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Research Article

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Ferritin and Prognosis in Elderly Patients with Heart Failure and Preserved Ejection Fraction

Jose Angel Satue Bartolome*, Pérez Martin Alejandro, Nieto Sandoval Barbara, Marrero Frances Jorge, Gonzalo Pascua Sonia, Belinchon Paraiso, Juan Carlos San Martin Prado Alberto, Bermejo-Rodriguez Alfredo, Gutierrez-Landaluce Carlos and Zapatero-Gaviria Antonio

Internal Medicine Service, University Hospital of Fuenlabrada, Fuenlabrada, Spain

***Corresponding author:** Dr. Satué Bartolomé José Angel, Comprehensive Management of the Patient with Heart Failure Unit (UMIPIC), Senior Specialist, Internal Medicine Service, University Hospital of Fuenlabrada, Fuenlabrada, Spain, Tel: 6006178/4529; E-mail: joseangel.satue@salud.madrid.org

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Abstract

Background: Iron deficiency (ID) and anaemia are frequent in Heart Failure (HF) patients, but there are few data about its prevalence and prognosis in elderly HF patients with preserved ejection fraction (HF-PEF).

Aim: The aim of this study is to ascertain if ID alone or associated with anaemia is related to negative clinical outcomes in elderly patients with HF-PEF.

Design/Methods: 139 consecutive patients discharged from our Internal Medicine Department with a diagnosis of HF-PEF from June 2011 to June 2014 were followed up until June 2015. All demographic and clinical data, echocardiography, biochemical parameters, treatment at discharge, new hospital admissions and death were registered in a specific database.

Results: Mean age was 79.1 years (SD 8.3 years), and 94 (67.6%) were women. Anaemia was present in 85 (61%), any iron deficiency in 92 (67%) and absolute iron deficiency in 67 (48%) of these patients. 33 patients (23%) died during a mean follow-up of 649 days. Increased mortality was related to age, previous hospital admissions, lower albumin level, lower Barthel score, and higher ferritin level. Using a composite end-point of HF readmission or death during first year after index admission, 54 patients (38.8%) had this negative outcome. Lower Barthel Score and albumin values, higher NT pro-BNP and ferritin level, and absence of iron deficiency, were related to this negative outcome.

Conclusion: Anaemia and Iron Deficiency are usual findings in our elderly HF-PEF patients, but only a high level of serum ferritin was associated with worse outcomes in this setting.

Keywords: Heart failure; Anaemia; Iron deficiency; Ferritin; Preserved ejection fraction; Prognosis; Elderly

Introduction

Heart Failure (HF) is an increasingly prevalent health problem in an ageing population. It is a major cause of hospital admissions, with a great morbidity and mortality rates [1]. The association of anaemia and heart failure is well known since long time ago [2] and it is usually associated with a worse prognosis in HF-REF and HF-PEF [3]. Many heart failure (HF) patients have also iron deficiency, with or without anaemia [4]. In patients with chronic heart failure (CHF), iron deficiency (ID) has been related to a decrease in functional capacity and quality of life, higher New York Heart Association class, higher N-terminal pro-brain-type natriuretic peptide levels, and higher mortality rates [4,5]. This association is appropriately described in patients with HF and Reduced Ejection Fraction (HF-REF) [6] but there are few studies about its prevalence, clinical association and effect on prognosis in patients with HF and Preserved Ejection Fraction (HF-PEF) [4,5]. HF-PEF is the most common form of heart failure in older adults, particularly in women, with increasing prevalence, morbidity and mortality, but it remains not well caracterized [7]. First of all, HF-PEF was defined only by diastolic dysfunction, but recently HFpEF in older persons is typified by a broad range of cardiac and non-cardiac abnormalities, reduced reserve capacity in multiple organ systems, and multiple, concomitant co-morbidities, beeing itself considered as a systemic disorder. Co-morbidities are usually the strongest predictors of outcomes, with approximately 50% of clinical events being non-cardiovascular, embracing HFpEF as a true geriatric syndrome, with complex, multi-factorial pathophysiology and clinical heterogeneity [7].

