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Osmotic Demyelination Syndrome in hospitalized patients with cirrhosis: analysis of the National Inpatient Sample (NIS)

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Abstract

GOAL: Characterize prevalence of Osmotic Demyelination Syndrome (ODS) in hospitalized patients with cirrhosis.

BACKGROUND: ODS is a serious complication of rapid serum sodium correction. Patients with cirrhosis experience labile sodium levels related to portal hypertension and diuretic use, often with rapid correction—intentional or unintentional—during hospitalizations.

STUDY: We used validated *ICD-9* codes to identify inpatients ≥ 18 years with cirrhosis from the 2009-2013 National Inpatient Sample, excluding those with liver transplantation during hospitalization. The primary outcome was ODS (*ICD-9 341.8*). Baveno IV defined decompensated cirrhosis (Stages 3 and 4); Charlson Comorbidity Index identified severe comorbid illness (score >3). Logistic regression modeled factors associated with ODS.

RESULTS: Of 547,544 adult inpatients with cirrhosis, 94 (0.02%) had ODS. Inpatients with vs. without ODS were younger (54 vs. 57y, p=0.0001), and more likely to have alcohol-related cirrhosis (58% vs. 33%, p<0.0001). ODS did not associate with decompensated cirrhosis (33% vs 37%, p=0.43), specific complications (ascites 33% vs 33%, p=0.97; hepatic encephalopathy 24% vs 17%, p=0.06), or severe comorbid illness (12% vs. 16%, p=0.24). In both univariable and multivariable analysis, age (OR_{adj} 0.97, 95% CI 0.95-0.99), female gender (OR_{adj} 1.53, 95% CI 1.01-2.30), Hispanic race (OR_{adj} 0.41, 95% CI 0.19-0.89), alcohol-related cirrhosis (OR_{adj} 2.65, 95% CI 1.71-4.09), and congestive heart failure (OR_{adj} 0.37 95% CI 0.15-0.95) significantly associated with ODS.

CONCLUSION: In hospitalized patients with cirrhosis, ODS is extremely rare, and associated with alcohol-related cirrhosis, younger age, and female gender. ODS is not associated with liver disease severity, specific complications including ascites, or comorbid disease.

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Keywords

central pontine myelinolysis; altered mental status; sex differences; diuretics; hospital admission

INTRODUCTION

Osmotic Demyelination Syndrome (ODS), also known as Central Pontine Myelinolysis, is a serious—and often irreversible—complication of rapid correction of serum sodium.[1] Patients with cirrhosis experience labile serum sodium levels related to portal hypertension and diuretic use, often with rapid correction—intentional or unintentional—during hospitalizations. Studies on ODS in cirrhosis have focused on patients undergoing liver transplantation.[2-6] These findings may not generalize to the cirrhosis population as a whole, yet the risk of ODS for inpatients with cirrhosis outside of the context of liver transplantation is not well-characterized. Such information is critical to inform management of severe hyponatremia in patients with cirrhosis, a common clinical scenario. Therefore, we aimed to characterize the prevalence and risk factors of ODS in this population.

MATERIALS & METHODS

We performed a cross-sectional study to determine overall prevalence of ODS in hospitalized patients with cirrhosis not receiving liver transplants, to compare those with and without ODS, and to determine whether cirrhosis and general illness severity correlated with prevalence of ODS. We used data from the Healthcare Cost and Utilization Project National Inpatient Sample (NIS), a nationally representative dataset of a stratified sample of US community hospitals, from years 2009-2013. This study was exempt from the need for informed consent. It was approved by the University of California, San Francisco institutional review board.

To develop our study sample, we selected all patients 18 years or older with any discharge diagnosis of cirrhosis using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes for cirrhosis, which have been previously validated for identifying inpatients with cirrhosis with a positive predictive power of 90% and a negative predictive value of 87%, as well as validated for identifying individual signs and severity of cirrhotic decompensation.[7] We excluded hospitalizations that included liver transplantation (*ICD-9 50.51* and *50.59*), and used the cohort of those who did not receive liver transplantation as the primary cohort.

