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Association Between Cirrhosis and 30-Day Rehospitalization After Index Hospitalization for Heart Failure

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Abstract: There are limited data on clinical outcomes in patients re-admitted with decompensated heart failure (HF) with concomitant liver cirrhosis. We conducted a cross sectional analysis of the Nationwide Readmissions Database (NRD) years 2010 thru 2012. An Index admission was defined as a hospitalization for decompensated heart failure among persons aged ≥ 18 years with an alive discharge status. The main outcome was 30 − day all-cause rehospitalization. Survey logistic regression provided the unadjusted and adjusted odds of 30 − day rehospitalization among persons with and without cirrhosis, accounting for age, gender, kidney dysfunction and other comorbidities. There were 2,147,363 heart failure (HF) hospitalizations among which 26,156 (1.2%) had comorbid

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cirrhosis. Patients with cirrhosis were more likely to have a diagnosis of acute kidney injury (AKI) during their index hospitalization (18.4% vs 15.2%). There were 469,111 (21.9%) patients with readmission within 30 − days. The adjusted odds of a 30 − day readmission was significantly higher among patients with cirrhosis compared to without after adjusting for comorbid conditions (adjusted Odds Ratio [aOR], 1.3; 95% Confidence Interval [CI}: 1.2 to 1.4). The relative risk of 30 − day readmission among those with cirrhosis but without renal disease (aOR, 1.3; 95% CI: 1.3 to 1.3) was lower than those with both cirrhosis and renal disease (aOR, 1.8; 95% CI: 1.6 to 2.0) when compared to persons without either comorbidities. Risk of 30 − day rehospitalization was significantly higher among patients with heart failure and underlying cirrhosis. Concurrent renal dysfunction among patients with cirrhosis hospitalized for decompensated HF was associated with a greater odds of rehospitalization. (Curr Probl Cardiol 2021;00:100993.)

Introduction

HF is highly prevalent and associated with frequent hospitalizations, high mortality, and cost.[1-4] The burden associated with HF is expected to continue to increase, with the disease burden exerting a significant challenge on the health care system in the United States as the leading cause of 30 − day hospital readmission rate among Medicare patients.[5] The Nationwide Readmission Database (NRD) reports the rates of re-admission for HF to be as high as 24%.[6,7] Meanwhile, the 30 − day readmission rate for cirrhosis is reported to be at 12.9%.[8,9] However, for patients with decompensation of liver disease, it can easily reach 40%.[10] There is a close relationship between HF and liver function with dysfunction in 1 organ system usually manifesting in dysfunction of the other. HF can lead to hepatic injury via mechanisms of ischemia-reperfusion in low flow states and hepatic venous congestion eventually leading to necrosis, atrophy and fibrosis.[11] On the other hand, cirrhosis-induced cardiomyopathy may be brought about by the proinflammatory state leading to myocyte apoptosis, shift in myosin heavy chain isoform, increased cardiac output from arterial dilatation, subsequent decrease in systolic functional reserve and decreasing effective

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circulating volume.[11] Moreover, both conditions are known to lead to renal dysfunction in terms of hepatorenal and cardiorenal syndromes. This potential for cardio-hepatic-renal interactions may further lead to poorer outcomes in this patient population. A substantial number of patients admitted with acute HF concurrently carry a diagnosis of liver cirrhosis.[5] A recent publication in December 2020 using the National Inpatient Study (NIS) elucidated the mortality rate, length of stay and hospital costs for those people with those comorbid conditions.[5] However, information on their 30-day hospital readmission rate and associated factors were not reported. To our knowledge, this is the first paper exploring the outcomes of patients with concomitant liver cirrhosis, heart failure and interaction with renal dysfunction.

Methods

We conducted a cross sectional analysis using the 2010 to 2012 Nationwide Readmissions Database (NRD). NRD databases have been described elsewhere.[12] Briefly, the NRD is a publicly available database sponsored by the Agency for Healthcare Research and Quality. It includes approximately 28 million annual hospital discharges along with linkage numbers allowing patient tracking for readmission within the same calendar year.

