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Research Article

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Predictors of Pulmonary Hypertension among Hospitalized Patients with Cirrhosis

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Abstract

Objectives: Liver cirrhosis portends significant morbidity and mortality. Pulmonary hypertension (PH) is a serious extra-hepatic complication of cirrhosis. Our objective was to define the demographic and clinical diagnosis associated with all forms of PH in a sample of hospitalized adult patients.

Methods: We analyzed the 2001 to 2010 Nationwide Inpatient Sample (NIS). Adult (aged ≥ 21 years) patients with cirrhosis were identified using International Classification of Disease 9th Revision, Clinical Modification (ICD9-CM) codes 571.2, 571.5 and 571.6. The prevalence of PH was the primary outcome, and was identified using ICD9-CM codes 416.0 and 416.8. We controlled for other known conditions associated with pulmonary hypertension. We also controlled for patient and hospital factors associated with the diagnosis of PH.

Results: Cirrhosis was a discharge diagnosis in 847,690 of cases. The majority of patients with cirrhosis were white (52.2%, n=442,813), male (61.8%, n=523,567), and insured (87.4%, n=802,975). A concurrent diagnosis of PH was recorded in 2.38% (n=20146). Patients with PH tended to be ≥ 60 years of age (54.3%), white (55.1%) with a predominance of non-alcoholic cirrhosis (64.6%). In a multivariable analysis, female gender (OR 1.35; 95% CI, 1.25-1.46), obesity (OR 1.71; 95%CI, 1.44-2.04), and Native American race (1.215; 95% CI, 1.014 -1.454) were associated with increased odds of PH. Hepatic encephalopathy was associated with a reduced odds of PH (OR 0.88; 95% CI, 0.81-0.97). No specific liver disease etiology was associated with PH, though non-alcoholic cirrhosis (1.377; 95% CI, 0.996-1.903) was marginally associated with greater odds.

Conclusion: Among hospitalized patients with liver cirrhosis, female gender, obesity, and Native American race were associated with increased odds, and hepatic encephalopathy was associated with a reduced odds for PH.

Keywords

Liver; Pulmonary hypertension; Ethnicity; Prevalence

Introduction

Cirrhosis is a significant cause of morbidity and mortality in hospitalized patients and in the community. More recently the success of direct acting antivirals in reducing the epidemic of cirrhosis secondary to Hepatitis C, may be mitigated by the rising incidence of that which is due to obesity related nonalcoholic fatty liver disease [1]. With this in mind and with the increase in migrants from Hepatitis B endemic region, the burden of liver cirrhosis is expected to increase over the next few years.

Pulmonary hypertension (PH) is a disease characterized by vascular remodeling, and may occur as a primary disorder, or in association with other diseases including liver cirrhosis. Patients with cirrhosis may develop PH as a complication termed: Porto pulmonary hypertension. PH may also develop independently of cirrhosis, in patients with other known conditions, such as connective tissue disorders and congenital heart disease that are linked to PH [2]. The reported frequencies of PH in patients with cirrhosis have been reported mostly in relation to Porto pulmonary hypertension, and have ranged from 1-8.5% [3,4]. The presence of any subgroup of PH in patients with cirrhosis is associated with increased mortality, especially following liver transplant [5-7].

Numerous studies have showed an association between PH and female gender in the general population. Studies of the risk factors for PH in the subgroup of patients with cirrhosis are limited [8]. We therefore conducted an analysis of a large database of patients hospitalized with cirrhosis. Our goal was to define the demographics and associated clinical diagnoses of all forms of PH among patients with concurrent PH and cirrhosis. We hypothesized that by excluding patients with other known risk factors for PH, we could describe the demographics and clinical diagnosis of PH associated with portal hypertension.

