantation, and underlying psychological disorders (other than alcohol abuse/dependence)(Dew et al., 2008; Egawa et al., 2014; Hartl et al., 2011).

Previous reports have shown that those with alcohol misuse/dependence are more likely to have other psychiatric conditions such as major depressive disorder, generalized anxiety disorder, and post-traumatic stress disorder compared to those without alcohol dependence (Petrakis IL et al.,2002; Kessler et al., 1996; Regier et al., 1990). Although psychological as well as pharmacological therapies for psychiatric disorders and alcohol use disorders can be offered to assist these patients, they frequently do not receive treatment(s) addressing both conditions (Petrakis IL et al., 2002). Despite epidemiological studies on the comorbidity of alcohol misuse and psychiatric disorders (Petrakis IL et al., 2002; Kessler et al., 1996; Regier et al., 1990), less is known about the prevalence of psychiatric disorders among patients with ALD. Understanding the scope of these problems among ALD patients is essential to develop comprehensive plans that address both alcohol and psychiatric disorders. The objective of our study was to determine the co-occurrence of psychiatric disorders among hospitalized ALD patients in the US.

METHODS

Data source

The National Inpatient Sample (NIS) 2011 data were used for the analyses. The NIS is the largest publicly available all-payer inpatient healthcare database, which was collected as part of the Healthcare Cost and utilization project (HCUP) by the Agency for healthcare Research and Quality (Healthcare Cost and Utilization project ., 2016). The data contain 8 million hospital stays from about 1,000 hospitals sampled to approximate a 20-percent stratified sample of U.S. community hospitals. In the NIS data, the U.S. community hospitals are

divided into strata using five hospital characteristics: ownership/control, bed size, teaching status, urban/rural location, and U.S. region. The sampling probabilities are proportional to the number of U.S. community hospitals in each stratum. Weights were provided to calculate national estimates. Sampling of hospitals and sample weights of the NIS data are described elsewhere (Healthcare Cost and Utilization project ., 2016).

Study cohort and variables identification

We identified 3 cohorts from the NIS 2011 data using the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM). The first cohort was patients with alcoholic hepatitis/cirrhosis and those with the diagnosis of alcohol-related disorder (as defined by ICD 9 codes in **supplementary table 1**) who presented with elevated liver enzymes in the absence of other liver etiologies such as viral hepatitis, biliary cirrhosis, autoimmune liver disease, nonalcoholic cirrhosis, etc. The second cohort was hospitalized patients with other chronic liver diseases (such as non-alcoholic steatohepatitis, hepatitis C infection, and biliary cirrhosis) not caused by alcohol. Any patients who had the diagnosis of alcohol dependence syndrome, nondependent alcohol abuse, and toxic effect of alcohol were excluded. For the last cohort, we randomly selected 5% of all hospitalized subjects with no known liver diseases.

We used the single level clinical classification software category to identify subjects with psychiatric and non-alcohol related substance use disorders. This software provides collapsed clinically meaningful categories of over 14,000 diagnostic codes as well as 3,900 procedural codes. The ICD-9-CM codes which were used in our study are provided in **supplementary table 1**.

Statistical analyses

All statistical analyses were performed using SAS 9.3 software (Cary, NC) accounting for the sampling weights and stratified sample design of the NIS data to attain nationally representative estimates (Healthcare Cost and Utilization project , 2016) . Basic descriptive statistics such as mean and standard deviation (for continuous variables) and percentages (for categorical variables) were used to describe the study cohorts.

The primary outcome of interest was the prevalence of psychiatric/mental disorders in hospitalized patients among the 3 cohorts. Chi-square (χ^2) analyses were used to compare the differences in the prevalence between/among groups. Logistic regression analyses adjusting for potential covariates such as age, sex, race, and income quartile were used to determine the independent predictors of psychiatric/mental disorders. All the analyses were two-tailed. The p value less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the study cohorts

The detailed characteristics of the study cohorts are summarized in **Table 1**. Patients with ALD were younger (53.3 ± 0.2 yrs) than those with chronic liver diseases not caused by alcohol (58.8 ± 0.4 yrs) and those without underlying liver diseases (57.6 ± 0.4 yrs). Among patients with ALD, most were men (71%), and White (69%). While Medicare was the primary payer (~45%) for patients with chronic liver disease not caused by alcohol, only 29% of patients with ALD were covered by Medicare ($p < 0.001$).