The primary outcome was ODS at any point during hospitalization (*ICD-9 341.8*). Patient age, sex, race, etiology of liver disease, general medical comorbidities, complications of cirrhosis, and hospital outcomes including discharge disposition, length of stay, and inflation-adjusted total cost (estimated with Cost-to-Charge Ratio Files) were also extracted as described in depth elsewhere.[7] In brief, we identified specific complications of cirrhosis using discharge diagnosis codes (e.g. *ICD-9 572.2* for Hepatic Encephalopathy); we identified specific patient comorbidities such as congestive heart failure using the Clinical Classification Software; and identified paracenteses and thoracenteses with procedure codes.[7] Charlson Comorbidity Index was used as a marker of general illness severity/degree of comorbidities, stratified into three groups: mild (score=0), moderate (score=1 to 3),

severe (score >3). Baveno IV consensus criteria was used as a marker of cirrhosis illness severity, where those with Stages 3 (ascites, with or without esophageal varices), and 4 (gastrointestinal bleeding, with or without ascites) represented decompensated cirrhosis.[7]

For descriptive statistics we presented categorical variables as percentages and continuous variables as medians with respective interquartile ranges (IQR). To compare characteristics between patients with vs. without ODS, we used Pearson chi-square test for dichotomous variables; nonparametric Kruskal-Wallis to compare categorical variables; and Wilcoxon rank-sum for continuous variables. We used univariable logistic regression to assess unadjusted odds ratios (OR) associated with ODS, and used stepwise backward selection to determine the final multivariable logistic model. Statistical analysis were performed using Stata (Version 16, StataCorp, College Station, Texas).

RESULTS

Of 551,695 adult inpatients with cirrhosis, 547,544 (99%) did not receive a liver transplantation during hospitalization, and were selected as the study sample. Median age was 57 (IQR 51-67); 39% were female and 17% were Hispanic. 33% had alcohol-related etiology of cirrhosis, 69% met criteria for moderate or severe Charlson Illness Severity, 37% had decompensated cirrhosis, 33% exhibited ascites, and 17% had hepatic encephalopathy.

94 inpatients (0.02%) had a discharge diagnosis of ODS. Compared to patients without ODS, inpatients with ODS were younger, more often female, less often of Hispanic race, more likely to have alcohol-related cirrhosis, and less likely to have congestive heart failure (Table 1). Inpatients with versus without ODS exhibited no differences in markers of cirrhosis or general illness severity: Equal proportions of individuals with versus without ODS had severe comorbid disease; equal proportions had severe overall liver disease; and equal proportions had specific cirrhosis complications including ascites and hepatic encephalopathy.

A higher proportion of those with vs. without ODS experienced death during hospitalization (17% vs. 6%, $p<0.001$) (Table 2). Lengths of hospital stays were longer for those with vs. without ODS [10 days (IQR 5-18) vs. 4 days (IQR 2-7), $p<0.001$], as were total cost estimates for services [$16,000 (IQR $10,000-$38,000) vs. $8400 (IQR $5000-$15000), $p<0.001$]. A lower proportion of inpatients with vs. without ODS received “home” discharge dispositions (35% vs. 60%); instead, a higher proportion of those with vs. without ODS experienced transfer to another hospital, death, discharge to a rehabilitation facility, or discharge to long-term care (65% vs. 40%, $p<0.001$).

In univariable logistic regression, age, female gender, Hispanic race, alcohol-related cirrhosis, and congestive heart failure were associated with ODS (Table 3). In multivariable analysis, age (OR 0.97, 95% CI 0.95-0.99), female gender (OR 1.53, 95% CI 1.01-2.30), Hispanic race (OR 0.41, 95% CI 0.19-0.89), alcohol-related cirrhosis (OR 2.65, 95% CI 1.71-4.09), and congestive heart failure (OR 0.37 95% CI 0.15-0.95) remained significantly associated with ODS.

DISCUSSION

In this investigation of the National Inpatient Sample, 2009-2013, we found that the prevalence of ODS in hospitalized patients with cirrhosis was extremely rare, and much lower than the prevalence reported in patients undergoing liver transplantation.[2-6,8] Alcohol-related cirrhosis, younger age, and female gender were associated with an inpatient diagnosis of ODS.

Notably, markers for cirrhotic decompensation and severity of comorbid illness were not found to be associated with ODS. This included no evidence for an association with ascites, which ran counter to our hypothesis that those with portal hypertension might be at higher risk for ODS due to labile serum sodium levels during hospitalization.

