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Letter

Causes of Hospitalization in Patients With Cardiorenal Syndrome Across the Spectrum of Ejection Fraction

Yosef Manla, MD[1], Obada Kholoki, MB, BCh, BAO[1], Nizar Attallah, MD[2], and Feras Bader, MD, MS, FACC, FHFSA[1]

[1]Department of Cardiology, Heart, Vascular, and Thoracic Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[2]Department of Nephrology, Medical Subspecialties Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

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Correspondence to
Feras Bader, MD, MS, FACC, FHFSA
Department of Cardiology, Heart, Vascular, and Thoracic Institute, Cleveland Clinic Abu Dhabi, Al Maryah Island, PO Box 112412, Abu Dhabi, United Arab Emirates.
Email: baderf@clevelandclinicabudhabi.ae

The coexistence of heart failure (HF) and chronic kidney disease (CKD), referred to as cardiorenal syndrome (CRS), complicates the clinical picture even further and may result in frequent hospitalizations and deaths.[1] Regardless of the left ventricular ejection fraction (LVEF), neurohormonal derangements coexist in patients with HF, including overactivation of the renin-angiotensin-aldosterone and sympathetic nervous systems, resulting in worsening intrarenal hemodynamics.[2] Data from landmark HF clinical trials of neurohormonal antagonists have shown hospitalization reduction benefits in patients with LVEF ≤40% or less; however, these agents have not been consistently effective in patients with LVEF >50%[3,4] Most recently, results of a pooled analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials have shown consistent hospitalization risk reduction benefits of empagliflozin among groups of patients with LVEF ranging from <25% to <65%.[3] Understanding why patients with CRS are hospitalized, and how the admission causes differ across the spectrum of LVEF might help inform current clinical practice and resource utilization. Therefore, we aim to investigate the causes and characteristics of hospitalizations in patients with CRS across the spectrum of LVEF quartiles.

In this study, we included patients with CRS, particularly those having a chronic status of symptomatic HF and a diagnosis of CKD (eGFR <60 mL/min/1.73 m^2), including both CRS type II (chronic HF leading to CKD) and CRS type IV (CKD leading to chronic HF), at their baseline visits to our HF clinic and recorded all hospitalizations for these patients up to the latest available encounter (between 09/2015 and 03/2023), or until a patient no longer fulfills the definition of CRS (eGFR became >60 mL/min/1.73 m^2). Causes of hospitalizations were categorized using the Medical Dictionary for Regulatory Activities (version 21.0) System Organ Classes.[5] Hospitalizations due to acute HF or acute kidney injury (AKI) were also reported separately. Cardiac and vascular causes were combined under the category of cardiovascular causes. Categorical variables were reported as absolute numbers (%), and continuous variables were reported as mean ± standard deviation or median (interquartile range [IQR]). The 1,116 hospitalizations were stratified into quartiles of LVEF measured at the time of each admission. LVEF cutoffs measured 22%, 35%, and 50%, for Q1, Q2, and Q3 groups, respectively. Differences in hospitalization characteristics between LVEF quartiles were evaluated using chi-square and Cochran Armitage trend tests for categorical variables, and analysis of variance or Kruskal–Wallis tests for numerical variables, as appropriate. A p value <0.05 was considered to be statistically significant. All statistical analyses were performed with JMP® Data Analysis (software version 16; SAS Institute Inc., Cary, NC, USA). The study was approved by the local Research Ethics Committee, and informed consent was waived due to the retrospective nature of the study.

Over a median follow-up of 1.6 years, a total of 1,116 hospitalizations were recorded, with an average of 1.8 admissions per patient year. About a quarter (24.3%) of the patients were admitted once only. cardiovascular disease (CVD) accounted for 43.5% of hospitalizations, with HF as the primary cause of admissions (36.6%), while only 8% of hospitalizations were due to AKI, suggesting that half of the hospitalizations are attributed to non-cardio-renal triggers (**Table 1**). With increasing LVEF, hospitalizations featured older patients, more females, and a higher burden of hypertension, diabetes mellitus, and hyperlipidemia (**Table 1**).

Causes of hospitalizations varied significantly across the spectrum of LVEF (p<0.001), with significant upward trends noticed in hospitalizations due to non-cardiovascular causes with the increase in LVEF (Q1: 42.3% vs. Q4: 74.1%, p<0.001), including renal, respiratory, gastrointestinal, and hematological causes. Conversely, there was a reduction in rates of HF hospitalizations with higher LVEF (Q1: 53.1% vs. Q4: 19.4%, p<0.001). There was no difference in length of stay across groups (p=0.6).

