



In-Hospital Outcomes of Patients With Pulmonary Hypertension and Cirrhosis: A 6-Year Population Cohort Study of Over One Million Patients

Yaser Khalid · Neethi Dasu · Raja Fawad Zafar · Herman Suga · Kirti Dasu · Brian Blair

Received: June 16, 2020 / Published online: July 20, 2020
© The Author(s) 2020

ABSTRACT

Introduction: There is a paucity of data on the influence of sex, race, insurance, pulmonary hypertension-related complications, and cirrhosis-related complications on mortality, hospital length of stay (LOS), and total hospital charges. The aim of this study was to identify risk factors in a national population cohort (in the USA) admitted to hospital between 2012 and 2017.

Digital Features To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12624791>.

Y. Khalid (✉)
Division of Internal Medicine, Memorial Healthcare System, Hollywood, FL, USA
e-mail: yskorosh1990@gmail.com

N. Dasu · B. Blair
Division of Gastroenterology, Jefferson Health New Jersey, Stratford, NJ, USA

R. F. Zafar
Department of Mathematics and Social Sciences, Sukkur Institute of Business Administration (IBA) University, Sukkur, Pakistan

H. Suga
Division of Internal Medicine, Rowan University School of Osteopathic Medicine, Stratford, NJ, USA

K. Dasu
Division of Biology, Syracuse University, Syracuse, NY, USA

Methods: All patients aged > 18 years with pulmonary hypertension and cirrhosis, who had been admitted to hospital between 2012 and 2017, were identified from the US Nationwide Inpatient Sample (NIS), a large publicly available all-payer inpatient care database in the USA. Multivariate regression analysis was used to estimate the odds ratios of in-hospital mortality, average length of hospital stay, and hospital charges, after adjusting for age, gender, race, primary insurance payer status, hospital type and size (number of beds), hospital region, hospital teaching status, and other demographic characteristics.

Results: Our study identified 1,111,594 patients who had been discharged from hospital from 2012 to 2017. Of these patients, 355,455 were admitted with pulmonary hypertension, with 9.8% having cirrhosis as a complication ($n = 34,986$). The analysis revealed that patients with both pulmonary hypertension and cirrhosis compared to patients with only pulmonary hypertension experience increased mortality, hospital LOS, total hospital charges, and pulmonary hypertension-related and cirrhosis-related complications. Independent positive predictors of mortality were Asian/Pacific Islander race and “other” insurance status (worker’s compensation; other US health benefits plans [CHAMPUS/TRICARE, CHAMPVA, Title V]). Independent positive predictors of increased hospital LOS were black race and “other” patients (more than one race/mixed). Independent positive predictors of increased total hospital charges

were male gender, Hispanic ethnicity, Asian/Pacific Islander race, and other insurance status. Pulmonary hypertension-related complications (cor pulmonale, pulmonary embolism, hemoptysis, cardiac arrest, atrial fibrillation, ventricular tachycardia) and cirrhosis-related complications (ascites, hepatorenal syndrome, hepatic encephalopathy, variceal bleeding, portal hypertension) were independent positive predictors of mortality, hospital LOS, and total hospital charges.

Conclusions: Patients with pulmonary hypertension and cirrhosis have increased mortality and hospital utilization compared to patients with only pulmonary hypertension. We identified key drivers for these outcomes. Targeted interventions, such as novel medications, right-to-left shunts, more evaluations for lung transplantation, and reversal of pulmonary vascular remodeling, are needed for the subgroups identified in this study in order to improve outcomes.

Keywords: Cirrhosis; Total hospital charges; Length of stay (LOS); Mortality; NIS; Pulmonary hypertension

Key Summary Points

Why carry out this study?

There is a paucity of data on the influence of sex, race, insurance, and pulmonary hypertension-related and cirrhosis-related complications on mortality, hospital length of stay (LOS), and total hospital charges.

The overall sample included 1,111,594 patients, of whom 355,455 were admitted with pulmonary hypertension, with 9.8% of the latter complicated with cirrhosis ($n = 34,986$).

What was learned from the study?

Patients with pulmonary hypertension and cirrhosis compared to patients with only pulmonary hypertension have increased mortality, hospital LOS, total hospital charges as well as pulmonary hypertension-related and cirrhosis-related complications.

Targeted interventions, such as novel medications, right-to-left shunts, more evaluations for lung transplantation, and reversal of pulmonary vascular remodeling, are needed for the subgroups identified in this study.

INTRODUCTION

Pulmonary hypertension is defined as a mean pulmonary arterial pressure > 20 mmHg as measured on right heart catheterization; it is further subdivided into five different categories based on the underlying etiology [1, 2]. Approximately 1% of the population is diagnosed with pulmonary hypertension every year [3]. This disease has subtle symptoms on presentation and complex underlying pathophysiological mechanisms that are not well understood. Pulmonary hypertension is also a chronic and progressive disease that has significantly increased morbidity and mortality. The 15-year survival rate from initial diagnosis has been reported to be as low as 34% [4]. Yet, frustratingly, there is currently no definitive cure or treatment.

Liver cirrhosis is the final and irreversible stage of chronic liver fibrosis. Many patients with cirrhosis develop complications, including ascites, hepatic encephalopathy, hepatorenal syndrome, portal hypertension, ascites, and variceal bleeding [5]. Alarming, cirrhosis is reported to account for almost 2% of all deaths worldwide, and it is the eighth leading cause of death in the USA [5, 6]. This disease is a major burden on the US healthcare system, with annual costs having increased from approximately 10,000 million US dollars in 2005 to 16,000 million US dollars in 2015 [5, 6]. This significant rise in costs is secondary to increased hospitalizations, a greater number of transplant evaluations, and surging levels of mortality from cirrhosis-related complications and decompensation [5].