Our findings that those with vs. without ODS experienced longer hospital stays, higher hospitalizations costs, and increased chance of receiving a discharge disposition to somewhere other than home (to long-term care, or to another hospital, for example) help to quantify the burden of ODS on the health care system. Furthermore, the increased health care burden and poorer outcomes we found in those with vs. without ODS provide additional evidence that we appropriately identified pronounced cases of ODS with our selection methods.

We acknowledge our study's limitations. As with all large database investigations, our results are susceptible to case ascertainment and measurement biases. While *ICD-9* codes have been well-validated for the selected measures of cirrhosis and overall disease,[7] *ICD-9* codes for ODS have not been systematically validated. In particular, we cannot know whether subtler cases of ODS might have gone unrecognized in the hospital setting only to be diagnosed at outpatient follow-up upon review of MRI imaging. Our low prevalence estimate likely reflects this, underestimating the total prevalence of ODS by failing to detect these subtler cases. That being said, we aimed to capture clinically-apparent cases of ODS, for which ICD-9 coding would be most specific. Finally, our study was limited by a paucity of sodium level data. Unfortunately, the NIS does not contain laboratory values, so we couldn't associate serum sodium changes with ODS. Additionally, hyponatremia as detected by ICD9 coding has been demonstrated to be variable and often lacking, representing perhaps only one third of inpatients experiencing hyponatremia.[9] Because of this, and because hyponatremia is already known as a major precipitant of ODS, we elected to focus our research questions on other risk factors beyond it.[1]

In conclusion, our investigation of a large nationwide database demonstrates that ODS is extremely rare, occurring in 0.02% of hospitalized patients with cirrhosis. ODS is associated with alcohol-related cirrhosis, younger age, and female gender. ODS is not associated with specific cirrhosis complications including ascites, nor with overall liver disease severity or general comorbid disease severity. These data may help inform management of hyponatremia in patients with cirrhosis by reassuring providers of the rarity of ODS, while reinforcing the consideration of a broad range of differential diagnoses in cirrhosis patients exhibiting altered mental status after hyponatremia correction.

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Abbreviations:

ODS	Osmotic Demyelination Syndrome
NIS	Healthcare Cost and Utilization Project National Inpatient Sample
ICD9	International Classification of Diseases, Ninth Revision
OR	odds ratio
CI	confidence interval
IQR	interquartile range

REFERENCES

1. Sterns RH. Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med. 2015;372(1):55–65. doi:10.1056/NEJMra1404489 [PubMed: 25551526]
2. Lee EM, Kang JK, Yun S-C, et al. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. Eur Neurol. 2009;62(6):362–368. doi:10.1159/000242426 [PubMed: 19797900]
3. Crivellin C, Cagnin A, Manara R, et al. Risk factors for central pontine and extrapontine myelinolysis after liver transplantation: a single-center study. Transplantation. 2015;99(6):1257–1264. doi:10.1097/TP.0000000000000496 [PubMed: 25427166]
4. Crismale JF, Meliambro KA, DeMaria SJ, et al. Prevention of the Osmotic Demyelination Syndrome After Liver Transplantation: A Multidisciplinary Perspective. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2017;17(10):2537–2545. doi:10.1111/ajt.14317
5. Leise M, Cárdenas A. Hyponatremia in Cirrhosis: Implications for Liver Transplantation. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2018;24(11):1612–1621. doi:10.1002/lt.25327
6. Bronster DJ, Emre S, Boccagni P, et al. Central nervous system complications in liver transplant recipients--incidence, timing, and long-term follow-up. Clin Transplant. 2000;14(1):1–7. doi:10.1034/j.1399-0012.2000.140101.x [PubMed: 10693627]
7. Rubin JB, Sundaram V, Lai JC. Gender Differences Among Patients Hospitalized With Cirrhosis in the United States. J Clin Gastroenterol. 2020;54(1):83–89. doi:10.1097/mcg.0000000000001192 [PubMed: 30807399]
8. Yun BC, Kim WR, Benson JT, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology. 2009;49(5):1610–1615. doi:10.1002/hep.22846 [PubMed: 19402063]
9. Movig KL, Leufkens HG, Lenderink AW, Egberts AC. Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia. J Clin Epidemiol. 2003 Jun;56(6):530–5. doi: 10.1016/s0895-4356(03)00006-4 [PubMed: 12873647]

Table 1.