Prevalence of psychiatric/non-alcohol related substance use disorders among study cohorts

The prevalence of adjustment disorder (0.58 vs. 0.42), anxiety disorder (8.84 vs 7.54), mood disorders (24.3 vs. 18.7), personality disorder (0.96 vs. 0.73), non-alcohol related substance abuse (12.4 vs. 9.9), suicide-related disorder (2.4 vs 1.1), tobacco use (43.8 vs. 27.8), post-traumatic stress disorder (1.14 vs. 0.82), and depression (3.9 vs. 2.1) was significantly higher among hospitalized patients with ALD when compared to those with chronic liver diseases not caused by alcohol (all with respective p value < 0.05) (**Table 2**). The prevalence of attention deficit disorder (0.54 vs. 0.43), delirium disorder (7.11 vs. 2.91), developmental disorder (0.8 vs. 0.5), impulse disorder (0.12 vs. 0.03), personality disorder (1.28 vs. 0.96), and schizo/psychotic disorder (3.44 vs. 2.35) was significantly higher in hospitalized ALD patients when compared to those without underlying liver diseases (**Table 2**). Given the high

prevalence of hepatitis C infection among patients with ALD, we also performed a separate analysis including patients with combination of ALD and hepatitis C infection, compared to those with chronic liver diseases not caused by alcohol. The results are shown in **supplementary table 2**.

Evaluation of the relationship between ALD and psychiatric/non-alcohol related substance abuse disorders by multivariate logistic regression

We next assessed the association between psychiatric/non-alcohol related substance use disorders in patients with the diagnosis of ALD compared to those with chronic liver diseases not caused by alcohol, those without underlying liver diseases using multivariate logistic regression models adjusting for potential covariates including age, sex, race, and income quartile (**Table 3**). Patients with ALD were 1.16, 1.37, 1.83, 1.76, 1.72, and 1.17 times more likely to have anxiety disorder, mood disorder, depression, suicide-related disorder, tobacco use, and post-traumatic stress disorder compared to those with chronic liver diseases not caused by alcohol(**Table 3**). Similar findings were found when we compared patients with ALD and those without underlying liver diseases, except that those without underlying liver diseases had less risk for suicide-related disorders (OR 0.81) when compared to those with ALD (**Table 3**).

Predictors of psychiatric/non-alcohol related substance use disorders among hospitalized patients with ALD

We next determined the predictors of psychiatric/non-alcohol substance use disorders among hospitalized patients with ALD (**Table 4**). There was an inverse association between patient's age and psychiatric/non-alcohol substance use disorders (aOR 0.97, 95%CI 0.96-0.97). When compared to Caucasians, Blacks (aOR 0.80, 95%CI 0.73-0.88) and Hispanics (aOR 0.56, 95%CI 0.51-0.61) had less risk for psychiatric/non-alcohol related substance use disorders. Women had a significantly higher risk for psychiatric/non-alcohol related substance use

disorders than men (aOR 1.58, 95%CI 1.51-1.66) . We did not observe the levels of income as an independent predictor for these disorders.

DISCUSSION

In our present study, we aimed to determine the magnitude of psychiatric and non-alcohol related substance use disorders among patients with ALD. The major findings of our study are as follows: 1) hospitalized ALD patients had significantly higher prevalence of several psychiatric and substance use disorders when compared to those with chronic liver diseases not caused by alcohol and those without underlying liver diseases and , 2) the presence of these disorders is most commonly seen in young Caucasian females with ALD.

Co-occurrence of psychiatric illnesses is not uncommon in patients with alcohol use disorder (Kessler et al., 1996; Regier et al., 1990; Helzer and Pryzbeck, 1988). In a large epidemiologic study in the US, underlying psychiatric disorders, notably antisocial personality, affective and anxiety disorders, were found in 37% among patients with alcohol use disorders (Regier et al., 1990). While the association between alcohol use and psychiatric disorders is well described (Kessler et al., 1996; Regier et al., 1990), less is known about the prevalence of psychiatric and substance use disorders in patients with ALD. We found a higher prevalence of several psychiatric and substance use disorders among hospitalized patients with ALD. Our results have several clinical implications. ALD patients seldom volunteer specific information or problems about their underlying drinking or psychiatric issues, unless they are asked (Helzer and Pryzbeck, 1988); however, even if they do, these patients may be in denial or trying to minimize the magnitude of the problems. Our data suggest that screening for underlying psychiatric disorders should be implemented as part of routine clinical cares of patients with ALD. Achieving long-term abstinence is the cornerstone of management for patients with ALD. If underlying psychiatric illnesses are undiagnosed, these patients will not receive appropriate treatment and likely relapse to alcohol use as a means of coping (Cuadrado et al., 2005; Hartl et al., 2011). Therefore, it is crucial for hepatologists to gather comprehensive mental health

