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Clinical outcomes in patients with heart failure with and without cirrhosis: an analysis from the national inpatient sample

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Outcomes of heart failure (HF) hospitalization are driven by the presence or absence of comorbid conditions. Cirrhosis is associated with worse outcomes in patients with HF, and both HF and cirrhosis are associated with worse renal outcomes. Using a nationally representative sample we describe inpatient outcomes of all-cause mortality and length of stay (LOS) among patients with and without cirrhosis hospitalized for decompensated with HF. We conducted a cross sectional analysis using Nationwide Inpatient Sample (2010–2014) data including patients hospitalized for decompensated HF, with or without cirrhosis. We calculated the adjusted odds of all-cause mortality, acute kidney injury (AKI), and target LOS after adjusting for potential confounders. Out of the 2,487,445 hospitalized for decompensated HF 39,950 had cirrhosis of which majority (75.1%) were non-alcoholic cirrhosis. Patients with comorbid cirrhosis were more likely to die (OR, 1.26; 95% CI, 1.11 to 1.43) and develop AKI (OR, 1.26; 95% CI, 1.16 to 1.36) as compared to those without cirrhosis. Underlying CKD was associated with a greater odds of AKI (OR, 4.99; 95% CI, 4.90 to 5.08), and the presence of cirrhosis amplified this risk (OR, 6.03; 95% CI, 5.59 to 6.51). There was approximately a 40% decrease in the relative odds of lower HF hospitalization length of stay among those with both CKD and cirrhosis, relative to those without either comorbidities. Cirrhosis in patients with hospitalizations for decompensated HF is associated with higher odds of mortality, decreased likelihood of discharge by the targeted LOS, and AKI. Among patients with HF the presence of cirrhosis increases the risk of AKI, which in turn is associated with poor clinical outcomes.

Keywords

Hepatorenal; Cardiorenal; Hepatocardiorenal; Heart Failure; Cirrhosis

1. Introduction

Heart failure (HF) and liver cirrhosis as separate disease entities contribute to significant morbidity and mortality in the United States and worldwide [1, 2]. Cirrhosis may influence HF outcomes as it promotes a hyperdynamic state, neurohormonal activation which can contribute to both systolic and diastolic myocardial dysfunction [3]. Furthermore, both liver cirrhosis and HF can independently lead to poor renal outcomes as reflected in the conditions of hepatorenal syndrome (HRS) and cardiorenal syndrome (CRS) [3, 4]. In hepatorenal syndrome, increased splanchnic blood flow with decreased central volume accompanied by neurohormonal activation leads to vasoconstriction decreasing renal blood flow and glomerular filtration rate [5]. However, more recently, this conventional liver-kidney or liver-heart crosstalk has been challenged by emerging evidence accentuating the role of the cardiac dysfunction as a potential mediator of renal impairment in liver cirrhosis [3, 4]. Interactions between the liver, heart, and kidney in the setting of CRS and HRS share several cardinal mechanistic pathways [5, 6], but clinical outcomes brought about by these interactions remain understudied.

We conducted a cross sectional analysis of nationally representative sample of hospitalizations for decompensated HF to assess the inpatient outcomes including all-cause mortality, acute kidney injury (AKI) and length of stay (LOS) duration among those with relative to without comorbid cirrhosis.

2. Methods

We conducted a cross sectional analysis of the 2010 thru 2014 years of the National Inpatient Sample (NIS). Briefly, the NIS of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ), is a survey design-based database of discharge data for inpatient care from non-federal (excludes Veterans Hospitals and other federal facilities), non-rehabilitation, acute-care, short-term hospitals. The NIS is an annual sample of hospital discharges that provides national

estimates of the characteristics of the patients, diagnoses, and hospital-based procedures performed in US acute-care hospitals. Annually NIS includes approximately 7 million hospital discharges. Detailed information on the NIS can be found on its website (https://www.hcup-us.ahrq.gov/databases.jsp).

In our study sample of interest, hospitalizations for decompensated HF, was identified using the hospitalization Diagnosis-Related Group (DRG) including 291, 292, and 293. Excluded were those aged younger than 18 years, and those with hemodialysis (ICD 9: 39.95, V45.1, V56.0, V56.1) or end stage renal disease (ICD-9: 585.6). HF subtype (diastolic, systolic, and combined systolic and diastolic) and comorbid conditions including cirrhosis (alcoholic and non-alcoholic), chronic kidney disease (CKD), cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and cancer were extracted using their respective ICD-9 codes (see **Supplemental Table 1**). Target LOS (tLOS) was defined as 2.8 days (d) for hospitalization as determined by median time to discharge by Medicare level DRG (DRG 293, 4.0 d for DRG 292, and 5.2 d for DRG of 291).

