

Acute heart failure (HF) is a leading cause of hospitalization, particularly in elderly people, and has an unacceptably dismal prognosis. The occurrence of acute kidney injury in the setting of a HF decompensation [type 1 cardio-renal syndrome (CRS)] has been suggested to be one of the most powerful determinants of outcome, and its recognition is essential to develop strategies aimed at improving our current treatment options and the outcomes of this population. Glomerular filtration rate (GFR) is the most useful index of kidney function, and changes in serum creatinine have generally been used clinically as surrogates for changes in GFR. Creatinine levels are influenced by several factors, and have low sensitivity to detect small decreases in GFR and a long delay period in achieving steady state. These characteristics make it an unreliable measure for accurate and timely diagnosis of kidney damage, and even for kidney dysfunction. Recent research has moved the focus towards potentially better and more sensitive biomarkers of kidney damage and function. Neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C are two promising renal biomarkers.

NGAL is an early marker of renal tubular damage that predicts the development of acute kidney injury in several settings, including acute HF. NGAL also revealed to have a prognostic role, but this has not been addressed in the HF population. Cystatin C is mainly a marker of renal function, but more sensitive and earlier than serum creatinine, and several cystatin C-based equations estimating GFR have been proposed. In comparison to serum creatinine and creatinine-based GFR estimating equations, serum cystatin C and cystatin C-based equations are similarly good markers of prognosis stratification in HF populations.

We aimed to explore the role of NGAL and cystatin C in diagnostic and prognostic assessment of acute renal injury in acute HF patients, addressing their performance in the early detection of type 1 CRS and their role in the short-term prognostic stratification in these patients. We also assessed the discrimination and predictive value of cystatin C- and creatinine-based GFR estimating equations, as well as a combined cystatin C- and creatinine-based eGFR equation, in predicting medium-term prognosis in acute HF patients, and, additionally, determined the possible added value of cystatin C in risk stratification in this population, compared to creatinine-based estimated GFR alone.

In our real world elderly acute HF population, a single NGAL measurement, at the first hospitalization morning, could identify all patients developing type 1 CRS within 48 to 72 hours with a 50% false positive rate and an area under the curve 0.93. No patient with <170 ng/mL first-morning NGAL developed type 1 CRS, and half of the patients with a first-morning value >170 ng/mL developed type 1 CRS. We concluded that serum NGAL anticipated the development of type 1 CRS, and therefore can help clinicians in the early recognition of patients developing very short-term renal deterioration. Serum NGAL levels at hospital admission were independently associated with short-term adverse outcomes, with levels above 167.5 ng/mL predicting a 2.7-fold increase in the risk of death from all

causes and a 2.9-fold increase in the risk of the first occurrence of either death or hospitalization. These results suggest a prognostic role of renal damage, besides that of renal function, upon the beginning of acute HF episodes. Additionally, we observed that renal function, measured at hospital discharge, is a major factor affecting medium-term adverse outcomes in acute HF, with the risk of 6-month death increasing progressively across categories of estimated GFR for all estimating equations used. In patients with normal renal function or with severe renal dysfunction, creatinine-based methods for estimating GFR, particularly the Cockcroft-Gault equation, were accurate predictors of prognosis. However, in patients with estimated GFR 30-59 mL/min/1.73 m<sup>2</sup> according to the Cockcroft-Gault equation, who had a 6-month risk of death of 17.5%, the combination of a creatinine-based and a cystatin C-based estimates of GFR augmented the discrimination. In these patients, the Chronic Kidney Disease Epidemiology Collaboration cystatin C equation (CKD-EPICysC) could redefine subgroups of patients with different outcomes, with those with a redefined estimated GFR <30 mL/min/1.73 m<sup>2</sup> having a significantly worse prognosis, expressed by a 6-month risk of death of 31.4%. In this group of patients, the Net Reclassification Improvement (NRI) values indicated an expressive improvement in risk classification (46%) after addition of the CKD-EPICysC equation to the Cockcroft-Gault equation. In conclusion, in patients with moderate renal dysfunction, cystatin C-based estimation of GFR proved to add prognostic value to creatinine-based estimates of GFR alone, thus refining the prognostic exercise of clinicians.