The aim of this study is to ascertain if ID alone or associated with anaemia is related to death or negative clinical outcomes in elderly patients with HF-PEF.

Methods

The present study is a retrospective analysis of all consecutive patients included into our Hospital Heart Failure Care Program after being discharged for a HF episode. Recruitment took place from June 2011 to June 2014 and patients were prospectively followed up until June 2015 as outpatients and by telephone. The study was conducted at Internal Medicine Department of Fuenlabrada University Hospital. Patients were notified at first visit of data collection with clinical and research purposes and gave their informed consent.

Outpatient Hospital Based HF Care Program is composed by a specific HF team with a nurse and four staff internists with an scheduled follow up protocol to educate and optimize treatment of patients during HF admission and after discharge, by phone or attending scheduled appointments as outpatient, with the purpose of better symptom control, higher quality of life and, as result, preventing new emergency assistance or readmissions for worsening HF.

Diagnosis of HF was established by experienced internist physicians based on validated clinical, laboratory and echocardiography criteria from the ESC [8].

Independent variables

Anaemia was diagnosed with a haemoglobin level under 12 g/dL in woman and 13 g/dL in men, according to standard WHO criteria. Blood cells analyser was a Sysmex XE-5000. Haemoglobin was

measured by Sodium Lauryl Sulphate (SLS) method and photometric absorption.

Iron deficiency (ID) was classified as absolute ID if ferritin level was<100 µg/L, and functional ID if it was<300 µg/L and TSAT<20%, using standard ESC criteria [8]. Iron status analyzer was a Beckman Coulter AU-2700. Serum iron was measured by a Colorimetric assay, serum transferrin and serum ferritin by Immuno-turbidimetric assay. Several categories of interest were analyzed by mingling the different categorical options of these two factors.

Outcome variable

Three end-points were considered. Patient's death during follow-up, hospitalization for any reason during first year after inclusion in the program and a composite endpoint measure that included hospitalization for HF or death in the first year of follow-up.

Patient's death was confirmed in follow-up or by telephone with patient's relatives. Hospitalisation and its cause were captured from discharge records in our electronic health record (EHR) system.

Co-variables

Demographic data, cardiovascular risk factors, clinical and biochemical parameters, treatment at discharge (including oral and intravenous iron sucrose) were registered in a specific database integrated in our EHR.

At first attending Barthel Index (BI) [9], Short Portable Mental Status Questionnaire (SPMSQ) [10] and Charlson Index (ChI) [11] were evaluated. Functional status was determined by assessment of basic activities of daily life (BI) [9] referred to abilities prior to hospital admission that resulted in HF Care Program. Results were interpreted as dependency when BI was less than 60 points. Cognitive status was assessed by SPMSQ [10]. Cognitive impairment was considered when more than 5 errors were committed. Comorbidity was evaluated using ChI [11]. A global comorbidity score was calculated. Given the non-normal distribution of ChI, this index was recoded into two categories, that is, absent/mild comorbidity corresponds to scores 2 or lower and high comorbidity (scores 3 or higher).

All laboratory data were collected during index HF admission that generated follow-up for HF Care Program.

Echocardiographic data were collected during index HF admission by a staff cardiologist using an Acuson Sequoia 512 (Siemens) and a Vivid I (GE) ultrasound system. Ejection Fraction (EF) was calculated using the standard Teichholtz and modified Simpson methods.

Statistical Analysis

A descriptive analysis of the study population was completed. Baseline characteristics were reported as percentages and as means and standard deviations (median and interquartile range (IQR) when no normal distribution), and were compared using Pearson chi-square tests for categorical variables and Mann– Whitney U-tests for continuous variables.

Investigation of the association between death, hospitalisation for any reason in the first year and composite endpoint outcome with ferritin was carried out using a bivariate analysis comparing ferritin levels with the remaining demographic, functional and comorbidity variables. Qualitative variables were compared using the X^2 test.

Quantitative variables were compared with the T-test or Mann-Whitney test for non-normal distributions, respectively. Two-sided P< .05 was considered significant.

Control for confounding and interaction was carried out by logistic regression. All analyses were performed using SPSS version (SPSS, Chicago, IL, USA).