We defined an index hospitalization as an admission among persons aged $\geq$ 18 who were discharged alive and with Diagnosis-Related Group (DRG) including 291, 292, and 293 representing HF. We excluded hospitalizations in the month of December in order to ensure a 30 − day post-discharge follow-up period, as linkage of hospitalization across calendar years is not possible when using NRD. The *International Classification of Diseases*, *Ninth revision*, Clinical Modification (ICD-9) codes were used to extract comorbid diagnoses among the index hospitalizations (see Supplemental Table 1). The main outcome of interest was 30 − day all-cause rehospitalization which was defined as the first rehospitalization within 30-day time period after discharge from the index hospitalization.

Categorical variables were expressed as weighted frequencies and percentages (%). Rao-Scott Chi-Square tests were used to test the association between categorical variables. Survey logistic regression was used to determine the unadjusted and adjusted odds of 30 − day rehospitalization among persons with relative to without cirrhosis. The adjusted logistic models accounted for chronic kidney disease (CKD), acute kidney injury (AKI), coronary artery disease (CAD), hypertension (HTN), cerebrovascular disease (CEVD), chronic obstructive pulmonary disease(COPD),

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cancer (CA), diabetes mellitus(DM), peripheral vascular disease(PVD) (Model B) and Model C which included confounders accounted for in Model B plus the Charlson comorbidity score (CCS).[13] The relative risk associated with the co-existence of either or both cirrhosis and renal dysfunction, defined as AKI and CKD, was assessed using a 4 − level categorial variable (Level I, without cirrhosis or renal disease; II, without cirrhosis but with renal disease; III, with cirrhosis but without renal disease; IV, with both cirrhosis and renal disease). Survey design features of NRD were incorporated into the analyses in order to provide population-based estimates. A two-sided test with a significance level of 0.05 was used for all hypothesis tests. All statistical analyses were conducted using SAS statistical software (SAS Corporation, Carey, NC).

Results

There were 2,147,363 index hospitalizations for decompensated heart failure of which 26,156 (1.2%) were with while 2,121,207 (98.8%) were without coexisting cirrhosis. (Table 1) displays patient characteristics by the presence or absence of comorbid cirrhosis. In comparison to patients without cirrhosis, patients with cirrhosis were less likely to be female (36.7% vs 51.7%), and also to have co-existing HTN (59.5% vs 71.8%),

TABLE 1. Characteristics of hospitalizations for heart failure by cirrhosis status

	Cirrhosis		*P* Value
	Not Cirrhosis *n* (%)	Cirrhosis *n* (%)	
Age category (y)			<0.001
18 to 40	45,797 (2.2)	488(1.9)	
40 to 65	501,214(23.6)	11,739(44.9)	
65 and older	1,574,196(74.2)	13,929(53.3)	
Female	1,096,021(51.7)	9,594(36.7)	<0.001
Chronic kidney disease	819,909(38.2)	10,164(38.9)	0.727
Acute kidney injury	322,023(15.2)	4,818(18.4)	<0.001
Coronary artery disease	31,389(1.5)	284(1.1)	0.002
Hypertension	1,523,746(71.8)	15,564(59.5)	<0.001
Cancer	79,802(3.8)	1,029(3.9)	0.44
Cerebrovascular disease	100781(4.8)	697(2.7)	<0.001
Chronic obstructive Pulmonary disease	715,494(33.7)	8,181(31.3)	<0.001
Diabetes mellitus	842,124(39.7)	9,883(37.8)	0.001
Peripheral vascular disease	168,421(7.9)	1,688(6.5)	<0.001
Charlson comorbidity score Category			<0.001
0 −3	1,379,264(65.0)	9,260(35.4)	
4 −6	698,628(32.9)	14,651(56.0)	
>7	43,307(2.0)	2,243(8.6)	

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CEVD (2.7% vs 4.8%), COPD (31.3% vs 33.7%), DM (37.8% vs 39.7%) and PVD (6.5% vs 7.9%). Those with cirrhosis were no more likely to have co-existing CKD (38.9% vs 38.2%) or cancer (3.9% vs 3.8%) than those without cirrhosis. There was no significant difference Nearly 2-thirds (64.6%) of those with comorbid cirrhosis had a CCS of 4 or higher as compared to approximately the 1-third (34.9%) among those without cirrhosis. Hospitalizations with comorbid cirrhosis were more likely than those without to have AKI during their index hospitalization (18.4% vs 15.2%).

