ORIGINAL ARTICLE

CONTENTS

Iron deficiency and heart failure with preserved ejection fraction

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ABSTRACT

Aim: We aimed to assess the prevalence of ID in among patients with HFpEF and its relation to functional capacity and quality of life.

Materials and Methods: We included in the analysis 121 consecutive outpatients newly diagnosed of HFpEF and tested with iron-related parameters. Patients were subdivided in two groups according to the presence of ID (n = 76, mean age 65.3 ± 7.1 years) or without ID (n =45, mean age 61.6 ± 7.4 years). Physical examination, routine laboratory tests, serum ferritin, transferrin saturation (TSAT), hs CRP, N-terminal proB-type natriuretic peptide (NT-proBNP), standard transthoracic echocardiogram examinations, functional capacity and quality were performed and assessed.

Results: Among all tested patients with iron-related parameters, 63% (76) met the European Society of Cardiology criteria for ID. Additionally, 29% (22) were found to have coexisting anemia. Patients with ID had more pronounced HF symptoms, higher NT-pro-BNP, hs CRP, ferritin and lower TSAT values and more severe diastolic dysfunction.

Patients with HFpEF and ID performed worse functional capacity during the 6MWT and had lower quality of life with Minnesota Living with Heart Failure Questionnaire.

Conclusions: ID as one of the most common comorbidities in HFpEF significantly impairs the functional capacity and quality of life.

KEY WORDS: heart failure with preserved ejection fraction, iron deficiency

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INTRODUCTION

Nowadays, the heart failure with preserved ejection fraction (HFpEF) is considered to be one of the major issue in healthcare system, due to its increasing prevalence among aged adults, high mortality and morbidity rates [1].

The diagnosis of HFpEF remains very challenging since there is a lack of universal diagnostic criteria with modest sensitivity and specificity, gaps in our understanding of the disease's pathophysiology, heterogeneity of HFpEF populations and presence of multiple noncardiac comorbidities contribute to this [2].

One of the common comorbidity in patients with HFpEF that affects up to 59% of individuals is iron deficiency [3]. Moreover, the recent studies have found much higher values of ID prevalence in patients with decompensated HFpEF as compared to compensated [4].

The pathophysiology of ID in HFpEF is complex and multifactorial. The reduction of iron intake such as poor appetite, impaired gastrointestinal absorption, co-administration of proton pump inhibitors, the increased iron losses due to anticoagulants or gastric ulceration and comorbidities such as chronic kidney disease, inflammatory activity etc. may contribute to ID [5,6].

The process of iron absorption and mobilization is regulated by hepcidin, its chronically elevated level in the setting of proinflammatory conditions such as HF, respectively impeding iron homeostasis and resulting in functional and absolute ID [7].

Recent study reveals the significant association between baseline hepcidin concentrations and the long-term risk of all-cause mortality, nonfatal cardiovascular events persisted after adjusting for established cardiovascular risk factors, medications, plasma hs CRP, plasma ferritin and other potential confounding factors [8].

Therefore, additional studies are required to assess the prognostic value of higher circulating hepcidin concentrations in predicting the future risk of adverse cardiovascular outcomes.

Since iron is *essential* in erythropoiesis, it also has a major role in mitochondrial energy production and many other cellular processes in myocardium and skeletal muscle, thus the likelihood of ID having an impact on exercise capacity is very high [9]. Thus, even in the absence of anaemia ID per se can be harmful.

The presence of ID in patients with HFpEF contributes to symptoms such as fatigue, tiredness, breathlessness,

reduced exercise tolerance, increased time to recover after exercise, impaired health related quality of life [10].

Moreover, it has been associated with worse clinical outcomes, higher risk of hospitalizations and all-cause mortality rates [11].

Also, a recent study have been shown that, among patients with chronic HF who were assessed for anemia and ID at baseline and 12 months, anemia developed in 16% of nonanemic patients and resolved in 23% of anemic patients [12].

Further investigations are required to understand the pathophysiology and potential distinct treatments for patients with HFpEF and ID phenotype.

