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Original Article

Prevalence and spectrum of iron deficiency in heart failure patients in south Rajasthan

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ABSTRACT

Objective: To estimate the prevalence and pattern of iron deficiency (ID) in heart failure (HF) patients with or without anemia.

Methods: This is a single-center observational study, conducted at a tertiary care hospital of south Rajasthan. Patients admitted to hospital with clinical diagnosis of HF based on validated clinical criteria were included in the study. ID was diagnosed based on complete Iron profile, including serum iron, serum ferritin, total iron binding capacity, and transferrin saturation (TSAT). Anemia was defined as hemoglobin (Hb) <13 g/dl for males and <12 g/dl for females, based on World Health Organization definition. Absolute ID was taken as serum ferritin < 100 μg/L and functional ID was defined as normal serum ferritin (100–300 μg/L) with low TSAT (<20%).

Results: A total of 150 patients of HF (68% males and 32% females) were studied. Most of the patients were of high-functional NYHA class (mean NYHA 2.89 ± 0.95). ID was present in 76% patients with 48.7% patients having absolute and 27.3% patients having functional ID. Females were having significantly higher prevalence of ID than males (91.6% vs 68.6%; $p = 0.002$). Nearly one-fourth of the patients were having ID but without anemia, signifying importance of workup of ID other than Hb.

Conclusion: Our study highlights the yet underestimated and neglected burden of ID in HF patients in India. This study suggests further large-scale studies to better characterize this easily treatable condition and considering routine testing in future Indian guidelines.

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1. Introduction

Heart failure (HF) is a common problem with a prevalence of 1–2% in general population and a major cause of mortality, morbidity, and impaired quality of life (QoL).[1,2] Anemia is a frequent comorbidity in stable HF patients[3] and it increases morbidity in terms of frequent hospital admissions, impaired exercise capacity, poor QoL, and increased mortality. Iron deficiency (ID) with or without anemia has been commonly associated with HF. Although ID is the commonest nutritional deficiency worldwide, affecting more than one-third of the population,[4] its association with HF with or without anemia is of growing interest.[5–7] As iron supplementation improves prognosis in patients with HF, ID is an attractive therapeutic target – a hypothesis that has recently been tested in clinical studies.[8,9]

In 2012, the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF recognized ID as a comorbidity in HF for the first time and recommended diagnosis of ID based on iron parameters in all patients suspected of having HF.[10,11]

Most of the studies of prevalence of ID associated with HF are from the western world. Few studies evaluated this association in Asian patients[12,13] but currently there are no data from India to permit an estimation of the prevalence of ID associated with HF. This study is intended to assess the prevalence of ID in HF and may help in formulating future guidelines in India for routine ID assessment in HF patients.

2. Material and methods

This study is a single-center observational study, conducted at a tertiary care hospital of south Rajasthan from January 2015 to July 2015. The objective of the study was to estimate the prevalence and spectrum of ID in HF patients.

Male or female patients above 18 years of age and clinically diagnosed with HF, who gave consent for the study, were included. Diagnosis of HF was established based on validated clinical criteria from the ESC,[10] the ESC guidelines for the diagnosis of HF with preserved ejection fraction (HFPEF),[14] and the Framingham criteria.[15] Excluded patients were those who had comorbid noncardiac conditions causing ID (e.g. hemorrhoids, malignancy, etc.) or confounding assignment of etiology for fluid overload (e.g. end-stage renal failure), as well as patients with specific etiologies (e.g. congenital heart disease), who would be expected to follow a different natural history compared with a 'typical' HF patient. All participants underwent thorough history (including dietary history) and clinical evaluation, blood sampling, and comprehensive transthoracic echocardiography using standardized equipment (Vivid 7 from General Electric Company). Patients were characterized as having normal Ejection Fraction (EF ≥ 50%) or mild (EF 45–50%), moderate (EF 31–44%), or severe (EF ≤ 30%) LV systolic dysfunction. Apart from routine hemogram, these patients were assessed for their iron status by measuring complete iron profile, including serum iron, serum ferritin, total iron binding capacity, and transferrin saturation (TSAT).

Anemia was defined as hemoglobin (Hb) < 13 g/dl for males and <12 g/dl for females, based on World Health Organization definition.[16] Although generally accepted serum ferritin cut-off level to diagnose absolute ID is 30 μg/L, in HF, both intracellular iron accumulation and inflammation stimulate the tissue expression of ferritin and increase its blood level. In such cases, for the diagnosis of absolute ID, a higher serum ferritin cut-off value is used (e.g. 100 μg/L).[4] In our study, absolute ID was taken as serum ferritin < 100 μg/L and functional ID was defined as normal serum ferritin (100–300 μg/L) with low TSAT (<20%).[6,8,17]

2.1. Statistical analysis

Categorical variables are expressed in numbers and percentages, whereas normally distributed data are presented as mean ± standard deviation. Chi-square test and Student's *t*-test were used to calculate *p*-value as appropriate.