The study outcomes included all-cause inpatient mortality, acute kidney injury (AKI), and length of stay (LOS) duration shorter than the DRG-level Medicare tLOS.

Descriptive and inferential statistics was calculated while incorporating the survey design features of the NIS data in order to provide population-based estimates. Descriptive statistics was calculated for categorical and continuous variables. Associations between categorical variables was determined using the design-adjusted Rao-Scott chi-square test. Survey logistic regression provided the odds of study outcome among those with related to without cirrhosis adjusting for age, gender, and additional comorbidities including CKD, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and cancer. Unadjusted and adjusted logistic regression by HF subtype provided the odds of study outcome among those with relative to without cirrhosis. A significance level of 0.05 with a 2-sided test was used for all hypotheses. All statistical analyses were conducted using SAS Statistical Software (SAS [9.4] Software, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Baseline characteristics

There were 2,487,445 hospitalizations for decompensated HF in our study sample including 850,280 with diastolic, 1,358,235 with systolic, and 278,930 with combined HF. The comorbid condition of cirrhosis was present among 39,950 patients, which was predominantly of the non-alcoholic type (75.1%) Systolic HF was the most prevalent subtype in both those with or without cirrhosis (22,475 (56.3%) vs. 1,335,760 (53.7%)), followed by diastolic HF (13,050 (32.7%) vs. 837,230 (33.7%)), and combined HF (4,425 (11.1%) vs. 274,505 (11.2%)). Table 1 displays characteristics of the HF hospitalizations by cirrhosis status. Those with cirrhosis were younger than those without cirrhosis (65.9 ± 0.2 vs. 73.2 ± 0.1 years (y); $p < 0.0001$). The average number of coexisting conditions (9.7 ± 0.04 vs. 8.6 ± 0.02) and the average Charlson index score (4.5 ± 0.02 vs. 3.2 ± 0.003) was higher among those with as compared to without cirrhosis. Patients with coexisting cirrhosis were less likely to be female (36.3% vs. 50.6%) or to have HTN (65.5% vs. 75.4%), CKD (35.8% vs. 37.4%), or COPD (34.5% vs. 37.1%).

Table 1. Characteristics of patients by cirrhosis status.

	Cirrhosis		*p* Value
	Yes	No	
	n (%) or μ ± SE	n (%) or μ ± SE	
Age (y)			<0.0001
18 to 40	775 (1.9)	51,825 (2.1)	
40 to 65	17,815 (44.6)	583,355 (23.5)	
65 and older	21,360 (53.5)	1,812,315 (72.9)	
Female	14,520 (36.3)	1,238,950 (50.6)	<0.0001
CKD	14,314 (35.8)	916,550 (37.4)	0.004
HTN	26,180 (65.5)	1,844,270 (75.4)	<0.0001
DM	16,565 (41.5)	1,039,115 (42.5)	0.08
COPD	13,785 (34.5)	906,810 (37.1)	<0.0001
Cancer	1,575 (3.9)	103,980 (4.2)	0.18
Charlson index	4.5 ± 0.02	3.2 ± 0.003	<0.0001
No. of chronic conditions	9.7 ± 0.04	8.6 ± 0.02	<0.0001

Abbreviations: n represents weighted frequency; %, percent; y, year; μ, mean; SE, standard Error; CKD, Chronic Kidney Disease; CHF, congestive heart failure; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