AIM

We aimed to assess the prevalence of ID in among patients with HFpEF and its relation to functional capacity and quality of life.

MATERIALS AND METHODS

We included in the analysis 121 consecutive outpatients newly diagnosed of HFpEF and tested with iron-related parameters in central city hospital between September 2023 and April 2024**.** Patients were subdivided in two groups according to the presence of ID (n = 76, mean age 65.3 ± 7.1 years) or without ID (n =45, mean age 61.6 ± 7.4 years). The average age was 63.4 ± 11.1 years, with females comprising 68 % of the patients.

Physical examination, routine laboratory tests such as complete blood count (CBC), fasting blood glucose, serum lipids, urea, creatinine, ALT, AST, uric acid, serum ferritin, transferrin saturation (TSAT), hs CRP, N-terminal proB-type natriuretic peptide (NT-proBNP) were performed and assessed.

The ESC and ACC/AHA/HFSA guidelines define ID as a ferritin concentration of <100 ng/mL, or 100-300 ng/mL plus a transferrin saturation (TSAT) <20%.

Anaemia was defined, using the World Health Organisation (WHO) criteria, as a haemoglobin of <12.0 g/dL in women and <13.0 g/dL in men.

There was no statistically significant difference between the study groups and subject controls regarding age, gender or smoking status.

The diagnosis of HFpEF was made according to current HF guidelines: symptoms ± signs of HF, elevated levels of B-type natriuretic peptide and relevant structural heart disease including LV hypertrophy and/or left atrial (LA) enlargement, and/or evidence of diastolic dysfunction on echocardiography.

Standard transthoracic echocardiogram (2D and Doppler) examinations were performed using commercially available equipment (GE Healthcare, Chicago, IL, USA) according to the current guidelines. Cardiac morphology was assessed in standard four- and two-chamber views. The biplane Simpson method was used to determine the left ventricular ejection fraction. The degree of diastolic dysfunction was stratified to one out of four grades [Grade I (impaired relaxation), Grade II (pseudonormal), Grade III (reversible restricted), and Grade IV (fixed restricted)].

Functional capacity was measured by the 6-min walking test (6MWT), which determining the submaximal exercise capacity.

Quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ). This test covers physical, emotional, and social issues with 21 items, each ranging from 0 to 5, with higher scores denoting worse quality of life.

Statistical analyses were carried out in SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois).

Continuous variables were presented as the mean ± standard deviation (SD) and were compared using an independent samples t test. The differences between groups were checked by Chi-square test for categorical variables and by independent t-test for continuous variables.

The results were analyzed with a 95% confidence interval at a significance level of $p < 0.05$ or with a 99% confidence interval at a high significance level of $p < 0.01$.

RESULTS

Among all tested patients with iron-related parameters, 63% (76) met the European Society of Cardiology criteria for ID. Additionally, 29% (22) were found to have coexisting anemia.

Patients with ID had more pronounced HF symptoms (paroxysmal nocturnal dyspnea – 74% vs 43%; $p < 0.05$, peripheral edema – 35% vs 19%; $p < 0.05$, worse New York Heart Association class (Class ≥ II-III) – 73% vs 54%; $p < 0.05$).

The values of SBP, DBP and HR did not significantly differ among HFpEF patients with and without ID ($p > 0.05$) (Table 1).

The fasting glucose, creatinine, lipid profile, uric acid, AST, ALT, TSH values were almost similar in both groups, but haemoglobin values - significantly lower mainly in female HFpEF patients with ID than in male (11.5 ± 1.7 g/dl vs 12.9 ± 1.8 g/dl respectively; $p < 0.05$).

HFpEF patients with ID had higher ferritin and lower TSAT values compare with HFpEF patients without ID mainly in female (224.3 ± 69 ng/mL,165.7 ± 72 ng/mL vs 99.2 ± 48 ng/mL,104.6 ± 55 ng/mL and 13.65 ± 4.1%, 17.92 ± 5.6% vs 28.75 ± 4.8%, 33.15 ± 5.2% respectively; $p < 0.05$).