Results

139 consecutive patients with HF-PEF (EF>50%) were included in our HF Care Program during study time. Baseline characteristics of patients are displayed in Table 1. Median follow-up in HF Care Program was 505 days (IQR 307-1021). No patients were lost during follow-up.

		N	Mean +/-SD, (%)
Socio-demographic	Age	139	79,1 SD 8,3
	Women	139	94 (67,6%)
	BMI	127	31,3 SD 5,9
	Barthel Index	131	83,8 SD 21,4
	SPMSQ	133	1,9 SD 1,8
Comorbidities	HTN	139	72(51,8%)
	Hch	139	43(30,9%)
	DM	139	38(27,3%)
	CKD	139	31(22,3%)
	Tabaquism	139	11(7,9%)
	Charlson Index	135	3,4 SD 2
	Hearth Failure	135	0,7 SD 1,3
	Global	138	1,1 SD 1,5
Analytical parameters	Haemoglobin (g/dL)	135	12,1 SD 1,8
	Anaemia	135	85 (63%)
	Serum Iron (µg/dL)	125	54,1 SD 28,5
	Tsat	125	16,3 SD 9,4
	Ferritin (µg/L)	122	151,8 SD 194,6
Hospitalizations	Hearth Failure	138	0,7 SD 1,3
	Global	138	1,1 SD 1,5

Table 1: Participant clinical characteristics.

BMI: Body Mass Index; SPMSQ: Short Portable Mental State Questionarie; HTA: Hypertension; HCh: Hypercholesterolemya; DM: diabetes mellitus; CKD: Chronic Kidney Disease; Tsat: Transferrin sturation. * Refers to hospitalizations in previous year.

Iron status was determined at first visit in 122 of 139 patients (87%). Patients with iron metabolism assessed vs. no assessed were comparable in every analyzed variable (data not shown). There was a

statistical tendency (p=0,08) to do not measure iron metabolism in patients with higher hemoglobin levels (12,8 DS 2,2 vs. 11,9 DS 1,7) and less comorbidity (ChI 2,3 DS 1,3 vs. 2,9 DS 1,6).

Functional ID was found in 92 (75%) and absolute ID in 67 (54.9%) of patients tested. Anaemia was present in 85 (61%) of patients. Anaemia and functional ID relationship are shown in Table 2.

	Functional ID*		Absolute ID	
	N	%	N	%
Anaemia and ID	63	52,9	42	34,4
Anaemia without ID	15	12,6	39	32,0
ID without anaemia	29	24,4	25	20,5
No anaemia No ID	12	10,1	16	13,1
Total	119		122	

Table 2: Anaemia and iron deficiency relationship.*ID: Iron Deficiency.

33 patients (23.7%) died during follow up. There were no differences in follow-up medians in both groups. Death was statistically associated with advanced age, lower albumin, and lower Body Index in SPMSQ inn bivariate analysis. The only association with statistical significance detected was that an increase in ferritin level was related to death in follow up.

68 patients (48,9%) had at least one hospitalisation during the first year of follow-up, with a total of 238 admissions. An amount of 99 admissions (41.6%) were for HF decompensating. 53 patients were hospitalized for this reason, with only one patient endured HF admission without other cause for admittance in the first year of follow-up. In bivariate analysis hospitalization was only associated with lower albumin level. As exposed with death, only ferritin showed a statistical association.

New HF admission or death during first year after index admission follow up was used as a composite end-point negative outcome. 9 patients died in the first year of follow-up. 54 patients (38.9%) had a composite negative outcome. In bivariate analysis, composite negative outcome was statistically associated with higher NT proBNP, lower albumin level and higher physical dependency. Relationship between death in follow-up, hospitalisations for any reason and negative outcome with iron metabolism or anaemia are shown in Table 3.