Methods

Data source

We studied hospital inpatient discharge data from the years 2001 to 2010 in the Nationwide Inpatient Sample (NIS) Database. The NIS is the largest all-payer inpatient care database that is publicly available in the United States. The data are from a 20 percent stratified sample of discharges from US community hospitals, comprising 95% of hospitalizations. To allow for population estimates, the data is weighted. The NIS is part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). In 2001, 33 states participated in the NIS, including 986 hospitals with 7,452,727 hospital discharges. By 2010, the number of participating states had increased to 45, comprising 1051 hospitals and 7,800,441 discharges. Only 4 states (Alabama, Delaware, Idaho, and North Dakota) and the District of Columbia do not participate in NIS.

Study sample

We identified adult patients, 21 years and older with cirrhosis using the International Classification of Disease 9th Revision, Clinical Modification (ICD9-CM) codes 571.2 , 571.5 and 571.6 in any of the 15 listed diagnostic columns. These diagnosis codes have been previously validated. After excluding patients less than 21 years old and discharges with missing variables on key patient factors,

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demographics and hospital factors 754,494 hospital discharges were identified.

Demographic variables included age, race, median household income quartile for patient's residential zip code, and primary insurance payer; hospital characteristics included bed size (small, medium, large), teaching status, ownership/control (non government, private, government), location (rural or urban), region (Northeast, Midwest, South, or West), and state.

Outcome measure

The prevalence of PH was the primary outcome, and was identified using ICD9-CM codes 416.0 and 416.8 and 416.9, as used in previous studies [9]. We controlled for both patient (age, sex, race/ethnicity, income by zip code, insurance payer type) and hospital factors (hospital bed size, hospital location, hospital teaching status) associated with the diagnosis of PH.

In a separate subgroup analysis, we excluded patients with concurrent conditions associated with PH such as connective tissue disorders (systemic sclerosis, Rheumatoid arthritis, and Raynaud's disease), pulmonary conditions (restrictive lung disease, chronic obstructive disease, pulmonary embolism, and obstructive sleep apnea), congestive heart disease, certain valvular heart conditions, hematological conditions (sickle cell disease, and associated hemoglobinopathies), HIV/AIDS, and malignancies. We hypothesized that by excluding patients with other known risk factors for PH, we could more closely describe the clinical diagnosis of PH associated with portal hypertension.

Statistical analysis

Univariate and bivariate analyses were conducted to provide descriptive statistics. The Pearson $\chi 2$ test was used to test distribution of categorical variables for bivariate analyses, while the student *t* test was used to test difference in means. Variables were assessed for collinearity. The estimated models used the "svy" procedure in STATA MP 12.1 which took into account the sampling design of the NIS. Discharge level weights were used to derive national patient estimates. Variables were assessed for collinearity. Multivariable logistic regression model was performed with PH status as the dependent variable and potential predictors as independent variables. Results were expressed as odds ratios (ORs). A subset analysis was performed excluding discharge records of known conditions associated with PH to further assess for liver etiologies that predict PH status. Analyses were performed on data without imputation. Because the data had many unique patterns, the Hosmer-Lemeshow goodness-of-fit test was used to assess model fit. All statistical analyses were performed using STATA/MP version 12.1 (StataCorp, College Station,TX). Statistical significance was defined as $P<0.05$.

Results

From the 2001 to 2010 NIS database, we identified 847,690 discharges with a diagnosis of cirrhosis that met our inclusion criteria. The majority were white (52.2%, n=442,813), male (61.8%, n=523,567), and had a form of health insurance (87.4%, n=802,975). Patients were predominantly treated at non teaching hospitals (52.6%, n=443,243), and resided in urban areas (89.5%, n=754,494). Forty-seven percent (n=396, 51) had alcoholic cirrhosis.

A concurrent diagnosis of PH was recorded in 2.4% (n=20146), with 1.9% (n=8,950) in years 2001 to 2005 and 3.0% (n=11,039) in years 2006 to 2010. Patients with PH tended to be >60 years of age (54.3%), white (55.1%) with a predominance of non-alcoholic cirrhosis (64.6%) (Table 1).