3. Results

During the period of study, 150 patients admitted to hospital with clinical diagnosis of HF were studied, out of which 102 (68%) were males and 48 (32%) were females. Mean age of the study subjects was 63.3 ± 14.4 years, with mean NYHA class of 2.89 ± 0.95 and mean EF of 38 ± 12%. Baseline characteristics of these patients are shown in Table 1.

Absolute ID (serum ferritin < 100 μg/L) was present in 73 (48.7%) patients. Absolute ID with anemia (Hb < 13 g% for male and <12 g% for females) was present in 47 (31.3%) patients.

Table 1 – Characteristics of study population.

Total patients	150
Males	102 (68%)
Females	48 (32%)
Mean age (years)	63.3 ± 14.4
Males	62.2 ± 14.3
Females	65.4 ± 14.4
Age groups	
<50 Years	40 (26.7%)
51–70 Years	65 (43.3%)
>70 Years	45 (30.0%)
NYHA class – Mean	2.89 ± 0.95
NYHA-I	16 (10.7%)
NYHA-II	27 (18.0%)
NYHA-III	64 (42.7%)
NYHA-IV	43 (28.7%)
Ejection fraction – Mean (%)	38 ± 12
<30%	54 (36.0%)
31–44%	54 (36.0%)
45–50%	5 (3.4%)
>50%	37 (24.7%)
Diabetes	23 (15.3%)
Hypertension	65 (43.3%)
Ischemic Heart Disease	81 (54.0%)
Primary valvular heart disease	23 (15.3%)
Secondary mitral regurgitation	57 (38.0%)
Atrial fibrillation	32 (21.3%)
Wide QRS	19 (12.7%)

Table 2 – Status of iron deficiency (ID) of study population.

	Males (n = 102)	Females (n = 48)	Total (n = 150)
Absolute ID	39 (38.2%)	34 (70.8%)	73 (48.7%)
With anemia	24	23	47 (31.3%)
Without anemia	15	11	26 (17.4%)
Functional ID	31 (30.3%)	10 (20.8%)	41 (27.3%)
With anemia	22	8	30 (20%)
Without anemia	9	2	11 (7.3%)
Absolute or functional ID	70 (68.6%)	44 (91.6%)	114 (76%)
With anemia	46	31	77 (51.3%)
Without anemia	24	13	37 (24.7%)

Functional ID (serum ferritin 100–300 μg/L with TSAT < 20%) was present in 41 (27.3%) patients and functional ID with anemia was present in 30 (20%) patients.

Thus ID (either absolute or functional) was found in 114 (76%) patients and ID with anemia was present in 77 (51.3%) patients (Table 2).

Females had a significantly higher prevalence of ID cf. males (91.6% vs 68.6%; $p = 0.002$).

Patients with ID with anemia were stratified as per their Hb level. Majority (68.8%) of these patients were having mild anemia (Hb:10–13 g/dl for males and 10–12 g/dl for females) (Table 3).

Patients with ID were further categorized as per their NYHA functional class and Left ventricular systolic function (as assessed by ejection fraction) (Table 4).

Those with absolute ID had mean NYHA class of 2.94 ± 0.87, those with functional ID – 2.90 ± 0.90, and without ID of 2.87 ± 0.97 (p value NS).

Table 3 – Characteristics of anemia in patients with ID with anemia.

Hemoglobin (g/dl)	Males	Females	Total
<13 for males and <12 for females	46	31	77
10–13 for males and 10–12 for females	36	17	53 (68.8%)
8–10	7	11	18 (23.4%)
<8	3	3	6 (7.8%)

Table 4 – Categorization of patients with ID as per their functional class and LV function.

	Males	Females	Total
NYHA class			
I	9	2	11 (9.6%)
II	17	6	23 (20.3%)
III	29	25	54 (46.3%)
IV	15	11	26 (22.8%)
LV function			
EF < 30%	21	13	34 (29.8%)
31–44%	31	16	47 (41.2%)
45–50%	1	2	3 (2.6%)
>50%	17	13	30 (26.4%)

4. Discussion

The findings from our study highlight a remarkably high prevalence of ID in HF patients in Indian population. ID is prevalent in HF patients even without anemia, which is already an established poor prognostic factor.

