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Scientific letters

Iron deficiency testing in acute heart failure. Much to do

Determinación del déficit de hierro en insuficiencia cardiaca aguda. Mucho por hacer

To the Editor:

Iron deficiency (ID) is described in approximately half of the patients with stable chronic heart failure (HF),[1] and up to 80% of patients admitted with acute HF (AHF).[1,2] ID is responsible for reduced exercise tolerance, affects quality of life and results in higher rates of hospitalizations and death in HF patients.[3] Therefore, is a well-recognized therapeutic target in patients with ID and stable HF.[4] Current HF-guidelines recommend ID testing in newly diagnosed HF and during outpatients monitoring.[4] However, there is not a specific recommendation in AHF.[4]

The recent AFFIRM-AHF trial showed that intravenous iron supplementation in patients with ID and left ventricular ejection fraction (LVEF) <50% stabilized after an episode of AHF reduced the risk of HF-hospitalizations.[5]

In this study, we aimed to evaluate the frequency, evolution over the years, and clinical factors associated with ID testing in patients with AHF.

This is a consecutive retrospective multicenter study conducted from 1 September 2014, to 1 September 2019, that included 3555 patients admitted for AHF in 3 third-level hospitals in Spain. By design, patients with acute coronary syndrome or intravenous iron therapy were excluded. Information related to demography, medical history, vital parameters, 12-lead electrocardiogram, standard laboratory tests (including ferritin and transferrin saturation), echocardiographic parameters, and pharmacological therapies was recorded. Anemia was defined as a hemoglobin level <12 g/dL in women and <13 g/dL in men. ID was defined as ferritin <100 μg/L and/or transferrin saturation <20% if ferritin 100–299 μg/L.[4] This study conformed to the principles outlined in the Declaration of Helsinki and was approved by an institutional review committee [*Comité Ético de Investigación Clínica, Fundación Investigación del Hospital Clínico Universitario de Valencia* (INCLIVA)].

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) when appropriate. Discrete variables were summarized as percentages. Logistic regression was used to analyze the factors associated with ID assessment. A final model was derived by using backward stepwise selection. The linearity assumption for all continuous variables was simultaneously tested, and the variable transformed, if appropriate, with fractional polynomials. R^2 evaluated the contribution of the covariates to the variability of the model.

Covariates included in the final multivariate model were age, gender, history of myocardial infarction, chronic renal failure, first admission for AHF, admission center, calendar year of admission, peripheral edema, heart rate, hemoglobin, estimated glomerular filtration rate, serum sodium, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and LVEF. The discriminative ability of the multivariate model evaluated by the area under the receiving operating curve was 0.705.

The mean age was 74.6 ± 11.0, 1610 (45.2%) patients were women, 1628 (45.8%) showed LVEF < 50%, and 1812 (51.0%) showed anemia. Measurement of ferritin and transferrin saturation was performed in 1700 (47.8%) patients. Isolated ferritin and transferrin saturation measurements were performed in 2402 (67.6%) and 1700 (47.8%) patients, respectively. Baseline characteristics across ID evaluation are shown in Table 1. Overall, ID assessment was more frequent in younger, diabetic patients, those without prior AHF admissions, higher heart rate and lower diastolic blood pressure, those with LVEF < 50%, and in more congestive patients (pleural effusion, peripheral edema, New York Heart Association class III–IV before admission, and lower serum sodium values). Among those with ID assessment, ID was found in 1246 (73.3%) patients,

Table 1 – Baseline characteristics across ID testing.

