EDITORIAL

Heart failure and mid-range ejection fraction and its relation to acute kidney injury and chronic kidney disease

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Heart failure (HF) is a significant and growing public health concern. Renal impairment on admission in patients with HF is freqent, present in approximately half of the population, and associated with high mortality.[1] Acute decompensated HF is a common reason for hospitalization and is associated with a high risk of acute kidney injury (AKI). The interaction of cardiac and renal dysfunction is well known as cardiorenal syndrome, and early identification of patients at risk for this condition is important. AKI is a prevalent syndrome with up to 8-fold higher mortality, a heavy burden of illness, increased length of hospital stay, and a high cost in hospitalized patients.[1]

The 2016 European Society of Cardiology guidelines for HF highlighted that more attention should be paid to patients with HF with mid-range ejection fraction (HFmrEF; left ventricular ejection fraction [LVEF], 40%–49%),[2] in whom the cumulative prevalence ranges from 10% to 20%[3] and the incidence of AKI is higher than in HF with severely reduced ejection fraction (HFrEF).[4] HFrEF (LVEF <40%) is a known risk factor for contrast-induced AKI (CI-AKI).[5] Furthermore, recent studies indicated that the incidence of CI-AKI in patients with LVEF of 40% or higher is 5.2% to 7.8%, ranging up to 12.0% in a subgroup with chronic kidney disease (CKD).[5] However, these studies included patients with unselected cardiac function, and it is well established that the incidence of renal insufficiency and other adverse events is higher in patients with HF than in those without HF.[5] In contrast, patients with HFmrEF may receive less attention than those with HFrEF, despite typically being older and thus more likely to have comorbidities associated with an increased risk for CI-AKI, such as hypertension, diabetes, anemia, and renal insufficiency.[6]

The serum creatinine level has a poor predictive accuracy and is a relatively late marker for renal injury; thus, identification of an early and simple biomarker for CI-AKI risk is essential, particularly for patients with HFmrEF.

In a study of Lala et al,[7] the incidence of CI-AKI was 12.1% in all patients and 19.3% in patients with CKD, which is consistent with the higher risk associated with HFmrEF. In all HF populations, an estimated half of the patients have been categorized as having diastolic HF (DHF). Arora et al[8] studied a cohort derived from the National Readmission Database 2013 to 2014, a subset of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. DHF was identified using *International Classification of Diseases, 9th Revision* (*ICD-9*) code 428.3× in the primary diagnosis field. Readmission etiologies were identified by *ICD-9* code 428.3× in the primary diagnosis field. In total, 19 394 patients with DHF were included, of which 40 927 patients (21.27%) were readmitted, with a total readmission number of 47 056 within 30 days. AKI was implicated, together with acute HF and infections, with higher rates of readmissions.

On the other hand, AKI frequently complicates hospitalizations and its incidence has been increasing over time. AKI contributes to the development and progression of CKD and excess mortality. Within a large, diverse community-based population of hospitalized adults, AKI was associated with significantly higher rates of cardiovascular events during the first 365 days after hospital discharge, even after adjustment for a wide range of characteristics, measures of acute severity of illness, predicted short-term mortality, and differences in medical therapy.[9] This excess risk was driven by HF events, as AKI was not significantly associated with atherosclerotic events after accounting for potential confounders. A retrospective cohort study included 12 493 consecutive patients admitted to

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Received: December 09, 2018.
Revision accepted: December 10, 2018.
Published online: December 21, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (12): 716-718
doi:10.20452/pamw.4401

the hospital over 12 months.[10] The authors investigated the patients who had a small creatinine increase between 1.2- and <1.5-fold the admission value and tested the association of creatinine changes with the prevalence of cardiovascular disease. Among patients with 2 or more creatinine measurements, 14.9% showed a small creatinine increase. It was detected in 36%, 26.6%, and 18.9% of patients with chronic HF, chronic ischemic heart disease, and acute myocardial infarction (MI), respectively. The mean (SD) follow-up was 26.7 (10.6) months with 770 all-cause deaths. An increase in serum creatinine levels above 20% was associated with a higher mortality compared with changes below 20% (adjusted hazard ratio, 1.577; P <0.001).

Lala et al[7] evaluated 365 health records of patients with a primary diagnosis of acute decompensated HF with HF with preserved ejection fraction (HFpEF; ≥50%), HFmrEF (40%–49%), and HFrEF (<40%). They also assessed the incidence of AKI according to Kidney Disease: Improving Global Outcomes criteria and its relation to in-hospital mortality. They found that AKI-associated in-hospital mortality odds ratios for the HFmrEF and HFrEF groups were high and significant. In addition, the authors stressed that AKI was significantly associated with higher risk of mortality in patients with HFmrEF when compared with those with HFrEF. In-hospital mortality in their study was 11%. It should be stressed that the prevalence of CKD in their population was relatively high, even in the non–AKI group, reaching 65% in the HFmrEF group with AKI. It would be also valuable to provide data on the pathogenesis of HF in studied population, namely, ischemic heart disease, valvular disease, or cardiomyopathy. But it appears that the sample size would be too small to allow such an analysis. As patients were admitted to the hospital between July 2012 and December 2016, it would also be interesting to assess the long-term mortality, and not only in-hospital mortality.