		N	Anaemia	Ferritin	Functional ID*	Absolute ID	Anaemia + Functional ID	Anaemia + Absolute ID
			N(%)	mg/dl	N(%)	N(%)	N(%)	N(%)
Global death								
	Yes	33	24(72,7%)	211,2 DS 266,5	21(67,7%)	14(45,2%)	16 (50%)	11 (34,4%)
	No	106	61(59,8%)	131,6 DS 160,1	71(80,7%)	53(58,2%)	47 (49%)	31 (31,3%)
	p		0,18	0,05	0,14	0,21	0,92	0,75
Global admissions								
	Yes	68	41 (62,1%)	192,7 DS 254,8	44 (73,3%)	33(54,1%)	29 (46%)	21 (32,8%)
	No	70	43 (63,2%)	111,8 DS 90,1	47 (81%)	33 (55%)	33 (51,6%)	20 (30,3%)
	p		0,89	0,02	0,32	0,92	0,53	0,76
Negative outcome: First year Death or HF** admission								
	Yes	54	31 (60,8%)	227,4 DS 277,3	31 (64,6%)	21 (43,8%)	20 (40%)	13 (26%)
	No	85	54 (64,3%)	102,8 DS 84	61 (85,9%)	46 (62,2%)	43 (55,1%)	29 (35,8%)
	p		0,79	<0,001	0,01	0,05	0,09	0,24

Table 3: Anaemia and Iron metabolism with their relationship with different outcomes. *ID: Iron Deficiency; **HF: Hearth Failure.

Adjusted effects of iron metabolism on negative outcome and death are presented in Table 4. After logistic regression controlled for sex, age, NT pro BNP, albumin level, BI dependency and cognitive impairment, statistical association between ferritin level and any analyzed outcome was retained. For each point of increase in ferritin level there was an increased odds ratio of higher mortality, hospital admission and composite negative outcome. Functional iron deficiency was a protective factor for HF or death in the first year of follow-up but not for death or hospitalization along follow-up.

Death		β	OR	95% CI OR		p
	Ferritin (µg/L)	0,003	1,003	1,000	-1,005	0,04
	Functional iron deficiency*	-0,980	0,375	0,101	-1,400	0,15
	Absolute iron deficiency**	-0,695	0,499	0,162	-1,535	0,23
Negative outcome						
	Ferritin (µg/L)	0,004	1,004	1,000	-1,008	0,03
	Functional iron deficiency*	-1,461	0,232	0,075	-0,715	0,01
	Absolute iron deficiency**	-0,497	0,609	0,259	-1,429	0,25

Table 4: Iron metabolism, death and negative outcome.

β are adjusted for sex, age, comorbidity (ChI), functional level (BI and SPMSQ), proBNP and albumin. * Functional iron deficiency: ferritin<300 µg/L and Transferrin saturation< 20%. ** Absolute iron deficiency: Ferritin leve<100 µg/L.

Sensitivity analysis for ferritin was carried out considering every missing value as median value in both outcome variables. There were no significant changes in parameters (beta, OR and statistical significance) shown in Table 3. In the same way a sensitivity analysis with absolute or functional ID were carried out assuming that every single missing value was negative for both values and later as positive. There were no significant changes except when considering negative every missing value for functional ID. In this case association with negative outcome showed a significant change with OR 0,495 (0,203-1,207) p=0,122 losing its statistical significance although there was a tendency with no change in the sense of association. There was no interaction between anaemia and absolute or functional ID.

Discussion

The major finding of our study is that to our knowledge, it is the first published study about ferritin level and prognosis after surviving an index HF-PEF admission, showing that mortality and HF readmissions are not statistically related to anaemia in these patients, and isolated low ferritin level has not a worse prognosis in our elderly HF-PEF patients.

Anaemia is a frequent comorbidity in patients with heart failure, and its presence has been related to the severity of disease and to a worse prognosis in several HF studies, the majority with HF-REF patients, only some of them including patients with HF-PEF [4,8,12-14]. In our cohort, death was higher in anaemic patients (72,7% vs. 59,8%), but this increase could be related to chance as no statistical association was detected at a significant level. Anaemia was neither related to HF readmission in the first year of follow-up or admission for any reason in patients presented in current study. Advanced age and HF-PEF could be responsible for the differences found with data from literature. [3,4-7].