Variables	All (*n* = 3555)	No ID assessment[c] (*n* = 1855)	ID assessment[c] (*n* = 1700)	P
Demographics and medical history				
Age, years	74.6 ± 11.0	75.1 ± 11.1	74.1 ± 10.9	.011
Gender (male), *n* (%)	1945 (54.7)	991 (53.2)	954 (56.1)	.107
Hypertension, *n* (%)	2849 (80.1)	1505 (81.1)	1344 (79.1)	.122
Diabetes mellitus, *n* (%)	1573 (44.2)	781 (42.1)	792 (46.6)	.007
Dyslipidemia, *n* (%)	1966 (55.3)	1000 (53.1)	966 (56.8)	.081
Smoker, *n* (%)	420 (11.8)	204 (11.0)	216 (12.7)	.115
Prior smoker, *n* (%)	1071 (30.2)	546 (29.5)	525 (30.9)	.363
IHD, *n* (%)	1123 (31.6)	606 (32.7)	517 (30.4)	.148
Valve heart disease, *n* (%)	1295 (36.4)	663 (35.7)	632 (37.2)	.374
First admission for AHF, *n* (%)	2486 (69.9)	1121 (60.4)	1365 (80.3)	<.001
Charlson index, points	2 (1–4)	2 (1–4)	2 (1–4)	.140
Pleural effusion, *n* (%)	1750 (49.2)	877 (47.3)	873 (51.3)	.015
Peripheral edema, *n* (%)	2260 (63.6)	1122 (60.5)	1138 (66.9)	<.001
Vital signs				
Heart rate, bpm	94 ± 27	92 ± 27	97 ± 27	<.001
SBP, mmHg	141 ± 29	141 ± 29	141 ± 29	.848
DBP, mmHg	79 ± 18	78 ± 18	80 ± 19	.001
Electrocardiogram				
Atrial fibrillation, *n* (%)	1674 (47.1)	845 (45.5)	829 (48.8)	.055
BBB, *n* (%)	1171 (32.9)	614 (33.1)	557 (32.8)	.832
Echocardiography				
LVEF, %	49.4 ± 15.2	50.6 ± 15.3	48.2 ± 15.1	<.001
LVEF < 50%, *n* (%)	1628 (45.8)	808 (43.6)	820 (48.2)	.005
LAD, mm	44.5 ± 7.5	44.5 ± 7.6	44.5 ± 7.4	.981
PASP, mmHg[a,b]	43 (35–52)	44 (35–54)	42 (34–51)	.011
Laboratory data				
Hemoglobin, g/dL	12.4 ± 2.0	12.4 ± 2.0	12.3 ± 2.0	.342
Hematocrit, %	38.8 ± 6.2	39.0 ± 6.0	38.7 ± 6.2	.553
Anemia (WHO criteria), *n* (%)	1812 (51.0)	937 (50.5)	875 (51.5)	.568
Creatinine, mg/dL	1.27 ± 0.70	1.28 ± 0.74	1.27 ± 0.66	.569
eGFR (MDRD formula), mL/min/1.73 m^2	63.6 ± 28.2	62.7 ± 26.9	64.7 ± 29.5	.032
Serum sodium, mEq/L	138 ± 4	139 ± 4	138 ± 4	<.001
Serum potassium, mEq/L	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	.115
NT-proBNP, pg/mL[a]	3917 (1920–8292)	3772 (1937–7807)	4065 (1900–8758)	.077

AHF, acute heart failure; BBB, bundle branch block; CA125, carbohydrate antigen 125; DBP: diastolic blood pressure; eGFR, estimated glomerular filtration rate; ID, iron deficiency; IHD, ischemic heart disease; LAD, left atrial diameter; MDRD, modification of diet in renal disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TSAT, transferrin saturation; WHO, World Heart Organization.
Values for continuous variables are expressed as mean ± standard deviation.

[a] Values expressed as mean (interquartile range).

[b] Data available in 2098 patients.

[c] Iron deficiency defined as serum ferritin <100 μg/L (absolute iron deficiency) or ferritin 100–299 and TSAT < 20% (functional iron deficiency).

without differences between LVEF status (71.6% in patients with LVEF < 50% vs 74.9% in those with LVEF ≥ 50%; *P* = .124). The rate of ID testing stepwise increased from 36.2% in 2014 to 54.7% in 2019, *P* < .001.

The 2 most important covariates, explaining 70% of the model variability, were first AHF-admission (R^2, 37.4%; *P* < .001) and calendar year (more recent admissions) (R^2, 33.1%; *P* < .001) (Fig. 1A). Patients with a first admission displayed a three-fold increased probability of ID testing [odds ratio (OR), 3.06; 95% confidence interval (95%CI), 2.60–3.61; *P* < .001].

Other covariates associated with higher odds of ID testing were, in order of importance, lower values of serum sodium (R^2, 10.0%; *P* < .001), admission center (R^2, 4.7%; *P* < .001), peripheral edema (R^2, 4.6%; *P* < .001), heart rate (R^2, 2.4%; *P* < .001), history of myocardial infarction (R^2, 1.8%; *P* = .023), age (R^2, 1.5; *P* = .015), and hemoglobin (R^2, 1.2; *P* = .007) (Fig. 1B–E).