3.2 Outcomes: acute kidney injury

AKI occurred in 561,095 (22.56%) of the HF hospitalizations with a significantly higher occurrence of AKI among those with as compared to without cirrhosis (26.49% vs. 22.49%; $p < 0.0001$). AKI occurred more commonly among those with cirrhosis across all subtypes of HF including Diastolic HF (3,330 (25.52%) vs. 198,075 (23.66%); $p = 0.03$), systolic HF (5,810 (25.85%) vs. 278,785 (20.87%); $p < 0.0001$), and combined HF (1,430 (32.32%) vs. 73,665 (26.84%); $p = 0.0002$). Table 2 displays the adjusted odds of AKI among HF hospitalizations with relative to without cirrhosis after adjusting for confounding characteristics. After adjusting for age, gender, and other comorbidities, HF hospitalizations with cirrhosis had a greater risk of AKI relative to those without (adjusted Odds Ratio (aOR), 1.23; 95% CI, 1.17 to 1.30). Relative to those without either CKD or cirrhosis, those with CKD without cirrhosis had a greater odds of AKI among HF hospitalization (aOR, 4.99; 95% CI, 4.90 to 5.08), the presence of concomitant CKD and cirrhosis amplified this heightened risk (aOR, 6.03; 95% CI, 5.59 to 6.51) (see Table 3).

3.3 Outcomes: LOS

Over half of the HF hospitalizations (53.0%) had a LOS below the tLOS. HF hospitalizations without cirrhosis were more likely to have a LOS below tLOS (53.1% vs. 45.1%; $p < 0.0001$). By HF subtype, those without cirrhosis were more

Table 2. Inpatient all-cause mortality, acute kidney injury, and discharge by target length of stay of those with relative to without cirrhosis.

	aOR	95% CI
Acute kidney injury		
Overall	1.23	(1.17, 1.30)
HF Sub Type		
DSCHF	1.31	(1.13, 1.53)
SCHF	1.27	(1.16, 1.39)
DCHF	1.10	(1.00, 1.21)
Target length of stay		
Overall	0.71	(0.68, 0.74)
HF Sub Type		
DSCHF	0.70	(0.61, 0.81)
SCHF	0.66	(0.61, 0.71)
DCHF	0.75	(0.69, 0.81)
All-cause mortality		
Overall	1.26	(1.11, 1.43)
HF Sub Type		
DSCHF	1.58	(1.12, 2.22)
SCHF	1.20	(0.97, 1.49)
DCHF	1.10	(0.85, 1.43)

Abbreviations: OR represents Adjusted Odds Ratio; CI, Confidence Interval; HF, Heart Failure; DSCHF, combined systolic and diastolic congestive heart failure; SCHF, systolic congestive heart failure; DCHF, diastolic congestive heart failure.

Table 3. Impact of CKD and cirrhosis on the odds of target length of stay and acute kidney injury among HF hospitalizations.

	tLOS		AKI	
	aOR	95% CI	aOR	95% CI
Overall				
A	Reference		Reference	
B	0.90	(0.89, 0.91)	4.99	(4.90, 5.08)
C	0.73	(0.69, 0.77)	1.26	(1.16, 1.36)
D	0.61	(0.56, 0.66)	6.03	(5.59, 6.51)
Sub Type				
DSCHF				
A	Reference		Reference	
B	0.97	(0.93, 1.00)	4.34	(4.16, 4.34)
C	0.73	(0.61, 0.87)	1.46	(1.18, 1.81)
D	0.65	(0.52, 0.81)	5.14	(4.19, 6.31)
SCHF				
A	Reference		Reference	
B	0.91	(0.89, 0.92)	4.46	(4.35, 4.58)
C	0.68	(0.62, 0.75)	1.23	(1.08, 1.39)
D	0.56	(0.50, 0.64)	5.86	(5.19, 6.61)
DCHF				
A	Reference		Reference	
B	0.95	(0.93, 0.97)	5.00	(4.87, 5.14)
C	0.77	(0.69, 0.85)	1.15	(1.01, 1.32)
D	0.68	(0.60, 0.78)	5.25	(4.57, 6.03)

Abbreviations: aOR represents Adjusted Odds Ratio; tLOS, target length of stay; AKI, acute kidney injury; CKD, chronic kidney disease; LOS, length of Stay; CI, Confidence Interval; A, no cirrhosis or Chronic Kidney Disease; B, no cirrhosis but with Chronic Kidney Disease; C, with cirrhosis but without CKD; D, with cirrhosis and CKD. DSCHF, Combined Diastolic and Systolic CHF; SCHF, Systolic CHF; DCHF, Diastolic CHF; Adjusted Model adjusts for age, gender, cerebrovascular disease, Chronic obstructive pulmonary disease, hypertension, diabetes, cancer.