The objective of our study was to determine if patients with both pulmonary hypertension and cirrhosis would have increased mortality,

hospital length of stay (LOS), and total hospital charges compared to patients with only pulmonary hypertension. There is minimal data in the literature on the influence of sex, race, insurance status, cirrhosis-related complications, and pulmonary hypertension-related complications on mortality, hospital LOS, and total hospitalization charges for this patient population. In this study we used data from a national population cohort admitted to hospital between 2012 and 2017 to identify risk factors.

METHODS

Study Population

The Nationwide Inpatient Sample (NIS) database is a large, publicly available all-payer inpatient healthcare database designed to produce US regional and national estimates of inpatient utilization, access, charges, quality, and outcomes. It contains data on approximately 7 million inpatient hospitalizations annually in the USA. It is one of the largest databases that was developed for the Healthcare Cost and Utilization Project (HCUP). This large nationwide population sample has been used to study regional and hospital-level patterns, quality of care, procedure-related patterns, and trends that would otherwise be impossible to analyze at a local or center-based study level [7]. For our study, data was extracted with the aim to investigate patients with a diagnosis of both pulmonary hypertension from any cause and cirrhosis from all etiologies during the time period of 2012–2017.

The datasets used in this study were fully de-identified and, therefore, Institutional Review Board (IRB) approval was not required. The datasets analyzed during the current study are publicly available on the NIS website (<https://www.hcup-us.ahrq.gov/nisoverview.jsp>).

Design

We performed a retrospective, observational, population cohort study using the HCUP NIS

database. A search of this database identified 1,111,594 patients who were discharged between 2012 and 2017. All patients were \geq 18 years of age and had a diagnosis of either “cirrhosis” or “pulmonary hypertension.” To identify patients with cirrhosis, we utilized the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes: ICD-9-CM codes for chronic liver disease and cirrhosis (571), alcoholic cirrhosis of liver (571.2), cirrhosis of liver without mention of alcohol (571.5), biliary cirrhosis (571.6); ICD-10-CM codes for alcoholic cirrhosis of the liver without ascites (K70.30), alcoholic cirrhosis of liver with ascites (K70.31), cirrhosis (K74.60), biliary cirrhosis (K74.5), unspecified cirrhosis of liver (K74.60), and other cirrhosis of the liver (K74.69). Pulmonary hypertension was defined as code 416.8 in ICD-9-CM and code I27.0, I27.2 in ICD-10-CM.

Secondary diagnoses, such as cirrhosis-related complications, were extracted with the following ICD-9-CM and ICD-10-CM codes: ascites (789.59 and R18.8), portal hypertension (572.3 and K76.6), hepatorenal syndrome (572.4 and K76.7), variceal bleeding (I85.01 and K920 K921 K922 I8500 I8510 I8501 I8511), and hepatic encephalopathy (572.2 and G93.4).

Pulmonary hypertension-related complications were extracted with the following codes: ICD-9-CM codes for cor-pulmonale (416.9, 415), heart failure (428.21, 428.23, 428.31, 428.33, 428.41, 428.43), pulmonary embolism (415.1, 415.11, 415.13, 415.19), pulmonary hemorrhage/hemoptysis (786.3, 786.39), atrial fibrillation (427.2, 427.3, 427.31, 427.32), ventricular tachycardia (427.4, 427.41, 427.42), cardiac arrest (427.5), and coronary artery disease (414.0, 414.07, 414.2, 414.9); ICD-10-CM codes for cor-pulmonale (I27.81, I26.09, I27.29), heart failure (I11.0, I13.0, I13.2, I50, I50.0, I50.1, I50.9), pulmonary embolism (I26.0, I26.02, I26.09, I26.92, I26.93, I26.94, I26.99), pulmonary hemorrhage/hemoptysis (R04.2, R04.8, R04.9), atrial fibrillation (I48), ventricular tachycardia (I47.2, I49.0), cardiac arrest (I46.9), and coronary artery disease (I25.10).

Primary and Secondary Outcomes and Variables

The primary outcome was mortality. The secondary outcomes were hospital LOS and total hospital charges among the patient cohort of pulmonary hypertension and cirrhosis compared to patients with only pulmonary hypertension. Multivariate logistic regression analysis was performed to understand possible differences in complications across the two groups. Cirrhosis-related complications were the following: hepatorenal syndrome, ascites, variceal bleeding, hepatic encephalopathy, and portal hypertension. Pulmonary hypertension-related complications were the following: cor pulmonale, heart failure, pulmonary embolism, pulmonary hemorrhage/hemoptysis, atrial fibrillation, ventricular tachycardia, cardiac arrest, and coronary artery disease.

In the USA, patients have the following types of insurance: Medicare, Medicaid, private insurance, self-pay, no charge, and “other”. Medicare is the federal government’s health insurance plan for people aged ≥ 65 years, certain younger people with disabilities, and people with end-stage renal disease. It covers inpatient hospital costs, outpatient medical visits, and prescription drug coverage at a fixed and lower cost than all other types of insurance. Medicaid is a public assistance program based largely on financial need for pregnant women, parents of minors or teenagers living alone, blind patients, patients with disabilities, and low-income individuals aged < 65 years without disability or minor children. However, unlike Medicare, which is completely federally funded, both the state and the federal government fund Medicaid. Private insurance refers to any health insurance coverage that is not offered by a state or federal government but rather by a private entity, such as an insurance company or broker. Self-pay is paying for all medical costs individually without an insurance plan. No charge means that the individual was exempt from hospital charges. Finally, other insurance includes other insurance status worker’s compensation (insurance that covers medical expenses and a portion of lost wages for employees who become injured or ill on the

job), CHAMPUS/TRICARE (a health care program of the US Department of Defense Military Health System which provides insurance for military personnel, military retirees, and their dependents), CHAMPVA (a healthcare program for veterans and family members not eligible for TRICARE), and Title 5 (health insurance for healthcare workers).