Complications

A diagnosis of hepatic encephalopathy was present in 17.7% (n =149,007); ascites in 32.0% (n=269,561), portal vein thrombosis in 1.0% (n=8,501); spontaneous bacterial peritonitis (SBP) was present in 1.2% (n=10,400) and varies in 3.2% (n=26,712). Table 2 shows the occurrence of complications by PH status. Overall mortality was 7.5% (n=63,254). Only 0.5 %(n=4,067) of patients with cirrhosis received right heart catherization during their hospital stay, and 6.8 %(1,123) of patients with the diagnosis of PH.

Etiology

Among our sample population, 20.7% (n=174,832) had hepatitis C, 1.6% had hepatitis B (n=13,242), and 0.6%(n=5,023) had concurrent hepatitis B and C. Non alcoholic fatty liver, biliary cirrhosis, and autoimmune hepatitis were diagnosed in 1.2% (n=10,356), 2.35% (n=19,888) and 0.27% (n=2,777), respectively.

In a multivariable analysis female gender (OR 1.27; 95% CI, 1.209-1.345), African American race (OR 1.349; 95% CI, 1.252- 1.454) and obesity (OR 1.985; 95% CI, 1.820-2.164) were associated with higher odds of PH. Hepatitis C (OR 0.786; 95% CI, 0.739-0.838) Hepatitis B (OR 0.59; 95% CI, 0.489-0.714) Hispanic ethnicity (OR 0.798; 95% CI, 0.714-0.893), and Asian/Pacific Islanders (OR 0.830; 95% CI, 0.707-0.974) were associated with lower odds of PH (Table 3).

Subgroup analysis

In a separate multivariable analysis, among a subgroup of patients in whom PH associated conditions were excluded, female gender (OR 1.35; 95% CI, 1.25–1.46), obesity (OR 1.71; 95% CI, 1.44-2.04), and Native American race (1.215; 95% CI, 1.014 -1.454) were associated with increased odds of PH. In contrast Asian/Pacific Islander race (OR 0.78; 95% CI, 0.61-0.99) and hepatic encephalopathy (OR 0.88; 95% CI, 0.81-0.97) were associated with reduced odds of PH (Table 4). No specific liver disease etiology was associated with PH in this analysis.

Discussion

In our sample population of hospitalizations for liver cirrhosis, we have shown that female gender, obesity, Native American race/ethnicity were all associated with a high risk of PH of any form; hepatic encephalopathy and Asian/Pacific Islander race/ethnicity were associated with a lower risk of PH. For Liver etiologies, Hepatitis C and Hepatitis B were associated with a reduced probability of PH, however in patients with no other known disease condition associated with PH, hepatitis B and C status were not linked to PH.

The findings from our first model (without the exclusion of PH associated conditions) are in concordance with the study by Kawut et al. [8] in which a protective effect for hepatitis C was seen, with female gender and autoimmune hepatitis conferring a higher risk of PH. Our study results also reveal an increased risk associated with concurrent hepatitis B and C and the development of PH, which has previously not been reported. With only one case of Hepatitis B, and no described case of concurrent Hepatitis B and C, the sample size in their study may have been too small to adequately estimate the influence of liver etiologies on the development of PH. To our knowledge, ours is the first study to demonstrate a protective effect of not only hepatitis C, but hepatitis B, in the development of any

Table 1: Baseline characteristics of cirrhosis admissions by Pulmonary hypertension status.

