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EDITORIAL COMMENT

The role of comorbidities in acute heart failure outcomes

O papel das comorbilidades na insuficiência cardíaca aguda

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Acute heart failure (AHF) is defined as new or worsening (decompensated HF (ADHF)) signs and symptoms of HF. ADHF is more frequent than de novo heart failure (HF) and is associated with worse long-term prognosis.[1]

The pathophysiology of AHF is still not fully understood and the clinical approach is challenging. In contrast to the significant improvement seen in the last decade in chronic HF treatment, the same is not true of AHF. This is a major issue as AHF is a main cause of hospitalizations in patients >65 years old and is associated with a high risk of in-hospital mortality, readmissions and long-term mortality.[2]

Patients' non-cardiovascular comorbidities have an important role in AHF management and a significant impact on AHF outcomes, as highlighted in the current issue. Marques et al. studied the outcomes in a cohort of 429 AHF patients included in the PRECIC study. In their research, the authors analyzed several comorbidity variables and concluded that besides elderly patients, higher urea, active cancer and red cell distribution width (RDW) and lower platelet distribution width (PDW) were predictors of one-year mortality.[3]

Chronic kidney disease (CKD) is present in approximately one third of HF patients. CKD and HF share common risk factors (e.g., hypertension, diabetes). In an acute setting, HF may lead to acute kidney injury (AKI) through the effects of neurohormonal and inflammatory activation, increased venous pressure and hypoperfusion (cardiorenal syndrome type 1). On the other hand, acute or worsening renal disease may cause hypertension and fluid retention leading to AHF (cardiorenal syndrome type 3).[4]

Chronic kidney disease or AKI have been increasingly recognized as major determinants of mortality in patients hospitalized due to AHF.[5,6] Although serum creatinine level is used as a marker of renal function, recent data from sodium-glucose co-transporter 2 (SGLT-2) inhibitors trials and diuretic studies in AHF showed that small and transient increases in serum creatinine during a treatment AHF was not associated with worse prognosis.[7,8] The limitation of serum creatinine in the assessment of renal function should promote the addition of other biomarkers to monitor renal function. Blood urea nitrogen (BUN) is easily assessed and reflected glomerular filtration, tubular reabsorption, and neurohormonal activation.[9] Neurohormonal activation led to a disproportional reabsorption of BUN in comparison with creatinine. Both the BUN and the BUN to creatinine ratio have been associated with an increased risk of adverse outcomes. Furthermore, the urine BUN to creatinine ratio predicted diuretic efficiency.[10]

Marques et al. showed that higher BUN was an independent predictor of one-year mortality in AHF patients (odds ratio (OR) 2.97, 95% confidence interval (CI) 1.84–4.80).

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Similarly, Fillipatos et al.,[11] after adjustment for covariates, demonstrated that BUN was a statistically significant predictor of both mortality and the composite endpoint of death or HF hospitalization at 60 days after hospital discharge. Their data revealed that even mildly elevated BUN may be predictive of worse outcome in patients with AHF. These findings emphasize the importance of BUN in AHF patients, together with creatinine levels. Indeed, several scores including BUN were developed to predict in-hospital and long-term mortality of AHF patients, such as ELAN-HF Scores.[12]

Active malignancies and their therapies can precipitate an AHF episode. For instance, AHF can be the first presentation of a pheochromocytoma with catecholamine-induced myocardial dysfunction or a carcinoid syndrome in a neuroendocrine tumor. On the other hand, several antineoplastic agents are associated with acute cardiac dysfunction, in form of acute toxicity (e.g., anthracyclines, HER-2 targeted therapies), toxic myocarditis (anthracyclines, cyclophosphamide, antimetabolites), immune-mediated myocarditis (IL-2, ICIs) or Takotsubo syndrome (5-FU, capecitabine, rituximab, trastuzumab). Finally, AHF can occur in the context of cardiac tumour invasion or in paraneoplastic syndrome (e.g., pericardial tamponade).[13]