Statistical Analyses

The patient data was analyzed using Stata version 16 (Stata Corp., College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The study population was generated from primary unit clusters that are representative of the diagnoses we studied, and then the patient-level and hospital-level weights provided in the dataset were used to generate national population estimate samples. Univariate and multivariate comparisons were performed utilizing Chi-squared analyses and Student’s *t* tests. Both fixed and random effects models were used to evaluate predictors of mortality for patients with pulmonary hypertension and cirrhosis. Odds ratios (OR), confidence intervals, and *p* values were reported for all of the outcomes. The statistical significance level was set at a *p* value of < 0.05 .

We generated propensity scores to compare our two analysis groups (pulmonary hypertension with cirrhosis vs. pulmonary hypertension without cirrhosis). For propensity scores, the psmatch2 algorithm was used. Psmatch2 provides propensity matching diagnostics and allows for nearest neighbor matching. A matching algorithm was used to balance covariates across our study groups through one-to-one matches.

RESULTS

The baseline characteristics for both patient cohorts are listed in Table 1. A total of 1,111,594 patient hospitalizations were identified during the study period of 2012–2017, of which 34,986 hospitalizations were for patients with pulmonary hypertension and cirrhosis and 355,455 of the hospitalizations were for patients with

Table 1 Baseline characteristics of patient cohorts

Characteristics	Pulmonary HTN with cirrhosis	Pulmonary HTN without cirrhosis	Total	<i>p</i> value
Number of patients				
Original sample	34,986 (3%)	1,076,608 (97%)	1,111,594 (100%)	
After propensity score matching	34,986 (50%)	34,960 (50%)	69,946 (100%)	
Women	16,793 (48%)	16,781 (48%)	33,574 (48%)	0.728*
Race/ethnicity				
White	21,691 (62%)	22,025 (63%)	43,716 (63%)	0.001*
Black	5598 (16%)	5594 (16%)	11,192 (16%)	0.068
Hispanic	4408 (13%)	4195 (12%)	8603 (13%)	0.410
Asian or Pacific Islander	699 (2%)	699 (2%)	1398 (2%)	0.376
Native American	350 (1%)	350 (1%)	700 (1%)	0.000*
Other	1,050 (3%)	1050 (2%)	2100 (3%)	0.034*
Age, years (mean \pm SD)	64.7 \pm 5.4	64.5 \pm 5.4	64.6 \pm 5.4	
Insurance type				
Medicare	22,391 (64%)	22,374 (64%)	44,765 (64%)	0.210
Medicaid	5,598 (16%)	5594 (16%)	11,192 (16%)	0.886
Private	5,248 (15%)	5244 (15%)	10,492 (15%)	0.240
Self-pay	1,050 (3%)	699 (2%)	1749 (3%)	0.004*
No charge	70 (0.2%)	70 (0.2%)	140 (0.2%)	0.053
Other	700 (2%)	699 (2%)	1399 (2%)	0.001*
Hospital region				
Northeast	6,297 (18%)	6293 (18%)	12,590 (18%)	0.595
Midwest	7,697 (22%)	7691 (22%)	15,388 (22%)	0.849
South	12,945 (37%)	12,935 (37%)	25,880 (37%)	0.332
West	8,047 (23%)	7691 (22%)	15,738 (23%)	0.155
Hospital location/teaching status				
Rural	2,099 (6%)	2098 (6%)	4197 (6%)	0.186
Urban non-teaching	9,096 (26%)	9090 (26%)	18,186 (26%)	0.582
Urban teaching	23,441 (67%)	23,773 (68%)	47,214 (67%)	0.232
Hospital bed size (<i>n</i> of beds)				
Small	4,898 (14%)	4894 (14%)	9792 (14%)	0.575
Medium	9,446 (27%)	9090 (26%)	18,536 (27%)	0.471

Table 1 continued

Characteristics	Pulmonary HTN with cirrhosis	Pulmonary HTN without cirrhosis	Total	<i>p</i> value
Large	20,992 (60%)	20,976 (60%)	41,968 (60%)	0.298
Household income (US dollars)				
\$1–24,999	11,545 (33%)	11,537 (33%)	23,082 (33%)	0.425
\$25,000–34,999	8,747 (25%)	9090 (26%)	17,837 (26%)	0.578
\$35,000–44,999	8,047 (23%)	7691 (22%)	15,738 (23%)	0.731
≥ 45,000	5,948 (17%)	5943 (17%)	11,891 (17%)	0.928

*Significant difference between patient cohorts at pre-determined significance level of $p < 0.05$

Values are presented as the number with the percentage in parenthesis unless indicated otherwise

HTN Hypertension, SD standard deviation

only pulmonary hypertension. After propensity matching, there were 34,986 patients with pulmonary hypertension and cirrhosis and 34,960 patients with only pulmonary hypertension, of whom 48% were female and 63% were Caucasian (in total patient cohort and in each separate patient cohort). The mean age of the total patient cohort was 64.6 (± 5.4 , standard deviation) years.

Most of the patients had Medicare (64%). Approximately 33% of the patients had an income of $< \$24,999$ (note: all values given in dollars in text refer to US dollars). Regarding hospital characteristics, 60% were large centers, 37% were located in the South, and 67% were urban teaching centers.