	Cirrhosis only Unweighted n= 831,137 Weighted n=1,655,685 (97.6%)	Pulmonary Hypertension and Cirrhosis Unweighted n= 20,146 Weighted n=100,730 (2.4%)	P value*
Age mean (95%CI)	61.50 (60.9- 62.1)	63.55(63.1-64.0)	
<50	26.4%	17.9%	<0.01
50-59	32.3%	27.8%	
60 years and above	41.3%	54.3%	
Female	38.0%	48.5%	<0.01
Race			<0.01
White	52.2%	55.1%	
Black	8.5%	11.1%	
Hispanic	15.3%	11.7%	
Asia/Pacific	1.7%	1.7%	
Native Americans	3.0%	3.0%	
Income by Zipcode**			<0.01
Lowest quartile ($1-$40,999)	28.3%	26.1%	
Second quartile ($41,000 - $50,999)	25.5%	24.2%	
Third quartile ($51,000 - $66,999)	22.3%	23.8%	
Highest quartile ($67,000+)	20.5%	22.7%	
Unknown	3.4%	3.2%	
Payer status			<0.01
Private Insurance	23.4%	20.7%	
Medicare	42.2%	56.2%	
Medicaid	21.7%	16.5%	
Self-pay	7.4%	3.5%	
No charge	0.9%	0.5%	

*Based on χ2 test for binary outcomes. Significance was attained at P<0.05
**Income guideline for 2010

Table 2: Most common complication by Pulmonary hypertension.

		Cirrhosis alone (%) Unweighted n=827,544	Pulmonary Hypertension and Cirrhosis(%) unweighted n=20,146	P value*
Hepatic Encephalopathy	No	680,129 (82.2%)	17,859 (88.7%)	<0.01
	Yes	147,415 (17.8%)	2,287 (11.4%)	
SBP	No	817,276 (98.8%)	19,931 (98.9%)	0.02
	Yes	10,268 (1.2%)	215 (1.1%)	
Ascites	No	562,959 (68.0%)	13,798 (68.5%)	0.16
	Yes	264,585 (32.0%)	6,348 (31.5%)	
Varices	No	801,066 (96.8%)	19,739 (98.0%)	<0.01
	Yes	26,478 (3.2%)	407 (2.0%)	
Portal Vein Thrombosis	No	819,204 (99.0%)	19,985 (99.2%)	<0.01
	Yes	8,340 (1.0%)	161 (0.8%)	
*Based on χ2 test for binary outcomes. Significance was attained at P<0.05				

form of PH in patients with cirrhosis. Kawut et al. [8] postulated a possible treatment effect of viral hepatitis for their findings. However our findings should be interpreted cautiously.

In a second more rigorous model, we employed analogous data exclusion criteria as used by Chen et al. [10] In contrast to their study, neither hepatitis C nor portal vein thrombosis was associated with a higher risk of PH; rather, our study revealed an increase in the odds of PH among Native Americans with cirrhosis compared to White Americans. Previous studies have not identified an association between Native American race and PH [11] our findings did not appear to be related to obesity, as Native Americans had significantly reduced odds of obesity compared to white race. Also viral hepatitis did not appear to explain the association of Native American race/ethnicity with PH; as though Native American race was associated with increased odds of viral hepatitis compared to white race, so was African American race and Asian/Pacific Islander race/ethnicity. Among Native Americans, cirrhosis and chronic liver disease represent the 5th most common cause of death, with a mortality rate of 12.2 per 100,000 compared to 10.3 per 100,000 in the general population [12]. In their study utilizing mortality data from the National Vital Statistic System (NVSS) and discharge data

Table 3: Multivariate logistic regression for odds of pulmonary hypertension in hospitalized patients with liver cirrhosis.