Table 1. Baseline characteristics of HFpEF patients with ID vs. without ID

	HFpEF patients with ID (n = 76)		HFpEF patients without ID (n = 45)		p value
	Female (n = 47)	Male (n = 29)	Female (n =25)	Male (n = 20)	
Heart rate (beats/min)	86 ± 19	89 ± 17	77 ± 14	79 ± 18	0.36
Systolic BP (mmHg)	130.7±22.5	133.6±27.4	132.5±23.1	134.2±29.5	0.25
Diastolic BP (mmHg)	80.3±11.4	81.2±9.6	75.3±12.5	78.5±10.9	0.17
Haemoglobin (g/dl)	11.5 ± 1.7	12.9 ± 1.8	12.7 ± 2.1	13.6 ± 1.5	0.02
Ferritin (ng/mL)	224.3 ± 69	165.7 ± 72	99.2 ± 48	104.6 ± 55	0.03
TSAT (%)	13.65 ± 4.1	17.92 ± 5.6	28.75 ± 4.8	33.15 ± 5.2	0.04
Creatinine (mg/dl)	1.09±2.7	1.1±2.8	0.97 ± 2.3	1.05 ± 2.5	0.19
Fasting glucose (mmol/l)	6.6 ± 2.1	6.7 ±2.7	6.1 ± 2.8	6.2 ±2.5	0.06
LDL-C (mmol/l)	3.53±2.16	3.72±2.49	3.27±3.52	3.68±3.45	0.62
HDL-C (mmol/l)	1.01±1.59	0.96±1.57	0.85±1.96	0.93±1.73	0.08
Triglyceride (mmol/l)	1.79±1.31	2.4±1.52	1.12±1.83	2.1±1.94	0.11
Uric acid (μmol/L)	358±29.3	432±26.5	336±34.5	420±38.2	0.84
TSH (mIU/mL)	3.5 ± 2.2	3.1±2.5	3.2±2.46	3.0±2.76	0.12
AST (U/L)	24.8 ± 4.67	29.3±5.17	23.3 ± 4.32	28.1± 5.26	0.36
ALT (U/L)	34.2±6.29	35.8±7.50	32.5±6.31	34.2±7.14	0.45
NT-proBNP (pg/ml)	567±23.4	569±28.5	347 ±33.8	350±37.2	0.03
hs CRP (mg/L)	3.2 ±1.2	2.9±1.3	1.7±1.2	1.9 ±1.1	0.04
LV diastolic dimension (mm)	52.9 ± 4.8	53.6 ±4.3	49.1 ±5.2	50.9 ±4.1	0.03
LV mass (g)	179 ± 55	187± 59	164±62	175±44	0.12
LV mass index (g/m^2)	78 ± 11	91 ± 14	57±12	80±13	0.04
Mitral annular e' (cm/s)	7±2	7±1	9±2	9±1	0.02
E/e ' ratio	13±2	12±2	10±1	10±2	0.06
LA volume index (ml/m^2)	27.5±2.8	29.7±3.2	24.8±3.3	26.1±2.5	0.04
EF, %	60.2±9.3	61.4±7.2	63.7±8.5	65.3±9.4	0.29

With regard to NT-proBNP as a biomarker of heart failure, the group analyses revealed higher values among all patients with ID vs without ID (567±23.4 pg/ml,569±28.5 pg/ml vs 347 ±33.8 pg/ml, 350±37.2 respectively; p <0.05).

The significant increased of serum hsCRP values were also observed in HFpEF patients with ID than in without ID (3.2 ±1.2 mg/L, 2.9±1.3 mg/L vs 1.7±1.2 mg/L, 1.9 ± 1.1 mg/L respectively; p < 0.05), indicating greater systemic inflammation.

An inflammatory biomarker (hs CRP) and NT-proBNP have also been associated with ID.

Furthermore, high values of hs CRP and NT-proBNP were inversely correlated with TSAT (r=-0.29, r=-0.25 respectively; p < 0,05).