Cardiovascular disease (CVD) in oncologic patients has been associated with higher all-cause mortality than CVD alone.[14] In a PRECIC study sub-analysis, active cancer was associated with a higher risk of one-year mortality in hospitalized patients due to AHF (OR 2.70, 95% CI 1.03–7.01). It would have been interesting if the patients' age at cancer diagnosis and time elapsed from diagnosis to hospitalization due to AHF had been considered. Indeed, younger age of diagnosis was associated with higher mortality. Likewise, the first year of disease diagnosis has been correlated with having the greatest risk for CVD mortality, which may be explained by the aggressive treatment shortly after disease detection.[14] Conversely, several complications of cancer or antineoplastic therapy, such as anemia and thrombocytopenia, may modify the management of CVD, particularly in an acute setting (e.g., invasive treatment in acute myocardial infarction) with implications for prognosis.

The findings in the current issue are very important considering the aging population in which cancer diagnosis may be more frequent. The AHF approach in oncologic patients should follow the usual recommendations with rapid recognition and treatment of potential reversible causes and triggers that can be related to malignancy. It is advised to withheld cancer therapy until the patient is stabilized and the next steps should be defined by a multidisciplinary team in a decision-making process shared with patient.[13] Patient prognosis related to cancer is an important concern for AHF treatment, especially if advanced HF therapies are required.

Frailty is a prevalent comorbidity in HF patients. It is associated with higher mortality, hospitalizations, and longer hospital stays.[15] Cognitive impairment and dementia could be also present in HF patients. Although dementia is associated with higher risk of death,[15] its impact on management and prognosis in AHF patients remains unclear. In the present issue, Marques et al. found dementia was an independent predictor of one-year mortality in AHF patients. This result needs to be confirmed in future studies.

With regard to laboratory measurements at admission, Marques et al. showed that higher RDW, a measure of anisocytosis, was a predictor of one-year mortality in AHF patients. In 2007, Felker et al. demonstrated that increased RDW was associated with higher mortality in two large chronic HF populations.[16] More recently, in a cohort of 9445 critically ill patients with HF, Zhang et al. concluded that higher RDW was associated with both in-hospital mortality and 90-day mortality after adjustment for other covariates.[17] Hence, RDW seems to be a prognostic marker in both chronic and acute settings. Besides HF, CKD, anemia, inflammatory-related disorders such as infection and cancer are associated with higher RDW. However, the specific mechanistic links between RDW and poor prognosis have not yet been fully understood. Multiple interlinked pathophysiologic mechanisms, including oxidative stress, enhanced immune system activation, inflammation, abnormal body iron distribution and malnutrition, are thought to be related to an increase in RDW and associated worse outcomes in patients with HF,[18] but more studies are needed to understand this correlation.

Besides the substantial impact of the results presented by Marques et al., a few limitations need to be addressed. It would be important to analyze how many patients had de novo or ADHF, since the latter was associated with worse long-term prognosis as referenced before. Moreover, echocardiography findings were not included in approximately 30 patients. Considering the importance of ejection fraction (EF) in the HF prognosis, it could be important to conduct a sub-analysis using only patients with EF quantification to confirm the data.

On the other hand, 30% of patients in the cohort studied had HF with reduced EF (EF <40%), in whom there is an indication for angiotensin-converting enzyme inhibitors/angiotensin receptor-neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists and SGLT-2 inhibitors to improve prognosis. However, this aspect was not included in the current mortality study. Likewise, information about implantable cardiac devices, such implantable cardioverter-defibrillator and cardiac resynchronization therapy were not analyzed despite their acknowledged effect on the survival of HF patients.

Finally, the severity of the baseline comorbidities was not integrated as mentioned by the authors, which could have influenced the all-cause mortality of those patients. For instance, stage of cancer, disease type and the response to treatment can affect one-year survival and therefore could eventually change the results presented.

Despite these limitations, the study by Marques et al. represents a very important step toward establishing the role of comorbidities in AHF outcomes, which is crucial to improve patient management. The recognition of the importance of each comorbidity in prognosis can help the risk stratification of AHF at admission. It can assist not only in the decision regarding immediate hospitalization or discharge from the emergency department and the level of acuity of care (standard nursery or intensive care unit), as well as in outlining a long-term follow-up strategy.

Conflicts of interest

The author has no conflicts of interest to declare.

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