There were 469,111 (21.9%) patients among the 2,147,363 index hospitalizations who had a readmission within 30 − days. (Table 2) displays characteristics at index hospitalization by 30 − day readmission status. Those with a readmission were more likely to have cirrhosis (1.5% vs 1.1%), AKI (17.3% vs 14.6%), CAD (1.7% vs 1.4%), CA (4.3% vs 3.6%), COPD (36.4% vs 32.9%), PVD (8.7% vs 7.7%), and DM (41.4% vs 39.2%). Tables 3 displays the odds of 30-day readmission by cirrhosis status and cirrhosis type. Those with co-existing cirrhosis has a greater odds of 30-day rehospitalization relative to those without cirrhosis (Odds Ratio [OR], 1.3; 95% Confidence Interval [CI}: 1.3 to 1.4). This increased odds of a 30 − day rehospitalization among cirrhotic patients

TABLE 2. Characteristics at index hospitalization by 30-day readmission status

	30-Day Readmission		*P* Value
	Not Readmitted *n* (%)	Readmitted *n* (%)	
Cirrhosis	19,062(1.1)	7,094(1.5)	<0.001
Age category (y)			<0.001
18 to 39	35,820(2.1)	10,465(2.2)	
40 to 65	397,320(23.7)	115,633(24.7)	
65 and older	1,245,112(74.2)	343,013(73.1)	
Female	866,485(51.6)	239,130(51.0)	<0.001
Chronic kidney disease	626,289(37.3)	203,785(43.4)	<0.001
Acute kidney injury	245,622(14.6)	81,219(17.3)	<0.001
Coronary artery disease	23,724(1.4)	7950(1.7)	<0.001
Hypertension	1,209,023(72.0)	330287(70.4)	<0.001
Cancer	60,821(3.6)	20,010(4.3)	<0.001
Cerebrovascular disease	78,881(4.7)	22,598(4.8)	0.08
Chronic obstructive Pulmonary disease	552,727(32.9)	170,948(36.4)	<0.001
Diabetes mellitus	129,374(7.7)	40,735(8.7)	<0.001
Peripheral vascular disease	657,715(39.2)	194,292(41.4)	<0.001
Charlson comorbidity score Category			<0.001
0 −3	1,108,147(66.0)	280,377(59.8)	
4-6	537,089(32.0)	176,190(37.6)	
>7	33,006(2.0)	12,544(2.7)	

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TABLE 3. Unadjusted and adjusted odds of 30-day readmission by cirrhosis status and cirrhosis type

	Model A OR (95% CI)	*P* Value	Model B OR (95% CI)	*P* Value	Model C OR (95% CI)	*P* Value
Cirrhosis status		<0.001		<0.001		<0.001
No cirrhosis	Reference		Reference		Reference	
Cirrhosis	1.34(1.27,1.41)		1.31(1.24,1.38)		1.29(1.23,1.36)	
Cirrhosis type		<0.001		<0.001		<0.001
No cirrhosis	Reference		Reference		Reference	
Alcoholic	1.21(1.11,1.32)		1.19(1.09,1.30)		1.13(1.04,1.24)	
Non-alcoholic	1.39(1.31,1.47)		1.35(1.27,1.43)		1.27(1.20,1.35)	

Abbreviations: CI, Confidence Interval; Model A, Unadjusted; Model B, adjusting for age, gender; Model C, Model B plus Charlson comorbidity Score; OR represents Odds Ratio.

remained after adjusting for confounders (adjusted OR [aOR], 1.3; 95% Confidence Interval [CI}: 1.2 to 1.4) and confounders plus Charlson comorbidity score (aOR, 1.3; 95% CI: 1.2 to 1.4). In analysis by cirrhosis type, the odds of rehospitalization was greater among those with non-alcoholic cirrhosis (aOR, 1.3; 95% CI: 1.2 to 1.4) than alcoholic cirrhosis (aOR, 1.1; 95% CI: 1.0 to 1.2) relative to those without cirrhosis.