It was been found that HFpEF patients with ID had more pronounced LV diastolic dysfunction.

Thus, ID patients had lower lower mitral annular lateral e' velocity (7±2 cm/s, 7±1 cm/s vs 9±2 cm/s, 9±1 cm/s respectively; p < 0.05), an increased LV diastolic dimension (52.9±4.8 mm, 53.6±4.3 mm vs 49.1±5.2 mm, 50.9±4.1 mm respectively; p < 0.05) and an increased LV mass index (78±11 g/m^2, 91±14 g/m^2 vs 57±12 g/m^2, 80±13 g/m^2 respectively; p < 0.05) as compare to HFpEF patients without ID.

The levels of left atrial volume index were also elevated in patients with HFpEF and ID than in without ID (27.5±2.8 ml/m^2, 29.7±3.2 ml/m^2 vs 24.8±3.3 ml/m^2, 26.1±2.5 ml/m^2 respectively; p < 0.05).

There was no clinically significant difference between the EF values among study groups (p < 0.05).

Patients with HFpEF and ID performed worse functional capacity during the 6MWT. The distance walked by HFpEF patients with ID was significantly lower than that walked by patients with normal iron status (398 ± 125 m vs. 461 ± 137 m; respectively; p < 0.05)(Fig.1).

In addition, the number of patients who had to discontinue the 6MWT before its completion was greater among patients with HFpEF and ID compared to patients without ID (6 vs 1). The worse exercise capacity

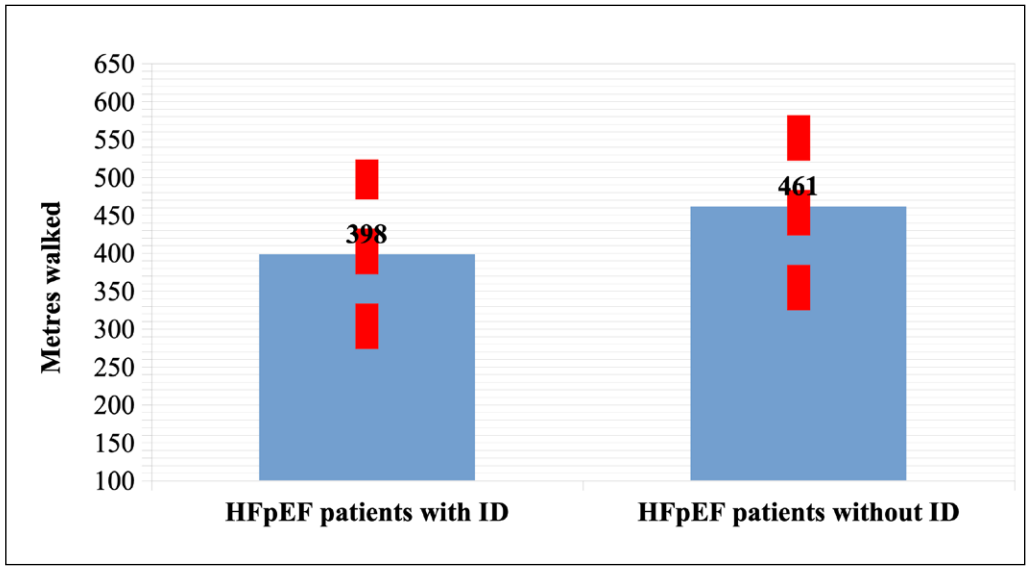

Fig. 1. Functional capacity (6MWT).