Multivariate logistic regression for odds of pulmonary hypertension in hospitalized patients with liver cirrhosis		
	Odds Ratio (95%CI b)	P value
Female	1.27(1.21- 1.35)	P<0.01
Obese	1.99(1.82-2.16)	P<0.01
Age Category		
<50 years	ref	
50-59 years	1.14(1.05- 1.24)	P<0.01
>59 years	1.31(1.21-1.42)	P<0.01
White	ref	
African American	1.35(1.25- 1.45)	P<0.01
Hispanic	0.80(0.71- 0.89)	P<0.01
Asian/Pacific Islanders	0.83(0.71- 0.97)	0.02
Native Americans	1.02(0.90- 1.16)	0.79
Hepatitis C	0.79(0.74- 0.84)	P<0.01
Hepatitis B	0.59(0.49- 0 .71)	P<0.01
Concurrent Hepatitis B and Hepatitis C	1.79(1.33- 2.43)	P<0.01
Alcoholic Cirrhosis	0.71(0.57- 0.88)	P<0.01
Non Alcoholic Cirrhosis	1.09(0.89-1.34)	0.40
Biliary Cirrhosis	0.94(0.76- 1.16)	0.54
Autoimmune Hepatitis	0.77(0.58- 1.01)	0.05
Nonalcoholic fatty liver	0.89(0.771- 1.02)	0.08
Hemochromatosis	1.22(0.49- 3.03)	0.66
Complications		
Hepatic Encephalopathy	0.57(0.54-0.61)	P<0.01
Ascites	1.07(1.03-1.1)	P<0.01
Spontaneous Bacterial Peritonitis	0.79(0.69- 0.90)	P<0.01
Varices	0.53(0.35-0.78)	P<0.01
Portal Vein Thrombosis	0.74(0.62- 0.87)	P<0.01
Abbreviations: CI: Confidence Interval.		

from the National Hospital Discharge Survey (NHDS), demonstrated a geographical clustering of PH hospitalizations and deaths amongst the states of Colorado, Montana, and Wyoming, which have a disproportionately high population of Native Americans [13]. They hypothesized that high altitude may play a role in the development of PH in such states. Their findings and ours necessitate additional investigation.

The quality of national data sets in determining racial disparity in groups other than whites and African Americans is open to discussion. Native Americans are increasingly underrepresented in national data sets [14]. The clustered sampling methods of the HCUP-NIS requires the use of weights which lend themselves to large sampling errors in estimating the Native American population, therefore our study results should be interpreted cautiously [15]. Further research utilizing the Indian Health Service data will be necessary to expatiate on our findings.

While Asian race/ethnicity has been associated with a higher risk of cirrhosis and the highest rate of hepatocellular carcinoma of any ethnic group [16]. Our results reveal a lower prevalence of PH among this group compared to white race. This finding was consistent in our two models. Further studies are needed among this subgroup to better describe this discovery

Interestingly, African American race which was initially associated with increased prevalence of PH did not show statistical significance, in our second model (Table 3). This may reflect that the pathology of PH in this population of patients may be more related to the prevalence of hematological disorders (Sickle cell, HIV, AIDS), pulmonary disorders (COPD, Obstructive sleep apnea), and connective tissue disorder (scleroderma) which disproportionately affect African Americans [17-24].

Comparable to other studies, hepatic encephalopathy was second to ascites as a complication of cirrhosis in patients with concurrent cirrhosis and PH [10]. A possible explanation for the negative relationship with hepatic encephalopathy may lie in the mechanism, prophylaxis and treatment for hepatic encephalopathy. Hepatic encephalopathy has been associated with a hyper ammonia state, and clinical improvements seen in reduction of serum ammonia [25]. Recently a study identified cases with PH as having a higher level of exhaled ammonia than controls, with the exhaled ammonia level correlating with PH severity [26]. The NIS provides no data on severity of cirrhosis, treatment of hepatic encephalopathy or serum ammonia levels.

As with studies in patients without liver cirrhosis, female gender was associated with increased odds of PH [27,28]. The mechanism for female preponderance remains undetermined. The influence of estrogen on the pulmonary vasculature is an ongoing area of research.

Table 4: Multivariate logistic regression for odds of PH in hospitalized patients with cirrhosis (excluding subgroup of patients with diagnosis known to be associated with PH).