In recent years, there is increasing awareness worldwide of the significance of ID in patients of HF. In the USA, a prospective study of community-dwelling adults with self-reported HF revealed a prevalence rate of 61.3%.[18] In Europe, prevalence rates ranging from 37% to 50%.[5,17] have been reported. In our study, we found the prevalence of ID being 76%, which is significantly higher than these studies. This also highlights the burden of this condition in Indian HF patients. A study by Yeo et al. done in multiethnic Asian population, suggesting HF patients of Indian ethnicity having highest rates of ID, also supports our findings.[21]

On gender-based analysis, we found that ID was significantly higher in women with HF as compared to men. With a mean age of 65.4 ± 14.4 years, the women in our study were mostly post-menopausal, making blood loss of menstruation (an otherwise common cause of ID in women) a very unlikely cause of ID. This finding is in accordance with previous studies that suggested female gender as an independent correlate of ID in HF.[5,12,17]

In this study, 76% patients were having ID and 51.3% had ID with anemia. A significant number of patients (24.7%) were having ID but no anemia. Thus, if Hb levels are taken into consideration for workup of ID in HF patients, a significant part of the putative iceberg would have been missed. With 27.3% prevalence, functional ID is also making a significant part of disease burden. This subset will remain unrevealed unless care is taken to consider TSAT and serum ferritin in the workup. A recent article by Yeo et al. also stressed regarding assessment of functional ID and correlated it with symptoms regardless of ejection fraction.[13] These findings lay emphasis on getting a complete iron profile (including TSAT) in HF patients, a practice still missing in the developing world, including India.

In the 2012 ESC Guidelines for the diagnosis and treatment of acute and chronic HF, the ESC recommended ID testing in HF patients based on the assessments of ferritin and TSAT.[10,11] This raises the question of which iron indices are the most useful. Two are currently used: ferritin (a measure of stored iron) and TSAT (a measure of circulating iron for functional utilization). However, ferritin is also an acute-phase protein

and can be falsely elevated if inflammation or subclinical infection is present, but a low ferritin level is a clear indication of ID (absolute). If ferritin is increased, TSAT (<20%) can be used for the diagnosis of ID (functional). The only limitation of TSAT is the circadian differences, since the calculated value is dependent on the serum iron. Due to their intrinsic limitations, the combination of thresholds of these two parameters is suggested, as in FAIR-HF study (ferritin <100 ng/mL or ferritin 100–300 ng/mL if TSAT <20%). The ideal marker would probably be the soluble transferrin receptor; however, this is not widely available or used in clinical practice.[4]

Recommendations worldwide are being changed to incorporate the need to assess and treat ID in patients with chronic HF.[19] As our study indicates, ID is a common neglected burden in Indian HF patients, and this requires the need for more routine testing in future Indian guidelines.

In this study, we did not find any significant difference regarding NYHA functional class among HF patients with or without ID. Prior large-scale studies have established that ID in HF patients correlates with NYHA functional class and work capacity of patients.[6,13] This difference may be attributed to higher baseline NYHA class of our study patients with 69% being in NYHA III/IV (mean 2.89 ± 0.95). Being a single-center study, the number of patients was also less compared to these large-scale studies. Furthermore, this was an observational study, so effect of iron supplementation on improvement of NYHA class could not be analyzed. Various studies with beneficial effect of Iron supplementation in HF have been published including two open, noncontrolled trials[20–21] and four randomized, placebo-controlled trials.[8,22–24] Apart from NYHA class and walking distance, Iron supplementation has been shown to improve echocardiographic parameters of myocardial performance.[25,26] Unfortunately, such trials are lacking in Indian patients. Our study tries to lay foundation for future large-scale multicenter observational as well as randomized interventional studies in Indian subjects.

4.1. *Limitations of the study*

This study is a single-center study conducted at a tertiary care center in south Rajasthan. India being a vast country with different cultures and food habits, it is difficult to generalize the findings necessitating multicenter larger studies. Secondly, the observational character of our study needs to be acknowledged. The study was not designed to elucidate the underlying detrimental mechanisms of ID in patients with HF. No controls were taken to compare ID in subjects with or without HF. Thirdly patients of both HFREF as well as HFPEF were included without any separate analysis for these two.

5. Conclusion

Our study highlights the yet underestimated and neglected burden of ID in HF patients in India. This study suggests further large-scale studies to better characterize this easily treatable condition and consider routine testing in future Indian guidelines.

Conflicts of interest

The authors have none to declare.

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