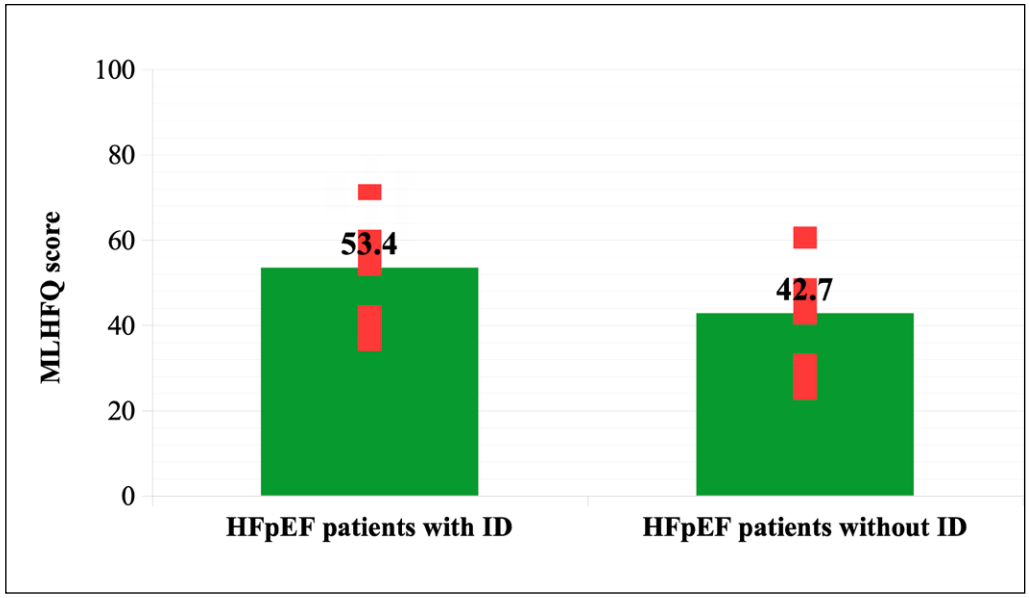

Fig. 2. Quality of life (MLHFQ).

was also observed in HFpEF patients without anemia ($p < 0.05$).

The assessment of quality of life with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) revealed significant higher global score in patients with HFpEF and ID compared to normal iron status (53.4±19.6 vs 42.7±20.3 points respectively; $p < 0.05$)), reflecting worse quality of life (Fig.2).

The most affected dimensions evaluated with MLHFQ in patients with HFpEF and ID were physical, social and personal.

DISCUSSION

Almost 50% of patients with HF are ID with a slightly higher prevalence in patients with HFpEF compared to their counterparts with midrange (HFmrEF) or reduced ejection fraction (HFrEF)[13].

ID affects a lot of physiological processes such as altered mitochondrial function and cardiac energetics, reduces exercise capacity (because of impaired cardiac and skeletal muscle function), reduced cardiac performance during exercise or higher heart rates in patients with HF [14].

Therefore, nowadays the prevalence of ID has been a growing area of interest for prediction of CV incident.

The largest observational study supports that low serum ferritin values have been associated with incident HF, worse diastolic function, higher LV filling pressure but were not associated with measures of LV size or mass or measures of LV systolic function after adjustment for multiple risk factors and other confounders [15].

A 50% lower plasma ferritin level is associated with a higher risk for incident HF overall (hazard ratio [HR],

1.20; 95% confidence interval [CI], 1.08-1.34) and a higher risk for incident HFpEF (HR, 1.28; 95% CI, 1.09-1.50; p = 0.002) both after adjustment for demographics and clinical risk factors [16].

The recent studies had shown the lowest mortality rate for those HFpEF patients with a serum ferritin <100 ng/mL and a TSAT >20% and highest for those with a serum ferritin >100 ng/mL with a TSAT <20% [17].

Univariable analysis revealed the lower TSAT, but higher serum ferritin, were associated with a higher all-cause and CV mortality [18].

TSAT better predicted all-cause mortality, as well as long-term risk for HF hospitalizations despite several iron metabolism biomarkers demonstrating strong association with severe outcomes [19].

Thus, it is important to incorporate additional biomarker data, beyond ferritin and TSAT, when assessing for ID in HF patients [20].

CONCLUSIONS

ID as one of the most common comorbidities in HFpEF significantly impairs the functional capacity and quality of life.

Nevertheless, further prospective investigations is warranted to investigate the potential mechanisms and future treatment possibilities.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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