Multivariate logistic regression analysis was used to remove confounders and revealed that mortality was 1.5-fold higher in patients with pulmonary hypertension and cirrhosis compared to patients with only pulmonary hypertension ($p < 0.0001$) (Table 2). Mean hospital LOS was 0.5 days longer for patients with pulmonary hypertension and cirrhosis ($p < 0.0001$). Mean total hospital charges were \$9804 higher for patients with pulmonary hypertension and cirrhosis ($p < 0.001$). There was a higher incidence of complications in patients with pulmonary hypertension and cirrhosis versus those with only pulmonary

hypertension that was statistically significant ($p < 0.001$) for all of the following cirrhosis-related complications as well as their odds ratios: 60.2-fold higher for hepatorenal syndrome; 24.3-fold higher for ascites; 122-fold higher for variceal bleeding; 74-fold higher for hepatic encephalopathy; 92.6-fold higher for portal hypertension. Apart from cor pulmonale (OR 1.25), all other pulmonary hypertension-related complications presented a lower incidence in patients with pulmonary hypertension and cirrhosis as compared to patients with pulmonary hypertension alone. Interestingly, the remainder of the pulmonary hypertension-related complications that were statistically significant ($p < 0.0001$) showed a decreased incidence in patients with pulmonary hypertension and cirrhosis with the following odds ratios: 0.8-fold for heart failure, 0.4-fold for pulmonary embolism, 0.8-fold for atrial fibrillation, 0.8-fold for ventricular tachycardia, and 0.7-fold for coronary artery disease.

The univariate logistic regression (Table 3) subsequently revealed that black patients with pulmonary hypertension and cirrhosis suffered 5% less mortality than black patients with only pulmonary hypertension ($p < 0.05$) compared to other races/ethnicities, whereas Asians/Pacific Islanders had 1.4-fold higher mortality ($p < 0.03$) compared to other races/ethnicities.

Table 2 Outcomes of patients with acute decompensated heart failure with and without cirrhosis

Outcomes	Pulmonary HTN with cirrhosis	Pulmonary HTN without cirrhosis	Multivariate beta distribution ^a	<i>p</i> value
Mortality	2554 (7.3%)	1538 (4.4%)	1.54 (1.48–1.61)	< 0.0001*
Mean length of stay (LOS), days (95% CI)	7.5 (5.9–8.1)	7.0 (5.8–8.2)	0.51 (0.32–0.73)	< 0.0001*
Mean total hospital charges, \$US (95% CI)	77,245 (75,555–79,444)	67,441 (61,223–73,454)	9804 (8882–10,565)	< 0.0001*
Hepatorenal syndrome	1260 (3.6%)	21 (0.06%)	60.2 (54.8–66.1)	< 0.0001*
Ascites	11,126 (31.8%)	839 (2.4%)	24.33 (23.70–24.99)	< 0.0001*
Variceal bleeding	2834 (8.1%)	70 (0.2%)	122 (113.0–132.6)	< 0.0001*
Hepatic encephalopathy	2834 (8.1%)	70 (0.2%)	74.0 (69.3–79.2)	< 0.0001*
Portal hypertension	7347 (21%)	105 (0.3%)	92.6 (88.6–96.7)	< 0.0001*
Cor pulmonale	665 (1.9%)	245 (0.7%)	1.25 (1.16–1.35)	< 0.0001*
Heart failure	10,356 (29.6%)	9334 (26.7%)	0.84 (0.82–0.86)	< 0.0001*
Pulmonary embolism	455 (1.3%)	114 (3.3%)	0.41 (0.38–0.45)	< 0.0001*
Pulmonary hemorrhage/hemoptysis	175 (0.5%)	70 (0.2%)	0.99 (0.85–1.16)	0.939
Atrial fibrillation	7837 (22.4%)	12,236 (35%)	0.76 (0.74–0.78)	< 0.0001*
Ventricular tachycardia	6645 (1.9%)	280 (0.8%)	0.83 (0.76–0.90)	< 0.0001*
Cardiac arrest	525 (1.5%)	524 (1.5%)	1.09 (0.99–1.20)	0.088
Coronary artery disease	11,300 (32.3%)	14,264 (40.8%)	0.70 (0.68–0.72)	< 0.001*

All outcomes are presented as a number with the percentage in parenthesis, unless indicated otherwise

*Significant difference between patient cohorts at pre-determined significance level of $p < 0.05$

^a Presented as the odds ratio (OR) with the 95% confidence interval (CI) in parenthesis

Patients with Medicare suffered 13% less mortality than those with all other insurances types, whereas patients with “other” insurance status suffered 1.6-fold more mortality than did patients with all other insurance types. Almost all cirrhosis-related and pulmonary hypertension-related complications increased mortality, which was statistically significant in all cases ($p < 0.0001$): 4.1-fold higher for hepatorenal syndrome; 1.7-fold higher for hepatic encephalopathy; 1.2-fold higher for ascites; 1.4-fold higher for cor pulmonale ($p < 0.035$); 2.6-fold higher for pulmonary embolism; 2.7-fold higher for hemoptysis/pulmonary hemorrhage; 2.6-fold higher for ventricular tachycardia; and

36.0-fold higher for cardiac arrest. The only complication that was associated with lower mortality (by 24%) was coronary artery disease ($p < 0.0001$).

Furthermore, black and “other” patients (more than one race) were associated with a longer hospital LOS by 0.4 ($p < 0.001$) and 1.2 days ($p < 0.001$), respectively, compared to LOS in patients of all other races/ethnicities. Medicare and no charge insurance were associated with decreased LOS by 0.4 ($p < 0.012$) and 2.3 days ($p < 0.016$), respectively. The following statistically significant ($p < 0.0001$) cirrhosis-related and pulmonary hypertension-related complications were associated with increased

Table 3 Multivariate regression of patients with pulmonary hypertension and cirrhosis