On sensitivity analysis, we analyzed causes of first hospitalization among our patients (n=259). The index LVEF distribution was similar to our primary analysis (median, 35%; IQR, 25–48). Additionally, a significant reduction in rates of HF hospitalization with higher LVEF (Q1: 49.2% vs. Q4: 21.9%, p=0.001) was observed, also aligning with our primary analysis.

The Middle East Region features a growing burden of heart failure with a concomitant high burden of cardio-renal-metabolic risk factors.[6,7] Limited data are available on patients with CRS and why they get hospitalized, particularly from the Middle East. In a previous analysis, we found that one-third (34.4%) of the patients visiting the HF clinic (n=968) had CRS (referring to type II or IV).[8] Our study provides insight into admission triggers in this challenging population and highlights that CVD was the leading cause of hospitalization in patients with CRS regardless of LVEF. Among these CVD hospitalization, acute HF accounted for the vast majority of hospitalizations, resulting in 36.6% of the hospitalizations overall. Acute HF has been associated with poor short- and

Table 1. Characteristics and causes of hospitalizations in patients with cardiorenal syndrome across the spectrum of LVEF

Characteristics	All (n=1,116)	LVEF				p value
		Quartile 1 (10–22)	Quartile 2 (22–35)	Quartile 3 (35–50)	Quartile 4 (50–76)	
Number of unique patients	-	75	111	107	77	-
Number of hospitalizations	-	279	279	279	279	-
Patient age (years)	69.3±11.3	65.4±12.0	70.0±11.0	70.5±10.7	71.1±11.3	<0.001
Female sex	373 (33.4)	37 (13.3)	70 (25.1)	82 (29.4)	184 (66.0)	<0.001*
Patient weight (kg)	78.0±18.8	73.7±19.8	77.0±19.4	79.5±15.7	81.8±20.0	<0.001
Hypertension	1002 (89.8)	231 (82.8)	234 (83.9)	267 (95.7)	270 (96.8)	<0.001*
Diabetes mellitus	878 (78.7)	183 (65.6)	209 (74.9)	233 (83.5)	253 (90.7)	<0.001*
Hyperlipidemia	872 (78.1)	184 (66.0)	220 (78.9)	241 (86.4)	227 (81.4)	<0.001*
Atrial fibrillation	448 (40.1)	123 (44.1)	115 (41.2)	105 (37.6)	105 (37.6)	0.3‡
History of smoking	509 (45.6)	184 (65.9)	109 (39.1)	121 (43.4)	95 (34.1)	<0.001*
Ischemic heart disease	690 (61.8)	155 (55.6)	187 (67.0)	208 (74.6)	140 (50.2)	<0.001†
Patient mean eGFR (mL/min/1.73 m^2)	36.8±14.1	39.3±13.1	36.8±13.3	34.2±14.6	36.9±15.1	<0.001
Cause of hospitalization						
Cardiac and vascular disorders	485 (43.5)	161 (57.7)	151 (54.1)	101 (36.2)	72 (25.8)	<0.001*
Acute heart failure	408 (36.6)	148 (53.1)	126 (45.2)	80 (28.7)	54 (19.4)	<0.001*
Non-cardiovascular causes	631 (56.5)	118 (42.3)	128 (45.9)	178 (63.8)	207 (74.2)	<0.001*
Renal and urinary disorders + surgical and medical procedures	124 (11.1)	18 (6.4)	33 (11.8)	39 (14)	34 (12.2)	0.02*
Acute kidney injury	89 (8.0)	12 (4.3)	25 (9.0)	27 (9.7)	25 (9.0)	<0.05*
Respiratory, thoracic, and mediastinal disorders	143 (12.8)	25 (9.0)	27 (9.7)	30 (10.8)	61 (21.9)	<0.001*
Gastrointestinal disorders	76 (6.8)	14 (5)	12 (4.3)	25 (9)	25 (9)	0.04*
Hepatobiliary disorders	22 (2)	3 (1.1)	8 (2.9)	3 (1.1)	8 (2.9)	0.3‡
Infections and infestations	131 (11.7)	28 (10)	24 (8.6)	47 (16.9)	32 (11.5)	0.01†
Blood and lymphatic system disorders	37 (3.3)	5 (1.8)	0 (0.0)	9 (3.2)	23 (8.2)	<0.001*
Metabolism and nutrition disorders	47 (4.2)	15 (5.4)	10 (3.6)	10 (3.6)	12 (4.3)	0.5‡
Nervous system, musculoskeletal, connective tissue, and eye disorders	51 (4.6)	10 (3.6)	14 (5.0)	15 (5.4)	12 (4.3)	0.7‡
Length of stay (days)	6 [3–12]	6 [3–13]	6 [3–13]	6.5 [4–12]	6 [3–11]	0.6

