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Editorial

Relative hypochromia in acute heart failure to predict outcome and guide treatment: Ready for prime time?

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Iron is a micronutrient necessary for erythropoietic function, oxidative metabolism and immune responses [1]. Increased iron requirements, limited iron intake, increased blood loss, and iron sequestration due to chronic inflammation may all result in iron deficiency (ID) [1]. ID is common in patients with stable HF, and is associated with worse clinical status and outcome [1]. Intravenous iron therapy improves functional capacity and quality of life and reduces the rates of hospitalization for worsening HF, although its impact on mortality is still undefined [2,3]. Based on these results, the European Society of Cardiology (ESC) Guidelines have issued a class IIa, level A recommendation for intravenous iron in symptomatic HF patients with ID, defined as serum ferritin <100 μg/L (reflecting absolute ID), or ferritin between 100 and 299 μg/L and transferrin saturation <20% (denoting functional ID, i.e. iron sequestration within tissues) [4].

When using the same criteria, the prevalence of ID in acute HF (AHF) is 69% in men and 75% in women [5]. In another study, severe ID, defined as serum hepcidin <14.5 ng/mL (demonstrating depleted body iron stores) plus soluble transferrin receptor ≥1.59 mg/L (reflecting increased cellular avidity for iron), was found in 37% of patients, while a preserved iron status was found only in 25%. Patients with severe ID displayed lower hemoglobin levels and greater congestion, as reflected by higher N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP) and greater prevalence of peripheral edema. They showed also greater in-hospital and 12-month mortality, even when considering separately anemic and non-anemic patients [6]. Moreover, some promising findings on the safety and efficacy of intravenous iron therapy have been reported in a pilot study on Southeast Asian patients [7]. The Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency (Affirm-AHF) is an ongoing randomized, double-blind, placebo-controlled trial assessing the efficacy of iron replacement therapy in patients with AHF and ID (defined according to the ESC criteria) (ClinicalTrials.gov Identifier: NCT02937454).

Despite these premises, assessment of iron status in HF is not widely performed in routine clinical practice. Among the possible reasons there are multiple diagnostic criteria for ID and the need for dedicated exams that may not be feasible in smaller hospitals. Relative hypochromia of erythrocytes, corresponding to decreased mean corpuscular hemoglobin concentration (MCHC), is a commonly available parameter and might represent a surrogate of these indicators. The relationship between MCHC and iron status [8], and the clinical and prognostic correlates of reduced MCHC [9] have been explored in chronic HF, whereas no evidence is currently available in the acute setting.

In this issue of the Journal, Kleber, Kozhuharov and Colleagues provide an analysis of the prospective, international study Basics in Acute Shortness of Breath EvaLuation (BASEL V) aiming to clarify the meaning of relative hypochromia in AHF [10]. Relative hypochromia was defined as MCHC ≤330 mg/L, and was determined at presentation to the emergency department. Out of 1574 patients, 455 (29%) displayed relative hypochromia, and a greater percentage of patients (n = 712, 45%) were anemic. Patients with relative hypochromia had higher NT-proBNP and high-sensitivity troponin T, denoting greater cardiac damage, and worse renal function, as demonstrated by lower estimated glomerular filtration rate (eGFR). Over 720 days, patients with relative hypochromia had higher rates of all-cause mortality, as well as of the composite endpoints "all-cause death or AHF rehospitalization" and "all-cause death or all-cause rehospitalization". Relative hypochromia showed an independent prognostic value after adjustment for established predictors of outcome in HF, namely age, sex, body mass index, eGFR, hemoglobin at admission, and NT-proBNP.

While these results add to our knowledge on ID in AHF, some points deserve consideration. An intriguing finding of this study is the relatively low prevalence (29%) of relative hypochromia, compared with the much higher (up to 70%) prevalence of ID estimated in a previous

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study assessing serum ferritin and transferrin saturation [5]. A possible explanation of these findings is that low MCHC is a later consequence of ID than decrease in usual plasma biomarkers. Unfortunately, this paper did not evaluate direct indicators of the iron status, so the strength of the association between reduced MCHC and ID cannot be evaluated. Furthermore, although no formal definition of relative hypochromia exists [8], the MCHC cut-off arbitrarily proposed by the Authors (330 g/L) falls within the normal range of MCHC (310–370 g/L) and was not validated against indicators of iron status, in particular with ferritin level; the 335 g/L best cut-off calculated by the Authors may be better suited for this purpose. The evaluation of the prognostic significance of relative hypochromia could have been usefully integrated by data on cardiovascular mortality and outcome measures at specific time-points, such as HF hospitalization at 30 days, which is critically important and particularly hard to predict.

Despite these limitations, this paper conveys the important message that a commonly available parameter such as MCHC, associated with ID, refines prognostic stratification in AHF, and could assist in the decision-making for iron replacement therapy. This last point warrants verification in future studies.

Conflict of interest

None.

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