As displayed in (Table 4), in comparison to patients with neither cirrhosis or renal disease, the risk of 30 − day readmission among those with cirrhosis but without renal disease (OR, 1.3; 95% CI: 1.3 to 1.3) was lower than those with both cirrhosis and renal disease (OR, 1.8; 95% CI: 1.6 to 2.0).

Discussion

Our study had 2 main findings. First, there is a significant relationship between the underlying diagnosis of cirrhosis and risk of 30 − day read-

TABLE 4. Odds of 30-day readmission by cirrhosis-renal status

	Model A OR (95% CI)	*P* Value	Model B OR (95% CI)	*P* Value	Model C OR (95% CI)	*P* Value
Cirrhosis-renal disease status		<0.001		<0.001		<0.001
I	Reference		Reference		Reference	
II	1.29(1.19,1.39)		1.26(1.67,2.05)		1.24(1.15,1.34)	
III	1.34(1.31,1.34)		1.34(1.32,1.36)		1.32(1.29,1.34)	
IV	1.85(1.69,2.04)		1.87(1.70,2.05)		1.79(1.63,1.97)	

Abbreviations: CI, Confidence Interval; Cirrhosis-Renal Status: I, without cirrhosis or renal disease; II, without cirrhosis but with renal disease; III, with cirrhosis but without renal disease; IV, with both cirrhosis and renal disease; Model A, Unadjusted; Model B, adjusting for age, gender, coronary artery disease, hypertension, cancer, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, peripheral vascular disease; Model C, Model B plus Charlson comorbidity score; OR represents Odds Ratio.

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mission specifically for HF. These study results add to a growing body of literature associating this underappreciated contribution to HF readmissions. Despite improvement in overall readmissions for HF, pneumonia and myocardial infarction,[14,15] readmissions in patients with cirrhosis within this cohort remained significantly higher than those without cirrhosis.[16] It is likely that any disease-specific interventions to reduce readmission for the aforementioned disease entities do not directly address the unique portal hypertensive complications of cirrhosis in the form of ascites and hepatic encephalopathy. Whilst this study did not specifically look at medication use, prognostic HF medications (such as ACE inhibitors or Angiotensin Receptor Blockers) may be poorly tolerated in patients with cirrhosis. Differences in medication use may also have contributed to 30 − day readmission rates. This is clinically relevant as the presence of cirrhosis among heart failure patients heralds poor outcomes via a complex, multifaceted interplay of cardiac and hepatic dysfunction in the form of cardiac cirrhosis or cirrhotic cardiomyopathy as well as their extra-hepatic and extra-cardiac complications. It is estimated that half of the patients undergoing liver transplantation show signs of heart dysfunction.[17,18] Despite normal ejection fraction, almost 2-thirds of these patients have diastolic dysfunction.[19,20] Although the exact incidence of cirrhotic cardiomyopathy is unknown as it remains underdiagnosed, it contributes to the high cardiovascular morbidity and mortality.[21] Furthermore, the combination of portal hypertension and decreased cardiac output complicates fluid management in patients with ascites who are at a higher risk of developing acute kidney injury from inherent altered hemodynamics compounded by the effects of under- or over-diuresis. More pointedly, these 2 conditions which are strongly associated with high readmission rates are very challenging to optimally manage in the outpatient setting. In fact, many cirrhotic patients struggle with adherence to complex medications and dietary regimen and have inadequate caregiver support.[22] Additionally, infections from acquired immunodeficiency in cirrhotic patients are associated with increased rate of readmission and are well-known risk factors for acute on chronic liver failure, multiple organ failures and high short-term mortality.[23] Interestingly, these same social and medical issues are commonly cited as diverse triggers for HF readmissions.[24]

Second, heart failure patients who also had cirrhosis were more likely to have AKI compared to those without cirrhosis both during the index hospitalization and the 30 − day readmissions. Readmitted HF patients also were more likely to have cirrhosis and hepatorenal syndromes on top of other co-morbidities. Unsurprisingly, the risk of 30 − day readmission