information when assessing patients with ALD. Specific inquiries focusing not only on the quantity and patterns of alcohol use but also on screening questions to evaluate for possible co-occurrence of underlying psychiatric disorders are needed and should be part of routine hepatology practice. Those with positive screens should be further evaluated for definitive diagnosis and treatment. Our results also provide certain patient characteristics (i.e., younger age, Caucasians, and female patients) which are independently associated with psychiatric and substance use disorders among patients with ALD. Special focus with extensive screening may be needed when we encounter patients with ALD having these characteristics to uncover possible underlying psychiatric issues.

The strengths of our study are the careful selection of the study cohort and its large sample size representing hospitalized patients in the US. However, our study also has several limitations. First, the prevalence of psychiatric disorders in our study is limited to those who were hospitalized. Further, the NIS data do not capture hospitalizations from Veterans Affairs hospital, short-term rehabilitation hospitals, long-term non-acute care hospitals, psychiatric hospitals, and alcoholism/chemical dependency treatment centers. There is also a possibility of underreporting of psychiatric and substance use disorders in our study cohorts. Therefore our results may be different if the study were performed in an outpatient-based or in specialized institutes. Second, laboratory tests are not available in the NIS data so we are not able to determine the severity of underlying ALD and its contribution to our findings. Third, each NIS data entry is equivalent to one hospitalization. It is plausible that one patient may contribute to multiple entries if he/she was re-hospitalized within the study period. Fourth, there is a possibility of misclassification of the study subjects when we used ICD-9CM coding to identify our study cohorts and underlying psychiatric and substance use disorders.

In conclusion, we found significantly higher prevalence of several psychiatric and substance use disorders among hospitalized patients with ALD when compared to those with chronic liver diseases not caused by alcohol and those without underlying liver diseases.

Screening and appropriate intervention should be implemented as part of routine clinical care for these patients.

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TABLE 1: Baseline demographic characteristics of the study cohort

	Alcoholic liver disease (N= 74,972)	Liver diseases from other etiologies, not caused by alcohol (N= 350,140)	p value**	Hospitalized patients without underlying liver diseases (N= 1,447,063)	p value**
Age in years (mean ± SD)	53.3 ± 0.2	58.8 ± 0.4	<0.001	57.6 ± 0.4	<0.001
Race (%)			<0.001		<0.001
White	68.9	64.4		69	
Black	11.7	17.4		15.6	
Hispanic	13.7	12.1		9.9	
Others	5.7	5.9		5.5	
Gender (male, %)	71.2	51.1	<0.001	44.3	<0.001
Household income (%)*			0.002		0.902
First quartile	29.5	32.7		29.6	
Second quartile	25	24.3		24.8	
Third quartile	24.8	24.1		25.1	
Fourth quartile	20.7	18.9		20.4	
Admission source (%)			<0.001		<0.001
Emergency department	56.8	46.9		36.4	
Another hospital	4.1	4.9		4.7	
Other facility including long-term care	1.9	2.7		2.9	

Court and law enforcement	0.1	0.2		0.1	
Routine/other	37.2	45.3		55.9	
Hospital location (%)			0.272		0.002
Rural	10.4	9.4		12.1	
Urban	89.6	90.6		87.9	
Teaching status of the hospital (%)			<0.001		0.053
Nonteaching	54.5	48.1		52.7	
Teaching	45.5	51.9		47.3	
Hospital bed size (%)			0.001		0.116
Small	11.6	10.6		12.5	
Medium	26.2	24.2		24.9	
Large	62.3	65.2		62.6	
Region of admitting hospital (%)			<0.001		<0.001
Northeast	19	19.6		20.8	
Midwest	22.1	20.8		23.1	
South	33.9	38.2		37.6	
West	25	21.5		18.5	
Patient Disposition (%)			<0.001		<0.001
Routine discharge to home	63.1	59.6		66.4	
Short-term hospital	3.5	3.4		2.2	
Skilled nursing facility	15.4	16.4		16.2	
Home healthcare	8.7	12.9		11.7	
Other	9.3	7.7		3.4	
Primary expected payer (%)			<0.001		<0.001
Medicare	29	46.4		45.3	
Medicaid	21.4	18.9		15	
Private insurance (including HMO)	25.8	23.8		28.8	
Others	23.8	10.9		10.9	