likely to have LOS below tLOS in the hospitalization for diastolic HF (53.1% vs. 45.6%; $p < 0.0001$), systolic HF (54.5% vs. 45.6%; $p < 0.0001$), and combined HF (49.6% vs. 41.4%; $p < 0.0001$). As displayed in Table 2, persons with relative to those without cirrhosis had a 29% decrease in the relative odds of having a LOS below tLOS (aOR, 0.71; 95% CI, 0.68 to 0.74). By HF subtype, persons with cirrhosis had the least likely to have LOS below tLOS, as measured by % decrease in relative odds, among systolic HF hospitalization (34%) followed by combined HF (30%) and diastolic HF (25%) (see Table 2). As shown in Table 3, HF hospitalizations with coexisting cirrhosis and CKD were least likely to have been discharged by tLOS relative to those without either cirrhosis and CKD.

3.4 Outcomes: all-cause mortality

A total of 71,450 (2.9%) deaths among HF hospitalizations with a higher mortality among patients with cirrhosis than without cirrhosis (3.4% vs. 2.8%; $p = 0.004$). The higher mortality among those with cirrhosis was noted among those with systolic HF (3.7% vs. 3.2%; $p = 0.03$), and combined HF (4.3% vs. 2.9%; $p = 0.01$) but not in the diastolic HF subtype (2.5% vs. 2.4%; $p = 0.55$). After adjusting for confounders, HF hospitalizations with comorbid cirrhosis had a higher risk of mortality relative to those without cirrhosis (OR, 1.26; 95% CI, 1.11 to 1.43). When assessed by HF subtype, the heightened risk of mortality with the coexistence of cirrhosis was noted among those with combined HF (OR, 1.58, 95% CI, 1.12 to 2.22) (See Table 2). Table 4 shows impact of AKI and cirrhosis on the odds of all-cause mortality among HF hospitalizations. As shown, those with coexisting cirrhosis and who had AKI during the HF hospitalization had a greater odds of mortality relative to those without either condition (OR, 4.20; 95% CI, 3.55 to 4.97). This pattern of heightened risk was noted across the HF subtypes.

4. Discussion

This analysis is, to the best of our knowledge, the first observational report from a nationally representative database on clinical outcomes in patients with hospitalized HF with/without cirrhosis including AKI, mortality and impact on hospital LOS. The presence of underlying cirrhosis increases mortality risk in patients with HF. A recent analysis by Khalid *et al.* [7] showed an in-patient mortality rate of 3.4% among HF hospitalized patients with cirrhosis. Cirrhosis leads to a chronic hyperdynamic circulatory state coupled with low systemic vascular resistance, and

Table 4. Impact of AKI and cirrhosis on the odds of mortality among HF hospitalizations.

	Adjusted OR	
	OR	95% CI
Mortality		
Overall		
A		Reference
B	2.97	(2.86, 3.09)
C	1.10	(0.91, 1.32)
D	4.20	(3.55, 4.97)
Sub Type		
DSCHF		
A		Reference
B	3.14	(2.82, 3.51)
C	1.36	(0.78, 2.38)
D	5.29	(3.45, 8.11)
SCHF		
A		Reference
B	3.49	(3.27, 3.72)
C	1.08	(0.76, 1.52)
D	3.49	(3.27, 3.72)
DCHF		
A		Reference
B	3.22	(3.01, 3.46)
C	0.97	(0.64, 1.45)
D	3.99	(2.81, 5.69)

Abbreviations: OR represents Odds Ratio; CI, Confidence Interval; A, no cirrhosis or Acute Kidney Injury; B, no cirrhosis but with Acute Kidney Injury; C, with cirrhosis but without Acute Kidney Injury; D, with cirrhosis and Acute Kidney Injury. DSCHF, Combined Diastolic and Systolic CHF; SCHF, Systolic CHF; DCHF, Diastolic CHF; Adjusted Model adjusts for age, gender, chronic kidney disease, cerebrovascular disease, Chronic obstructive pulmonary disease, hypertension, diabetes, cancer.

provides a backdrop for independent cardiomyopathy from the risk factors for the etiology of cirrhosis in itself (such as NASH/amyloid/hemochromatosis) [8]. In the compensated state, the hemodynamic derangements predominantly in the form of arterial vasodilation are counterbalanced by the augmentation of cardiac output [9]. However, in the decompensated state, cardiac output may be inadequate to compensate for the much more pronounced systemic vascular resistance reduction that eventually leads to central hypovolemia and arterial hypotension, feeding into vicious cycle of sympathetic, renin-angiotensin-aldosterone, and vasopressin systems activation common to both cirrhosis as well as HF [10]. Furthermore, due to hepatic dysfunction, metabolism of drugs such as those used in HF may be impaired potentially limiting the use of guideline directed medical therapy in this specific patient population that may affect subsequent clinical outcomes [11]. This particular cohort of patients with "hepato-cardiac" disease represent a potentially high-risk group for poor outcomes when hospitalized for HF, given the close crosstalk between HF and cirrhosis, with several common aberrant, maladaptive pathways and possible limitations to therapy.