Higher NT-proBNP was independently associated with the odds of ID testing, with a however, marginal contribution to the model's predicatibility (R^2 < 0.01%; *P* = .030) (Fig. 1F). LVEF < 50% (OR, 1.13; 95%CI, 0.97–1.33; *P* = .117) and estimated glomerular filtration rate (OR, 1.03; 95%CI, 0.99–1.06; *P* = .056 per increase in 10 mL/min/1.73 m^2) were not independently associated with ID testing.

In the present study, performed in a representative contemporary cohort of patients with AHF, ID was tested in near 50% of the patients. ID assessment rates increased over the inclusion period, which emerged as the second most important variable, after the absence of a prior admission for AHF. Other

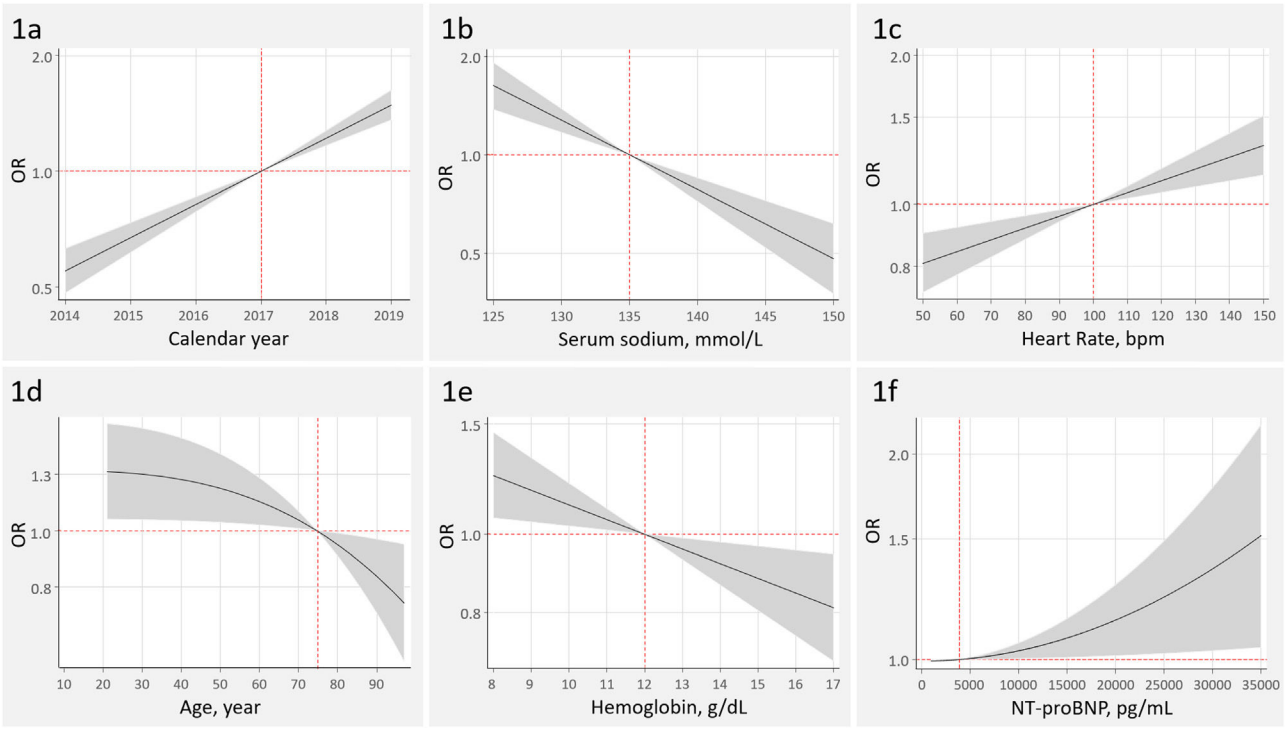

Fig. 1 – The functional form of continuous variables associated with higher odds of iron deficiency assessment. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

factors associated with a higher odds of ID assessment were those related to greater severity of the episode. Of note, NT-proBNP and traditional factors associated with ID, such as lower hemoglobin, renal dysfunction, and left ventricular systolic dysfunction, were marginally or not associated with ID assessment.