Variables	Mortality (%)		Length of stay (days)		Total charge of hospitalization (\$US)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Gender						
Male	1.01 (0.91–1.11)	0.903	-0.046 (-0.23 to 0.13)	0.617	5139 (2185–8093)	0.001*
Race/ethnicity						
Black	0.95 (0.84–1.08)	0.05*	0.43 (0.18–0.69)	0.001*	-2792 (-6981 to 1397)	0.191
Hispanic	1.03 (0.91–1.17)	0.706	0.12 (-0.16 to 0.40)	0.391	25,341 (20,742–29,941)	<0.0001*
Asian/Pacific Islander	1.37 (1.03–1.83)	0.030*	0.048 (-0.14 to 1.10)	0.126	30,214 (20,078–40,351)	<0.001*
Native American	1.10 (0.71–1.72)	0.669	-0.16 (-1.02 to 0.70)	0.715	-8912 (-22,285 to 5900)	0.255
Other	1.13 (0.86–1.49)	0.391	1.21 (0.66–1.76)	0.05	29,351 (20,424–38,277)	<0.0001*
Primary insurance						
Medicare	0.87 (0.75–1.00)	0.05	-0.35 (-0.62 to -0.08)	0.012*	-12,522 (-16,964 to -8080)	<0.0001*
Medicaid	0.95 (0.79–1.13)	0.541	0.08 (-0.24 to 0.41)	0.623	-7534 (-12,853 to -2214)	<0.006*
Self-pay	1.20 (0.89–1.63)	0.224	-0.50 (-1.09 to 0.09)	0.098	-20,591 (-30,611 to -10,570)	<0.0001*
No charge	0.83 (0.26–2.68)	0.755	-2.33 (-4.23 to -0.43)	0.016*	-51,893 (-87,980 to -15,807)	0.005*
Other	1.62 (1.21–2.18)	0.001*	0.38 (-0.27 to 1.03)	0.252	-1992 (-12,600 to 8617)	0.713
Complications						
Hepatorenal syndrome	4.07 (3.45–4.80)	<0.0001*	4.77 (4.29–5.25)	<0.0001*	81,036 (73,254–88,817)	<0.0001*
Hepatic encephalopathy	1.67 (1.43–1.96)	<0.0001*	1.25 (0.89–1.61)	0.05	6989 (582–13,395)	0.033*
Ascites	1.24 (1.12–1.37)	<0.0001*	0.92 (0.73–1.12)	0.05	5366 (2146–8586)	0.001*
Portal hypertension	1.08 (0.96–1.22)	0.181	0.60 (0.37–0.83)	<0.0001*	10,951 (7232–14,670)	<0.0001*
Variceal bleeding	0.85 (0.70–1.02)	0.085	-0.33 (-0.68–0.03)	0.074	-2500 (-8825 to 3826)	0.439
Cor pulmonale	1.36 (1.02–1.82)	0.035*	0.11 (-0.50–0.72)	0.724	-7679 (-16,956 to 1598)	0.105
Heart failure	0.96 (0.86–1.07)	0.470	1.17 (0.97–1.37)	0.05	11,313 (8121–14,505)	<0.0001*
Pulmonary embolism	2.58 (1.92–3.46)	<0.0001*	2.74 (1.91–3.51)	<0.0001*	28,648 (16,365–40,931)	<0.0001*

Table 3 continued

Variables	Mortality (%)		Length of stay (days)		Total charge of hospitalization (\$US)	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Hemoptysis/pulmonary hemorrhage	2.73 (1.73–4.32)	< 0.0001*	3.07 (1.86–4.27)	< 0.0001*	51,316 (33,130–69,503)	< 0.0001*
Atrial fibrillation	1.12 (0.99–1.26)	0.064	0.72 (0.49–0.95)	< 0.0001*	– 1195 (– 5364 to 2975)	0.574
Ventricular tachycardia	2.62 (2.03–3.37)	< 0.0001*	3.15 (2.50–3.79)	< 0.0001*	50,572 (40,781–60,363)	< 0.0001*
Cardiac arrest	35.97 (28.96–44.68)	< 0.0001*	1.33 (0.601–2.06)	0.05	56,632 (44,607–60,362)	< 0.0001*
Coronary artery disease	0.76 (0.68–0.84)	< 0.0001*	– 0.29 (– 0.49–0.09)	0.004*	– 2357 (– 5609 to 895)	0.155

*Significant difference between patient cohorts at pre-determined significance level of *p* < 0.05

hospital LOS for patients with pulmonary hypertension and cirrhosis compared to those with pulmonary hypertension alone: hepatorenal syndrome (4.8 days longer); hepatic encephalopathy (1.3 days longer); ascites (0.9 days longer); portal hypertension (0.6 days longer); heart failure (1.2 days longer); pulmonary embolism (2.7 days longer); hemoptysis/pulmonary hemorrhage (3.1 days longer); atrial fibrillation (0.7 days longer); ventricular tachycardia (3.2 days longer); cardiac arrest (1.3 days longer). Only coronary artery disease decreased hospital LOS by – 0.3 days (*p* < 0.0001).

Finally, male patients had \$5139 of increased total hospital charges (*p* < 0.001) compared to female patients. The hospital charges for Hispanic, Asian/Pacific Islander, and “other” patients were higher than those for patients of all other races/ethnicities by \$25,341 (*p* < 0.001), \$30,214 (*p* < 0.001), and \$29,351 (*p* < 0.0001), respectively. Interestingly, patients with the following insurance type had decreased total hospital charges: Medicare (\$12,522; *p* < 0.0001), Medicaid (\$7534; *p* < 0.006), self-pay (\$20,591; *p* < 0.001), no charge (\$51,893; *p* < 0.005). All statistically significant cirrhosis-related and pulmonary hypertension-related complications increased total hospital charges by the following amounts: \$81,036 for hepatorenal syndrome (*p* < 0.001); \$6989 for hepatic encephalopathy (*p* < 0.033); \$5366 for ascites (*p* < 0.001); \$10,951 for portal hypertension (*p* < 0.0001); \$11,313 for heart failure (*p* < 0.0001); \$28,648 for pulmonary embolism (*p* < 0.0001); \$51,316 for hemoptysis/pulmonary hemorrhage (*p* < 0.0001); \$50,572 for ventricular tachycardia (*p* < 0.0001); \$56,632 for cardiac arrest (*p* < 0.0001).