Cirrhosis and HF are independent drivers of worsening kidney function in their respective decompensated states vis a vis hepatorenal syndrome (HRS) and cardiorenal syndrome (CRS) respectively [4–6]. Interestingly, interactions between these organs share cardinal mechanistic pathways including neurohormonal activation and endothelial dysfunction [12]. In decompensated cirrhosis cardiomyopathy, the massive renal vasoconstriction coupled with reduced cardiac output adversely affects renal function [4, 13, 14]. A proof of concept study in 2003 examined cardiac output during and after resolution of spontaneous bacterial peritonitis in cirrhotic patients [15]. Eight of the patients who developed HRS were found to have lower cardiac output at baseline and declined further at infection resolution, compared with the fifteen who had normal function. This is the first clear evidence that cardiac dysfunction may play a collateral pathogenic role in HRS, with the use of the term "hepatocardiorenal syndrome" in the literature gaining recent traction [4]. Similarly, congestive hepatopathy in the setting of decompensated HF from elevated right atrial pressures adds the risk of further decompensation of liver function, with secondary effects on worsening kidney function [16–18]. Thus, the interplay of "hepato-cardiac" disease in those with HF and underlying cirrhosis is potentially a major driver for poor kidney outcomes as well as higher mortality and LOS with its attendant health care resource utilization, as shown in this analysis.

In this analysis, the impact of underlying cirrhosis and the development of worsening kidney function did not have a differential effect in those with HFrEF vs HFpEF. This is of clinical importance, as EF per se may not be the primary determinant of outcomes with the maladaptive "hepato-cardio-renal-axis" [4]. In fact, LV systolic dysfunction may be latent in cirrhosis, and may require provocative testing to identify the presence of cardiomyopathy [19]. Thus, the mere preservation of EF should not be a deterrent to a more nuanced approach to diagnosing cardiomyopathy in patients with cirrhosis, especially with the consideration to be able to modify the disease trajectory with appropriate guideline directed medical therapies for HF early in the course, given the high burden of mortality and resource utilization in the decompensated state, as shown in this cross-sectional analysis.

5. Limitations

Our study has several limitations. The use of an administrative dataset and the cross-sectional nature of our study design limit the ability to capture patient level data. Other limitations include the lack of information in the database regarding the severity of the conditions described lack of an indicator for whether a condition was present on admission or not, and non-availability a disease state relevant to the outcome of interest, and potential residual confounding. Also, we relied on hospitalization DRG to identify the main indication

for the hospitalization to have been for HF which allows for administrative error. We were not able to look at the influence of potential suboptimal use of guideline directed medical therapy given the more complex hemodynamic nature of the interplay of cirrhosis and heart failure with potentially lower blood pressure ranges. Nevertheless, these results describe the high burden of poor outcomes in patients with "cardiohepatic" disease and its attendant costs on the health system, and are hypothesis generating towards design of future studies to alter the trajectory of this axis with the recognition of high-risk phenotypes and institution of appropriate guideline based medical therapies.

6. Conclusions

Patients hospitalized with HF and underlying cirrhosis may be at higher risk for poorer clinical outcomes. Prospective studies with control for potential confounders may better delineate this association.

Author contributions

All authors were involved with the conceptualization and the design of the study. AY was involved with data extraction and analysis. AY, MHM, JP, JS, EQ, KBL were involved with the first manuscript draft. ROM and JR served as the supervising senior authors who edited at every phase of the manuscript including multiple revisions. All authors reviewed and approved the final form of the manuscript submitted.

Ethics approval and consent to participate

This research has been performed on the National Inpatient Sample as part of the databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP). This research project was reviewed and approved by the Institutional IRB under expedited review due to its nature of a database study with no patient identifiers involved and no informed consent involved. IRB number: IRB-2021-602.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2203100.

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