Regarding these findings, some issues deserve to be highlighted. First, the most relevant factors associated with the odds of ID testing were the absence of a prior AHF hospitalization, the year of admission (a stepwise increase over the years), and greater signs of congestion. In the absence of specific recommendations, we postulate the increase of the diagnostic/prognostic awareness resulting from these situations may explain these findings. Second, traditional risk factors for ID, left ventricular systolic dysfunction and NT-proBNP values did not emerge as relevant factors. The validation of the present results is endorsed by recent studies showing similar ID rates (about 70%–80% of patients).[1,2]

Some crucial limitations should be acknowledged. This is a retrospective observational in which important unmeasured confounders might be playing a relevant role. Indeed, the model has a limited discriminative capacity, suggesting that many variables have not been taken into account. Furthermore, this study only included three sites in Spain. Thus, the external validation of the present findings needs to be confirmed in contemporary registries.

ID assessment in patients with AHF remains low, despite increasing over the last years. Further HF-guidelines should expressly state a recommendation about ID testing in AHF syndromes.

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Authors' contributions

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Conflicts of interest

None.

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Situación actual de las unidades cardiorrenales en España

Current state of cardiorenal units in Spain

Sr. Editor:

La insuficiencia renal es una de las comorbilidades más prevalentes en los pacientes con insuficiencia cardiaca crónica[1]. Alrededor del 40-50% de los pacientes con insuficiencia cardiaca crónica asocian algún grado de insuficiencia renal[2]. La coexistencia de ambas situaciones dificulta el tratamiento y confiere un peor pronóstico, lo que supone un verdadero reto desde el punto de vista clínico. Partiendo de esta relación bidireccional, durante años se han hecho esfuerzos cada vez mayores para intentar integrar ambas entidades dentro de un espectro clínico común conocido como síndrome cardiorrenal (SCR)[3].

Aunque el interés y las publicaciones sobre esta entidad han evolucionado significativamente en los últimos años[4], el enfoque combinado multidisciplinar del SCR todavía es deficitario en nuestro medio, y la falta de un abordaje integral y coordinado deriva a menudo en estrategias parciales e incluso antagónicas debido a una perspectiva no holística del síndrome cardiorrenal.

La unidad cardiorrenal se define como el conjunto de intervenciones coordinadas y multidisciplinares diseñadas para estabilizar, enlentecer o incluso revertir la progresión del SCR, y surge como modelo asistencial para cubrir estas limitaciones y mejorar la atención y el abordaje clínico integral de los pacientes con SCR.

Con el fin de evaluar la implementación actual y las características de estas unidades en el ámbito hospitalario en España, desde el grupo de trabajo de síndrome cardiorrenal y estrategias de tratamiento de la congestión de la insuficiencia cardiaca, de la Asociación de Insuficiencia Cardiaca de la Sociedad Española de Cardiología (SEC), hemos realizado un estudio observacional descriptivo transversal, cuyo objetivo final es conocer las necesidades asistenciales y áreas de mejora en la atención del paciente con SCR en nuestro territorio. Dado que el objetivo inicial de la encuesta fue evaluar la situación actual del proceso con un fin organizativo, no se consideró evaluación previa por el comité de ética de investigación.

Se diseñó una encuesta que se remitió por correo electrónico a los responsables de las 69 unidades de insuficiencia cardiaca (UIC) acreditadas actualmente por la SEC. La inclusión de toda la información se llevó a cabo en enero y febrero de 2021.

La encuesta constaba de 11 ítems englobados en estos 4 apartados: *a)* nivel tecnológico del hospital; *b)* tipo de UIC (comunitaria, especializada, avanzada)[5]; *c)* características de la unidad (disponibilidad de enfermería y servicios involucrados); y *d)* presencia de: unidad cardiorrenal; protocolos de actuación conjunta cardiología-nefrología-medicina interna; referentes de nefrología para pacientes con IC; y diálisis peritoneal para tratamiento de la congestión refractaria. De las 69 unidades de IC consultadas, 59 (85%) respondieron a la encuesta (fig. 1).

En función del nivel tecnológico, se incluyeron 38 hospitales de tercer nivel (64%), 16 de segundo nivel (27%) y 5 de primer nivel (9%). Respecto al tipo de unidad, el 59% de los hospitales cuenta con una UIC especializada, el 27% son unidades de IC avanzada y el 14% UIC comunitaria. La orga-