While it is feasible to assess mortality based on a national registry of deaths, it might not be possible to obtain data on the cause of death. Hertzberg et al[11] reported that HF was a risk factor for postoperative AKI in patients who underwent coronary artery bypass grafting. Among patients with HF, a severely reduced EF was associated with AKI compared with patients with preserved EF. The same group assessed a possible relation between the presence of chest pain in patients admitted to the emergency department and AKI status at arrival. They also focused on the most common discharge diagnoses and on long-term mortality. Hertzberg et al[12] found that AKI patients were more likely to be diagnosed with HF and had an increased long-term mortality compared with patients with no AKI. In a study of Kanic et al[13] in 5859 patients with MI undergoing percutaneous coronary intervention, AKI was documented in 499 patients (8.5%). Patients with AKI had a higher long-term mortality (57.3% vs 20.6%; P <0.0001). All-cause mortality was assessed over a mean (SD) follow-up of 4.2 (3.0) years up to January 1, 2018. HF, renal dysfunction, and other factors (eg, diabetes, age, ST-segment elevation MI) were associated with the development of AKI. Mathew et al[14] evaluated 8480 patients with acute MI, of whom 476 (5.6%) had AKI. AKI patients were older and had more comorbidities, including HF. AKI was associated with long-term mortality during a median follow-up of 3.2 years (37% vs 16%). Guisado-Espartero et al[15] studied prospectively 2753 patients admitted with HF to an internal medicine unit; 10.2% of patients had HFmrEF. They were more likely to be men and to have a history of CKD, and higher levels of N-terminal pro-B-type natriuretic peptide than those with HFpEF. However, 1-year mortality in patients with HFmrEF and HFpEF was similar (20% and 22%, respectively), but it was lower than in patients with HFrEF (28%, P <0.001). Similarly, in the BIOSTAT-CHF trial (BIOlogy Study to TAilored Treatment in Chronic Heart Failure),[16] the most prevalent comorbidity was CKD (50%). However, only in HFpEF, the presence of CKD, anemia, and COPD was associated with higher mortality risks. In the Swedish Heart Failure Registry, CKD was more common in HFpEF than in HFmrEF and HFrEF; however, in HFpEF, the presence of CKD was less associated with mortality and had lower prognostic discrimination.[17]

In conclusion, the added value of the study by Lala et al[9] is that they show the association between AKI and higher risk of death in patients with HFmrEF in comparison with those with HFrEF. HFmrEF, as an emerging category, seems to have distinct characteristics, including a stronger AKI impact on, at least, in-hospital outcomes. However, the association between AKI and HFmrEF should be proved to be causal. The presence of AKI in this population may be related to different effects of aberrations in inflammatory parameters, endothelial dysfunction, and other pathways, as well as to possible differences in therapy (eg, use or dosage of renin–angiotensin system inhibitors or diuretics).

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REFERENCES

1 Palmer JB, Friedman HS, Waltman Johnson K, et al. Association of persistent and transient worsening renal function with mortality risk, readmissions risk, length of stay, and costs in patients hospitalized with acute heart failure. Clinicoecon Outcomes Res. 2015; 7: 357-367.

2 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016; 37: 2129-2200.

3 Lam CSP, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail. 2014; 16: 1049-1055.

4 Sweitzer NK, Lopatin M, Yancy CW, et al. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (≥55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. Am J Cardiol. 2008; 101: 1151-1156.

5 Koo HM, Doh FM, Ko KI, et al. Diastolic dysfunction is associated with an increased risk of contrast-induced nephropathy: a retrospective cohort study. BMC Nephrol. 2013; 14: 146.

6 Lam CS, Teng TH. Understanding heart failure with mid-range ejection fraction. JACC Heart Fail. 2016; 4: 473-476.

7 Lala RI, Lungeanu D, Puschita M, et al. Acute kidney injury: a clinical issue in hospitalized patients with heart failure with mid-range ejection fraction. Pol Arch Intern Med. 2018; 128: 746-754.

8 Arora S, Lahewala S, Hassan Virk HU, et al. Etiologies, trends, and predictors of 30-day readmissions in patients with diastolic heart failure. Am J Cardiol. 2017; 120: 616-624.

9 Go AS, Hsu CY, Yang J, et al. Acute kidney injury and risk of heart failure and atherosclerotic events. Clin J Am Soc Nephrol. 2018; 13: 833-841.

10 Losito A, NunziE, Pittavini L, et al. Cardiovascular morbidity and long term mortality associated with in hospital small increases of serum creatinine. J Nephrol. 2018; 31: 71-77.

11 Hertzberg D, Sartipy U, Lund LH, et al. Heart failure and the risk of acute kidney injury in relation to ejection fraction in patients undergoing coronary artery bypass grafting. Int J Cardiol. 2019; 274: 66-70.

12 Hertzberg D, Holzmann MJ, Than M, Pickering JW. Acute kidney injury in patients presenting with chest pain to the emergency department, a descriptive study of the most common discharge diagnoses and mortality. Eur J Emerg Med. 2018 Jun 6. [Epub ahead of print].

13 Kanic V, Kompara G, Suran D, et al. Impact of KDIGO-Defined acute kidney injury on mortality after percutaneous coronary intervention for acute myocardial infarction. Cardiorenal Med. 2018; 8: 332-339.

14 Mathew RO, Rangaswami J, Othersen JB, et al. Community acute kidney injury is associated with short- and long-term adverse outcomes in patients admitted with acute myocardial infarction. Clin Nephrol. 2018; 90: 404-412.

15 Guisado-Espartero ME, Salamanca-Bautista P, Aramburu-Bodas Ó, et al. RICA investigators group. Heart failure with mid-range ejection fraction in patients admitted to internal medicine departments: Findings from the RICA Registry. Int J Cardiol. 2018; 255: 124-128.

16 Streng KW, Nauta JF, Hillege HL, et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. Int J Cardiol. 2018; 271: 132-139.

17 Löfman I, Szummer K, Dahlström U, et al. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017; 19: 1606-1614.