Multivariate logistic regression for odds of PH in hospitalized patients with cirrhosis (excluding subgroup of patients with diagnosis known to be associated with PH)		
	Odds Ratio (95%CI b)	P value
Hepatitis C	0.98(0.99 -1.06)	0.62
Hepatitis B	0.86 (0.64 -1.45)	0.30
Concurrent Hepatitis B and Hepatitis C	1.51 (0.96-2.35)	0.06
Alcoholic Cirrhosis	0.89 (0.64-1.22)	0.46
Non Alcoholic Cirrhosis	1.38 (0.99-1.90)	0.05
Biliary Cirrhosis	1.25 (0.89-1.75)	0.20
Autoimmune Hepatitis	1.36(1.25-1.46)	0.66
Nonalcoholic fatty liver	1.00(0.78-1.29)	0.97
Hemochromatosis	0.67(0.09-4.72)	0.68
Complications		
Hepatic Encephalopathy	0.89 (0.81 -0.97)	P<0.01
Ascites	1.07 (1.00-1.14)	0.06
Spontaneous Bacterial Peritonitis	1.04 (0.89-1.26)	0.64
Varices	0.86(0.61-1.23)	0.41
Portal Vein Thrombosis	1.04 (0.82 -1.32)	0.76
Female	1.36 (1.25-1.46)	P<0.01
Obese	1.72 (1.45-2.04)	P<0.01
Age Category		
<50 years	ref	
50-59 years	1.00 (0.92-1.09)	0.98
>59 years	0.91 (0.83 -1.01)	0.06
White	ref	
Black	1.10 (0.97 -1.24)	0.15
Hispanic	0.90 (0.80 -1.02)	0.09
Asian/Pacific Islanders	0.78 (0.61 -0.99)	0.04
Native Americans	1.22 (1.01-1.45)	0.03
Abbreviations: CI: Confidence interval		

Lahm et al. postulate that acute physiologic increases in estrogen, as seen in menstruating females , diminishes the vaso-constrictive effect of the pulmonary arterial bed in both the hypoxic and non-hypoxic state [29]. While experimental data suggests that chronic exposure to estrogen promotes pulmonary vascular proliferation through migration of endothelial cells, Tamoxifen antiestrogen blocks this effect [29-31]. In patients with cirrhosis, Robert et al. also buttress the role of estrogen by demonstrating an increased risk of developing PH with higher genetic variation of the estrogen receptor and aromatase (the rate limiting enzyme in estrogen metabolism) [32].

This study had a number of strengths, which include the largest published study of any clinical diagnosis of PH in hospitalized patients with cirrhosis, and excellent statistical power. In addition, by excluding other known PH associated conditions, we are better able to approximate PH associated with portal hypertension, which was the limitation of smaller studies.

Limitations

As with all administrative databases our diagnosis is subject to reporting and coding errors. The NIS database is only a sample and therefore was not designed for large database scientific inquiry such as the Framingham database. We are unable to ascertain the criteria used for the diagnosis of PH, as the diagnosis may vary depending on echocardiography or right heart catherization. Additionally, the ICD9-CM codes used to identify PH discharge diagnosis does not differentiate between the 5 major groups of PH. Also, because the ICD 9 codes did not reliably identify primary and secondary pulmonary hypertension consistently, we decided to combine both classes. We hoped that by excluding associated conditions, our inferences would closely approximate PH associated with portal hypertension.

Another limitation to our study is that the NIS database does not include clinical and laboratory variables so we were unable to compute validated liver cirrhosis severity scores such as a MELD or Child Pugh, although earlier studies have not shown an association between disease severity and PH [10]. Despite these limitations, this cross sectional study can help generate more hypotheses for future longitudinal studies, as there is an obvious need for molecular studies explaining the mechanism of association between PH and Native American race/ethnicity.

In summary, in patients with cirrhosis without known PH associated conditions, female gender, obese status, Native American race were factors showing significant independent association with PH. The clinical diagnosis of hepatic encephalopathy, a complication of cirrhosis, was associated with reduced odds of PH, as well as Asian/Pacific Islander race.

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