Values are presented as mean ± standard deviation, median [interquartile range], or number (%).
LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate.
*In addition to the significant p values obtained from the χ^2 test, the trend examined through the Cochran-Armitage trend test was statistically significant at a level of p<0.05.
†Although the χ^2 test yielded a significant p value, the Cochran-Armitage trend test did not reach statistical significance at p<0.05.
‡Neither the χ^2 nor Cochran-Armitage trend test revealed a statistically significant difference.

medium-term outcomes including (early readmission and mortality), therefore quantifying its burden is of clinical significance.[9]

Another significant finding is that non-cardiorenal triggers accounted for almost half of the hospitalizations. The latter-mentioned events impose a significant morbidity and mortality burden as they are hard to prevent, manage, and might result in a more complex clinical picture of HF decompensation or worsening renal function. This might require multifaceted approaches when managing these patients in the hospital to further manage these comorbidities. In addition, the current real-world data is confirmatory in nature, expanding on previous findings in clinical trials of higher rates of non-CVD events among patients with HF with preserved ejection fraction.[10] Our study had several limitations, including being a retrospective study that included only hospitalizations at one center. In addition, we did not evaluate clinical outcomes (such as other major adverse cardiac events) or guideline-directed medical therapy prescription patterns. The current study features high hospitalization rates in patients with CRS and provides insight into outcomes at a busy Middle Eastern HF Clinic with high comorbidity burden and can be used for quality assurance and health policy development. Future multicenter studies are warranted to further explore variations in admission triggers among patients with CRS.

ORCID iDs
Yosef Manla
https://orcid.org/0000-0003-3096-1067
Obada Kholoki
https://orcid.org/0000-0002-3835-7676
Nizar Attallah
https://orcid.org/0000-0002-1862-4415
Feras Bader
https://orcid.org/0009-0003-4384-2670

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
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REFERENCES

1. Bansal N, Zelnick L, Bhat Z, et al. Burden and outcomes of heart failure hospitalizations in adults with chronic kidney disease. J Am Coll Cardiol 2019;73:2691-700. PUBMED | CROSSREF
2. Bader FM, Attallah N. Insights into cardiorenal interactions in acute decompensated heart failure. Curr Opin Cardiol 2017;32:203-8. PUBMED | CROSSREF
3. Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. Eur Heart J 2022;43:416-26. PUBMED | CROSSREF
4. Docherty KF, Bayes-Genis A, Butler J, et al. The four pillars of HFrEF therapy: is it time to treat heart failure regardless of ejection fraction? Eur Heart J Suppl 2022;24:L10-9. PUBMED | CROSSREF
5. Introductory Guide MedDRA Version 21.0. Notice to Reader MedDRA ICH MedDRA Management Committee; 2018.
6. Bader F, Manla Y, Ghalib H, Al Matrooshi N, Khaliel F, Skouri HN. Advanced heart failure therapies in the Eastern Mediterranean Region: current status, challenges, and future directions. Curr Probl Cardiol 2024;49:102564. PUBMED | CROSSREF
7. Malekpour MR, Abbasi-Kangevari M, Ghamari SH, et al. The burden of metabolic risk factors in North Africa and the Middle East, 1990-2019: findings from the Global Burden of Disease Study. EClinicalMedicine 2023;60:102022. PUBMED | CROSSREF
8. Manla Y, Kholoki O, Bader F, et al. The prevalence of cardiorenal anemia syndrome among patients with heart failure and its association with all-cause hospitalizations: a retrospective single-center study from the Middle East. Front Cardiovasc Med 2023;10:1244275. PUBMED | CROSSREF
9. Cotter G, Davison BA, Lam CS, et al. Acute heart failure is a malignant process: but we can induce remission. J Am Heart Assoc 2023;12:e031745. PUBMED | CROSSREF
10. Santas E, Llácer P, Palau P, et al. Noncardiovascular morbidity and mortality across left ventricular ejection fraction categories following hospitalization for heart failure. Rev Esp Cardiol (Engl Ed) 2024;77:206-14. PUBMED | CROSSREF