DISCUSSION

This is the first large, retrospective population cohort study of patients with a diagnosis of both pulmonary hypertension from any cause and cirrhosis from all etiologies using patient data from the HCUP NIS database. We identified 1,111,594 patients in the NIS database who

had been discharged from hospital during the period under study (2012–2017). Of these, after propensity matching, our patient sample comprised 34,986 patients with pulmonary hypertension and cirrhosis and 34,960 patients with only pulmonary hypertension. Our findings suggest that compared to patients without cirrhosis, patients with pulmonary hypertension and cirrhosis had 1.5-fold higher mortality, which was our primary outcome, as well as a 0.5-fold increase in hospital LOS and an increase in total hospital charges per visit of \$10,000, which were our secondary outcomes.

The statistically significant findings in our study were:

Independent positive predictors of mortality were Asian/Pacific Islander race, other insurance status, hepatorenal syndrome, hepatic encephalopathy, ascites, cor pulmonale, pulmonary embolism, hemoptysis, ventricular tachycardia, and cardiac arrest.

Independent negative predictors of mortality were black race, Medicare insurance, and coronary artery disease.

Independent positive predictors of increased hospital LOS were black race, other patients (more than one race/ethnicity), hepatorenal syndrome, hepatic encephalopathy, ascites, portal hypertension, heart failure, pulmonary embolism, hemoptysis, atrial fibrillation, and ventricular tachycardia.

Independent negative predictors of increased hospital LOS were Medicare insurance, no charge instead of insurance, and coronary artery disease.

Independent positive predictors of increased total charges were male gender, Hispanic ethnicity, Asian race, other insurance status, hepatorenal syndrome, hepatic encephalopathy, ascites, portal hypertension, heart failure, pulmonary embolism, hemoptysis, ventricular tachycardia, and cardiac arrest.

Independent negative predictors of increased total hospital charges were Medicaid insurance, self-pay for insurance, and no charge for insurance.

In patients with pulmonary hypertension, recent studies have reported a 13% increase in hospital LOS (11.8 days longer), initial diagnosis

at an older age (> 65 years), a small percentage patients with private insurance, doubled hospital charges, and a 23% decrease in mortality [8]. Mortality has decreased due to advancements in treatment and the new pharmacotherapies that are now available. Despite the decrease in mortality reported in patients with pulmonary hypertension, the increase in mortality seen with patients with pulmonary hypertension and cirrhosis may be explained by comparing this patient population to the one that is most similar, namely, patients with portopulmonary hypertension. This latter disease occurs due to portal hypertension, mostly resulting from underlying cirrhosis, and pulmonary hypertension. It is a difficult disease to understand and it is associated with a mortality at 5 years of 51% [9]. However, there is no current consensus on survival or prognostic factors for portopulmonary hypertension due to a scarcity of studies as well as a lack of data secondary to a small number of patients enrolled in clinical trials, a situation similar to that for patients with pulmonary hypertension and cirrhosis [10].

Cirrhosis, alone or in combination with pulmonary hypertension, is known to increase total hospital charges, but this disease decreases mortality and hospital LOS independently of other risk factors, likely due to improvements in management and the rise of palliative care [10]. However, this is not the same for patients with cirrhosis-related complications, as can be seen in our study as well. Patients with cirrhosis-related complications continue to experience higher mortality rates, increased hospital LOS, and greater total hospital charges for all complications [5, 6]. Our study further shows that high-risk cirrhosis patient populations, such as our cohort with pulmonary hypertension, also continue to have significantly higher mortality that is further magnified in association with deadly cirrhosis-related complications [5]. In previous studies, cirrhosis has been shown to increase hospitalizations for white patients, females, and holders of public insurance (e.g., Medicare or Medicaid) [5]. For our patients with pulmonary hypertension and cirrhosis, the opposite was true: black, Asian/Pacific Islander, and Hispanic patients experienced significant

increases in either mortality, hospital LOS, and/or total hospital charges, whereas patients with Medicare had better outcomes.

Interestingly, we observed an unexpected decrease in mortality for black patients among all patients with pulmonary hypertension and cirrhosis. One of the largest studies evaluating the impact of race and ethnicity on patient outcomes for pulmonary hypertension was the study using data from the REVEAL registry ($n = 3515$ patients). The results of this study showed that following adjustments for insurance status, hemodynamic monitoring, and 5-year follow-up, black patients no longer experienced increased mortality [4, 5, 9]. These results strongly suggest that a greater investment in insurance, more patient education on the diseases, increased availability of resources to patients suffering from these comorbidities, and increased hospital resources (such as follow-up, scheduling help, community-based resources, etc.) could further decrease mortality and possibly help decrease hospital LOS and total hospital charges in this patient group.

Surprisingly, Asians/Pacific Islanders showed the greatest increase in mortality and total hospital charges of any race or ethnicity. Until the REVEAL registry, it was unclear whether different races or ethnicities had differing prognosis following the diagnosis of pulmonary hypertension; however, the authors of the REVEAL study concluded that race and ethnicity did not impact outcomes for patients with pulmonary hypertension [11, 12]. In contrast, our study results show that Asians/Pacific Islanders are at a significantly higher risk than other races and ethnicities for mortality. Also, Asian/Pacific Islander patients are more likely to have congenital heart disease-associated pulmonary hypertension, which would significantly increase their lifelong morbidity and mortality compared to patients first diagnosed with pulmonary hypertension in adulthood because those diagnosed in adulthood would likely have decreased lifetime survival and hospitalizations [11]. Genetic mutations in interaction with epigenetics and environmental factors, which may be present for Asians/Pacific Islanders, could also theoretically increase

mortality in this patient group. Cirrhosis, especially with decompensation, has been known to increase in-hospital mortality for Asians/Pacific Islanders, which may also further explain our results [6].