There is also growing evidence that iron deficiency (ID), with or without anaemia, is common in HF, and it is also associated with increased morbidity and mortality in acute [15-17] and chronic heart failure, especially in HF-REF [4,5,18]. Measurement of iron metabolism is actually recommended in all HF patients according with new HF guidelines, mainly because iron intravenous treatment with endovenous Ferric Carboximaltose (FCM) has been associated with reduction of the risk of hospitalisation for worsening HF in HF-REF patients [19]. Diagnosis of ID in clinical practice is based on circulating biomarkers including ferritin, iron, and transferrin saturation. The definition of ID commonly used in HF is a ferritin<100 in combination with TSAT<20%) if ferritin 100–300 ng/Ml, but this cut-off values have not been yet validated using the gold standard (bone marrow iron staining) because of the difficulty to obtain a bone marrow confirmation in this patients [20].

A high percentage of our HF-PEF patients (close to 75%) showed some type of iron deficiency (ID). Functional ID (Ferritin<300 µg/L and TSAT<20%) in our patients had a protective effect on negative outcome during first year of follow-up. In this way ID patients were less prone to death or admission for HF in the first year after inclusion in Hearth Failure Program. Isolated low ferritin level (Absolute Iron deficiency, with ferritn<100 µg/L) confirmed this tendency of protective effect outspread to hospitalisation or death along study period. Few data are found in literature about iron deficiency and prognosis in HF-PEF, and sometimes with opposite conclusions. Absolute but not functional ID was also associated with an excess risk for early readmission in a single Spanish study with a high prevalence of HFpEF [21], but there are no data provided about risk of death or prognosis in long term follow up. Another study has found a relationship between iron deficiency and functional capacity in HF-PEF patients but prognosis or follow up is not included [22]. Some studies, comprising patients with HF-REF and others with HF-PEF, have found a stronger relation of anaemia and mortality, rather than iron deficiency, but ferritin was excluded of final data [23].

These differences with our data could be explained by several characteristics of the patients presented. Firstly, all patients had HF-PEF, secondly advanced age, and thirdly genre with women preponderance. The data of the present study are more in the way presented in a subgroup analysis of a large international pooled study of patients with chronic HF and iron deficiency disclosing that patients with iron deficiency, female gender and HF-PEF had a lower risk of death, in contrast with HF-REF and male patients 5. Similar data are exposed in a New Zealand cohort, with 280 HF-PEF patients enrolled in People Study, some of them hospitalized with HF and other seen in clinic, showing that iron deficiency did not predict mortality in these patients [24,25]. In a recent study of 42 patients with HF and a reduced left ventricular ejection fraction (<45%) with Bone marrow aspiration and iron staining to confirm ID, low TSAT and serum iron, but not ferritin, were independently associated with mortality. In this study,

patients with isolated low ferritin levels, which did not correlate with bone marrow Iron Deficiency, had similar prognosis to those with normal ferritin and TSAT levels [20].

High ferritin level deserves further consideration. It has been recently described as the best predictive marker for new onset heart failure development, especially in women, in a Dutch community cohort study [26], and in a longstanding cohort community of Cardiovascular Risk factors study in the USA [27]. Ferritin can be viewed as a simple and widely available marker, that can reflect iron stores deficiency, but it is also an acute phase reactant, and his levels tend to rise in inflammatory conditions; a high ferritin level is specially related with risk of new onset HE-PEF in women, reflecting a possible role of a subclinical inflammatory state leading to micro vascular damage and diastolic dysfunction as the basis of new onset HF-PEF [28] and this low-grade inflammation that frequently accompanies HF can explain this worse outcomes also in stablished HF-PEF. Our data do support these findings.

Conclusion

Our study is a small size, single Centre observational cohort that challenges the current knowledge about iron metabolism and prognosis. In spite these considerations; this study represents a cohort without exclusions with real world frail older HF patients. Other inflammatory markers as high-sensitive C-reactive protein, soluble transferrin receptor or hepcidin could be of value but were not available in our study and are not usually measured in real life clinical practice. By contrast, iron metabolism and hemoglobin could be routinely evaluated adding information to prognosis in our patients.

The timing of iron metabolism determination and its prognostic implications requires further studies, especially in older HF-PEF patients. Extrapolations from observations made in patients with other HF characteristics could be flawed. Adding iron treatment to HF-PEP patients requires even further studies.

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