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for heart failure was higher in patients with both cirrhosis and renal dysfunction (acute and/or chronic). These accentuate the multidirectional interactions of both liver and heart in the development of renal dysfunction in the form of cardiorenal syndrome (CRS) and hepatorenal syndrome (HRS). Patients who have developed cardiac cirrhosis from chronic passive congestion of the liver are likely to have high central venous pressure (CVP) from intrinsic right ventricular dysfunction due to a biventricular disease process or pulmonary hypertension with secondary tricuspid regurgitation. Studies have shown that elevated CVP is the single most important factor associated with worsening renal function in HF patients or CRS type.[25] Patients with cirrhosis also have systemic vasodilatation and are likely to develop worsening hypotension with afterload reduction and diuretics, used as mainstay of therapy in HF patients, which could lead to AKI. Over the recent years, there has been a growing evidence challenging the traditional heart-kidney (CRS) or Iiver-kidney (HRS) crosstalk while accentuating the underappreciated contribution of the heart to the development of worsening renal function, raising the possibility of a less studied liver-heart-kidney connection (hepatocardiorenal syndrome).[26–29] Subclinical cardiac dysfunction in cirrhotic patients is seen in the form of diastolic dysfunction, impaired chronotropic reserve and impaired cardiac contractility in response to stress. It has been demonstrated that cirrhotic patients who develop HRS have evidence of low cardiac output prior to the onset of renal dysfunction; a finding further supported by improvement seen in HRS by the use of inotropes. Interestingly, both cardiorenal and hepatorenal syndromes share several pathophysiologic pathways. This becomes clinically relevant as emerging treatments with potential benefit in heart failure may also find application in HRS, potentially reducing HF readmission rates.

This study has limitations that are inherent to the nature of administrative datasets. First, any database relying on DRG and ICD-9-CM codes is prone to administrative error, although this is the same methodology Centers for Medicaid and Medicare Services (CMS) utilizes to determine and issue penalties. Second, this database did not include readmission for the other 2 targeted conditions by the HRRP – pneumonia and MI. Third, reliance on diagnostic codes to diagnose cirrhosis could be prone to error, especially in patients with only ascites or portal hypertension, which can be secondary to extrahepatic causes. However, due to patients with cirrhosis comprising a very small proportion of our cohort, misdiagnosis was unlikely to have influenced the result in a meaningful way. Lastly, information regarding clinical parameters during hospitalization for HF

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clinical risk scoring and use of medications during index hospitalization, was lacking for this study as it was not available from the NRD.

In this analysis of HF readmissions, comorbid cirrhosis was associated with a higher risk of readmission at 30 days. Although these patients may only account for a minority of total discharges, their complex underlying medical condition should allow for increased resources to assist in caring for them. They are critically ill and vulnerable population that need disease-specific interventions through a multispecialty consensus approach in order to prevent the emergence of complications including hepatocardiorenal syndromes. It is then imperative to identify causes of avoidable readmissions and other barriers so that changes can be made by our healthcare systems to benefit this complex patient population and optimize clinical outcome.

Conclusion

In our study, readmission rates were significantly higher among patients with cirrhosis and heart failure. Patients with combined heart failure, cirrhosis and renal disease have higher odds of readmissions. A high index of suspicion is necessary for early recognition and management of hepatocardiorenal syndrome through a multi-disciplinary approach in order to improve the outcomes of this condition.

Author's Contribution Statement

Ali Yazdanyar: conceptualization, data curation, data collection, formal analysis, methodology, writing original draft. **Kevin Bryan Lo**: conceptualization, methodology, formal analysis, writing (review and editing). **Jerald Pelayo**: writing (review and editing), submission. **Julien Sanon:** writing (review and editing). **Ardel Romero**: writing (review and editing). **Eduardo Quintero**: writing (review and editing). **Arjan S Ahluwalia:** data collection, writing (review and editing). **Shuchita Gupta:** data collection, writing (review and editing). **Rajiv Sankaranarayanan**: writing (review and editing). **Roy O. Mathew**: writing (review and editing). **Janani Rangaswami:** conceptualization, supervision, methodology writing (review and editing)

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100993.

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