Characteristics of adult inpatients with cirrhosis not receiving liver transplantation, by Osmotic Demyelination Syndrome

Characteristics		All *n=547,544 (100%)*	By Osmotic Demyelination Syndrome		p-value
			With ODS *n=94 (0.02%)*	Without ODS *n=547,450 (99.98%)*	
Age, years		57 (51-67)	54 (47-61)	57 (51-67)	**<0.001**
Female Gender		39%	46%	39%	0.18
Race/ Ethnicity	**White**	66%	74%	65%	**0.03**
	Black	11%	16%	11%	
	Hispanic	17%	8%	17%	
	Asian or Pacific Island	2%	0%	2%	
	Native American	1%	1%	1%	
	Other	3%	0%	3%	
Etiology of liver disease	**Alcohol**	33%	58%	33%	**<0.001**
	Viral Hepatitis	32%	26%	32%	
	Autoimmune	1%	0%	1%	
	Other/Unspecified	33%	16%	33%	
Congestive Heart Failure		15%	5%	15%	**0.009**
Baveno Criteria	**Stage 1**	56%	63%%	56%	0.15
	Stage 2	7%	4%	7%	
	Stage 3	31%	32%	31%	
	Stage 4	6%	1%	6%	
Ascites		33%	33%	33%	0.97
Hepatic Encephalopathy		17%	24%	17%	0.06
Spontaneous Bacterial Peritonitis		4%	2%	4%	0.44
Hepatorenal Syndrome		4%	6%	4%	0.14
Paracentesis		19%	21%	19%	0.66
Thoracentesis		3%	2%	3%	0.70
Charlson-Severity	**Mild**	31%	33%	31%	0.33
	Moderate	53%	55%	53%	
	Severe	16%	12%	16%	

*Median (interquartile range) or %

Table 2.

Characteristics of hospital course for those with and without ODS

Characteristics		All *n=547,544 (100%)*	By Osmotic Demyelination Syndrome		p-value
			With ODS *n=94 (0.02%)*	Without ODS *n=547,450 (99.98%)*	
Length of Hospital Stay, days		4 (2-7)	10 (5-18)	4 (2-7)	<0.001
Death during hospitalization		6%	17%	6%	<0.001
Total cost estimate for services **		$8400 ($5000-$15000)	$16,000 ($10,000-$38,000)	$8400 ($5000-$15000)	<0.001
Discharge Disposition	Home	60%	35%	60%	<0.001
	Other (Transfer, Rehab, Long-term care, or Death)	40%	65%	40%	

* Median (interquartile range) or %

** By Cost-to-Charge Files; inflation-adjusted

Table 3.

Factors associated with Osmotic Demyelination Syndrome in adult inpatients with cirrhosis not receiving liver transplantation

Factor		Univariable Models* Odds Ratio (95% CI) p-value	Multivariable Model† Odds Ratio (95% CI) p-value
Age, per year		**0.97 (0.95-0.98) p<0.001**	**0.97 (0.95-0.99) p=0.001**
Female gender		1.32 (0.88-1.98) p=0.18	**1.53 (1.02-2.32) p=0.04**
Hispanic race/ethnicity		**0.43 (0.20-0.92) p=0.03**	**0.41 (0.19-0.89) p=0.02**
Alcoholic cirrhosis		**2.84 (1.88-4.28) p<0.001**	**2.75 (1.80-4.21) p<0.001**
Congestive heart failure		**0.32 (0.13-0.78) p<0.001**	**0.37 (0.15-0.94) p=0.04**
Varices		1.04 (0.57-1.91) p=0.90	--
Hepatic encephalopathy		1.56 (0.97-2.49) p=0.065	--
Ascites		0.99 (0.64-1.52) p=0.97	--
Spontaneous bacterial peritonitis		0.58 (0.14-2.36) p=0.45	--
Hepatorenal syndrome		1.84 (0.81-4.22) 0.15	--
Charlson-Severity	**Mild**	Reference	Reference
	Moderate	0.98 (0.63-1.52) p=0.91	1.52 (0.95-2.41) p=0.08
	Severe	0.68 (0.34-1.35) p=0.27	1.72 (0.82-3.60) p=0.15