Not only race and ethnicity, but insurance status also impacted mortality. In earlier studies in US populations, insurance status was the single most important prognosticator of increased mortality, even greater than race, further highlighting the importance of insurance coverage for our patient populations [4]. Our patients were mostly of lower socioeconomic status, which has been shown to significantly further worsen outcomes due to poor access to care, later disease presentation, and limited availability of treatment options for advanced stages of these diseases [9, 12]. Our results highlight why good insurance coverage, especially for those of lower socioeconomic status with access to limited resources, is vital for improving outcomes because patients with Medicare were associated with better outcomes in our study. Even though Medicare insurance does not provide the same level of coverage as private insurance, having insurance itself improved outcomes for our patients with pulmonary hypertension and cirrhosis. Pulmonary hypertension has been associated with longer hospital LOS, especially in patients with Medicare insurance. Total hospital charges for patients with pulmonary hypertension with commercial insurance were almost threefold higher, but there was also a substantial increase in total hospital charges of \$16,000 for patients with Medicare [13]. Yet our study reveals that patients with both pulmonary hypertension and cirrhosis with Medicare had significantly decreased total hospital charges. Also, patients with decompensated cirrhosis and complications have been known to have a lower risk for in-hospital mortality with any type of insurance [6].

Regarding complications, cardiac arrest had the greatest impact on mortality. Our study showed a catastrophic 36-fold increase in mortality for patients with pulmonary hypertension and cirrhosis complicated by cardiac arrest. The second largest risk factor for mortality is hepatorenal syndrome, with a fourfold increase in

mortality, which pales in comparison to cardiac arrest. Cardiac arrest is an especially extremely life-threatening complication for our patient population due to the difficulty in resuscitating patients with severe underlying hypoxia and acidosis as a result of pulmonary hypertension and cirrhosis [14]. Of all cardiac arrests in patients with pulmonary hypertension, 50% are due to the progression of the underlying disease, so this complication must be prevented from occurring in the first place due to the very low chance of recovery [15]. Similarly for patients with cirrhosis, cardiac arrest is a marker of a very poor prognosis; in one study, only 19% of these patients survived and of these patients, most had very poor neurological recovery 1 month after surviving cardiac arrest [16].

The complications hepatorenal syndrome, pulmonary embolism, hemoptysis, and ventricular tachycardia also significantly worsened mortality, but to a lesser extent than cardiac arrest, and they also simultaneously increased hospital LOS and total hospital charges. Hepatorenal syndrome is the most lethal complication of cirrhosis, with patients having a 37% mortality rate; this condition almost always requires hospitalization and is associated with the worst prognosis [17]. Pulmonary embolism leads to chronic thromboembolic pulmonary hypertension in up to 3.8% of survivors of acute pulmonary embolism [18]. Patients with pulmonary hypertension and cirrhosis complicated by pulmonary embolism likely need close surveillance and a high index of suspicion to diagnose chronic thromboembolic pulmonary hypertension. This must be done in a timely manner to reduce mortality in this patient population. Data on the independent impact of pulmonary hemorrhage/hemoptysis for hospital outcomes are limited, but the small amount of data that is available shows that these patients have a higher mortality [19]. Ventricular tachycardia has been seen in up to 24% of patients with pulmonary hypertension [20], which is a very low incidence. However, alarmingly, in a 3-year study in which over 500 patients with pulmonary hypertension died, 17% of the deaths were due to sudden and unexpected causes attributed to ventricular tachycardia [20, 21]. The results of our study

show that ventricular tachycardia slightly worsened outcomes so there may need to be more vigilance for monitoring patients for the development of ventricular tachycardia in this patient population.

Study Limitations

Our study had several limitations. First, despite extensive literature searches, we were unable to find studies from which we could draw significant conclusions on the relationship between these two highly prevalent issues, pulmonary hypertension and cirrhosis, in medicine today. We therefore analyzed a collection of the most recent years of the NIS database from the years 2012 to 2017. However, the NIS dataset does not provide laboratory data or account for treatments for cirrhosis with diuretics, beta blockers, albumin, terlipressin, vasoactive agents, midodrine, or for the various treatments for different types of pulmonary hypertension, such as blood vessel dilators/vasodilators, guanylate cyclase stimulators, endothelin receptor antagonists, phosphodiesterase inhibitors, high-dose calcium channel blocks, warfarin, digoxin, and chronic oxygen therapy. Secondly, individually, there are currently few studies on either pulmonary hypertension and its complications with regards to our parameters for cirrhosis. Thirdly, long-term outcomes post hospitalization were also unaccounted for as the database only allows for analysis of data ranging from admission to discharge. Fourthly, we did not sub-categorize the type of pulmonary hypertension because we wanted to examine all patients with primary or secondary pulmonary hypertension; such an analysis would have allowed us to further elaborate on risk specificity. The stratification of pulmonary hypertension etiology would have provided insight into specific treatment directions and options presented to the patient that ultimately have an effect on hospital data (i.e., LOS, cost), but we were not able to stratify the study population for these data as there are currently no explicit ICD codes outlining the five sub-categorizations in as much depth as we would have liked to investigate. Lastly, our results may not be

generalizable to international populations despite a broad spectrum of localities represented within the weighted data. Due to the regional differences and hospital types found in the NIS from across the USA, there is no way currently to extrapolate these findings to international regions, hospitals, or populations.