*First quartile as \$1-\$38,999, second as \$39,000-\$47,999, third as \$48,000-62,999 and forth as \$63,000 or more, **compared to alcoholic liver disease

TABLE 2. Comparison on the prevalence of psychiatric/substance use disorders among study cohorts

Disorder	Alcoholic liver disease (N= 74,972)		Liver diseases from other etiologies, not caused by alcohol (N= 350,140)		P value*	Hospitalized patients without underlying liver diseases (N= 1,447,063)		P value*
	%	N	%	N		%	N	
Adjustment disorder	0.58	435	0.42	1,471	0.001	0.60	8,682	0.59
Anxiety disorder	8.84	6,628	7.54	26,401	0.001	7.91	114,463	0.001
Attention deficit disorder	0.43	322	0.41	1,436	0.54	0.54	7,814	0.002
Delirium disorder	2.91	2,182	5.79	20,273	0.001	7.11	102,886	0.001
Development disorder	0.51	382	0.77	2,696	0.001	0.80	11,577	0.001
Impulse disorder	0.03	22	0.05	175	0.05	0.12	1,736	0.001
Mood disorder	24.32	18,233	18.78	65,756	0.001	19.16	277,257	0.001
Personality disorder	0.96	720	0.73	2,556	0.001	1.28	18,522	0.004
Schizo and psychotic disorder	2.35	1,762	3.16	11,064	0.001	3.44	49,779	0.0001
Substance abuse and its related disorder	12.38	9,282	9.98	34,944	0.001	8.14	117,791	0.001
Suicide related disorder	2.43	1,822	1.12	3,922	0.001	2.48	35,887	0.72
Tobacco use	43.83	32,860	27.87	97,584	0.001	26.80	387,813	0.001
PTSD	1.14	855	0.82	2,871	0.001	0.96	13,892	0.003
Depression	3.96	2,969	2.12	7,423	0.001	3.21	46,451	.001

*compared to those with alcoholic liver disease

TABLE 3. Adjusted odds ratio (aOR) of psychiatric/substance use disorders among hospitalized patients with alcoholic liver disease

Disorder	aOR (95% CI) as compared to patients with chronic liver diseases, not caused by alcohol*	aOR (95% CI) as compared to hospitalized patients without liver diseases+
Anxiety disorder	1.16 (1.09-1.22)	1.16 (1.10-1.23)
Mood disorder	1.37 (1.30-1.44)	1.35 (1.28-1.41)
Depression	1.83 (1.62-2.06)	1.14 (1.02-1.28)
Personality disorder	1.11 (0.91-1.36)	0.71 (0.58-0.85)
Substance abuse and its related disorder	1.01 (0.92-1.10)	1.28 (1.20-1.37)
Suicide- related disorder	1.76 (1.54-2.02)	0.81 (0.73-0.90)
Tobacco use	1.72 (1.66-1.79)	1.76 (1.70-1.82)
PTSD	1.17 (1.04-1.32)	1.10 (0.99-1.22)

*using patients with chronic liver diseases, not caused by alcohol as reference

+using hospitalized patients without liver diseases as reference

TABLE 4. Predictors of psychiatric/substance use disorders among hospitalized patients with alcoholic liver disease

Variable	Adjusted odds ratio, aOR (95% CI)
Age	0.97 (0.96-0.97)
Race (white as reference 1.0)	
Black	0.80 (0.73-0.88)
Hispanic	0.56 (0.51-0.61)
Other	0.61 (0.55-0.68)
Sex (male as reference 1.0)	
Female	1.58 (1.51-1.66)
Income quartile (first quartile as reference 1.0)*	
Second quartile	1.00 (0.93-1.08)
Third quartile	0.97 (0.90-1.04)
Forth quartile	1.06 (0.98-1.16)
Hospital region (northeast as reference 1.0)	
Midwest	1.13 (0.98-1.31)
South	0.85 (0.74-0.97)
West	0.94 (0.81-1.08)
Primary expected payer (medicare as reference 1.0)	
Medicaid	0.77 (0.71-0.84)
Private including HMO	0.67 (0.64-0.73)
Other	0.64 (0.59-0.70)

*First quartile as \$1-\$38,999, second as \$39,000-\$47,999, third as \$48,000-62,999 and forth as \$63,000 or more