CONCLUSION

In conclusion, we found that patients with pulmonary hypertension and cirrhosis have higher mortality, hospital LOS, and total hospital charges compared to patients with only pulmonary hypertension. Health care cost data for pulmonary hypertension and cirrhosis as well as pulmonary hypertension is currently scarce. The relationship between race and ethnicity and pulmonary hypertension and cirrhosis is complex, but understanding this relationship may help us improve outcomes in the future for these patient populations. In contrast to other cardiovascular diseases, such as heart failure and hypertension, there are no specific treatment guidelines for patients based on race or ethnicity for patients with pulmonary hypertension, so this must be investigated in future studies. Targeted interventions, such as novel medications, right-to-left shunts, more evaluations for lung transplantation, and reversal of pulmonary vasculature remodeling, are needed for the subgroups identified in this study.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Yaser Khalid, Neethi Dasu, Raja Fawad Zafar, Herman Suga, Kirti Dasu, and Brian Blair have nothing to disclose.

Compliance with Ethics Guidelines. The datasets used in this study were fully de-identified and, therefore, Institutional Review Board (IRB) approval was not required. The datasets analyzed during the current study are publicly available on the NIS website (<https://www.hcup-us.ahrq.gov/nisoverview.jsp>).

Data Availability. The datasets analyzed during the current study are publicly available on the NIS website and can be found at: <https://www.hcup-us.ahrq.gov/nisoverview.jsp>.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Post MC, van der Wall EE. Pulmonary hypertension: the importance of a multidisciplinary approach. *Neth Heart J*. 2016;24(6):369–71.
2. Elia D, Caminati A, Zompatori M, et al. Pulmonary hypertension and chronic lung disease: where are we headed? *Eur Respir Rev*. 2019;28(153):190065.
3. Hoepfer MM, Ghofrani H-A, Grünig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary hypertension. *Dtsch Arztebl Int*. 2017;114(5):73–84.

4. Parikh KS, Stackhouse KA, Hart SA, Bashore TM, Krasuski RA. Health insurance and racial disparities in pulmonary hypertension outcomes. *Am J Manag Care*. 2017;23(8):474–80.
5. Zou B, Yeo YH, Jeong D, et al. A nationwide study of inpatient admissions, mortality, and costs for patients with cirrhosis from 2005 to 2015 in the USA. *Dig Dis Sci*. 2020;65(5):1520–8.
6. Kim D, Cholankeril G, Li AA, et al. Trends in hospitalizations for chronic liver disease-related liver failure in the United States, 2005–2014. *Liver Int*. 2019;39(9):1661–71.
7. Valbusa F, Bonapace S, Agnoletti D, et al. Nonalcoholic fatty liver disease and increased risk of 1-year all-cause and cardiac hospital readmissions in elderly patients admitted for acute heart failure. *PLoS One*. 2017;12(3). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5348001/>.
8. Sikachi RR, Sahni S, Mehta D, Agarwal A, Agrawal A. Nationwide trends in inpatient admissions of pulmonary hypertension in the United States from 2000 to 2013. *Adv Respir Med*. 2017;85(2):11.
9. Talwar A, Sahni S, Talwar A, Kohn N, Klinger JR. Socioeconomic status affects pulmonary hypertension disease severity at time of first evaluation. *Pulm Circ*. 2016;6(2):191–5.
10. Khalid YS, Reja D, Dasu NR, Suga HP, Dasu KN, Joo LM. In-hospital outcomes of patients with acute decompensated heart failure and cirrhosis: an analysis of the national inpatient sample. *Cardiol Ther*. 2020. <https://doi.org/10.1007/s40119-020-00183-6>.
11. Medrek S, Sahay S, Zhao C, Selej M, Frost A. Impact of race on survival in pulmonary arterial hypertension: results from the REVEAL registry. *J Heart Lung Transplant*. 2020;39(4):321–30.
12. Medrek SK, Sahay S. Ethnicity in pulmonary arterial hypertension. *Chest*. 2018;153(2):310–20.
13. Lacey M, Hunsche E, Buzinec P, Drake W, Nagao M, Régulier E. Hospitalization costs related to pulmonary hypertension (PH) among medicare advantage or commercially insured patients with pulmonary arterial hypertension (PAH) in the United States. *Value Health*. 2013;16(3):A233.
14. Bredmose PP, Buskop C, Lømo AB. Inhaled nitric oxide might be a contributing tool for successful resuscitation of cardiac arrest related to pulmonary hypertension. *Scand J Trauma Resusc Emerg Med*. 2019;27(1):22. <https://doi.org/10.1186/s13049-019-0602-x>.
15. Hoepfer MM, Galiè N, Murali S, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2002;165(3):341–4.
16. Roedel K, Wallmüller C, Drolz A, Horvatits T, Rutter K, Spiel A, et al. Outcome of in- and out-of-hospital cardiac arrest survivors with liver cirrhosis. *Ann Intensive Care*. 2017;7:103. <https://doi.org/10.1186/s13613-017-0322-1>.
17. Jamil K, Huang X, Lovelace B, Pham AT, Lodaya K, Wan G. The burden of illness of hepatorenal syndrome (HRS) in the United States: a retrospective analysis of electronic health records. *J Med Econ*. 2019;22(5):421–9.
18. Tapson VF, Platt DM, Xia F, et al. Monitoring for pulmonary hypertension following pulmonary embolism: the INFORM study. *Am J Med*. 2016;129(9):978–85.
19. Hirshberg B, Biran I, Glazer M, Kramer MR. Hemoptysis: etiology, evaluation, and outcome in a tertiary referral hospital. *Chest*. 1997;112(2):440–4.
20. Temple IP. Arrhythmias in pulmonary arterial hypertension. *J Congenit Cardiol*. 2017;1(1):2.
21. Middleton JT, Maulik A, Lewis R, et al. Arrhythmic burden and outcomes in pulmonary arterial hypertension. *Front Med (Lausanne)*. 2019;6:119. <https://doi.org/10.3389/fmed.2019.00169>.