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Original Research Article

Prevalence and spectrum of iron deficiency anaemia in heart failure patients

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ABSTRACT

Background: To study the prevalence and pattern of iron deficiency (ID)in heart failure (HF) patients with or without anaemia.
Methods: This is a single-centre observational study, conducted at a tertiary care hospital of Punjab. Patients were selected based on validated clinical criteria-Framingham criteria. The iron parameters were done during the study including serum iron, serum ferritin, total iron binding capacity, and transferrin saturation (TSAT), to diagnose iron deficiency anaemia. Anaemia was defined as haemoglobin (Hb) < 13g/dl in males and <12 g/dL in females, based on WHO definition. Absolute iron deficiency is defined as serum ferritin < 100 mg/L and functional ID was defined as normal serum ferritin (100–300 mg/L) with low TSAT (<20%).
Results: A total of 120 patients of Heart Failure (54% males and 46% females) were studied. Most of the patients were of high-functional NYHA class (Class IV NYHA n=45). Iron Deficiency was present in 60% patients with 31.66% patients having absolute and 28.33% patients having functional ID. Nearly one-fifth of the patients were having ID but without anemia, signifying importance of workup of Iron deficiency other than haemoglobin levels.
Conclusions: Study highlights the 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.

Keywords: Absolute Iron deficiency, Anaemia, Dyspnea, Functional Iron Deficiency, Heart failure

INTRODUCTION

Heart failure (HF) is a very common co morbid condition impairing the quality of life of the general population in the form of frequent hospital outpatient visits and admissions, thus responsible for being an important financial burden on the society.[1-3]Anaemia is associated with increased disease severity and may contribute to worse outcome. Iron deficiency (ID) with or without anaemia leads to decreased aerobic performance and exercise intolerance. Although ID is the commonest nutritional deficiency worldwide, affecting more than one-third of the population, its association with HF with or without anaemia is of growing interest.[4-7] As iron supplementation improves functional status and quality of life of HF patients, 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 co morbidity in HF for the first time and recommended diagnosis of ID based on iron parameters in all patients suspected of having HF.[10,11]The findings from this 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.

Recommendations worldwide are being changed to incorporate the need to assess and treat ID in patients with chronicHF.[12] Most of the studies of prevalence of ID associated with HF are from the western world. Few studies evaluated this association in Asian patients but currently there are no data from India to permit an estimation of the prevalence of ID associated with HF. [12,13] 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.

METHODS

This study is a single-center observational study, conducted at a tertiary care hospital of North India - Amritsar from January 2018 to July 2019. The prime objective of the study was to estimate the prevalence and spectrum of Iron Deficiency in Heart Failure patients.

In the study, 120 patients of heart failure visiting Indoor/OPD of SGRDIMSAR were included who fulfilled the inclusion criteria. Diagnosis of HF is established based on the ESC10 guidelines for the diagnosis of HF, and the Framingham criteria 13.

Inclusion criteria

Male or female patients above 18 years of age and clinically diagnosed with HF, who gave written consent for the study, were included.

Exclusion criteria

- Patients having co morbidnon-cardiac conditions causing Iron Deficiency (e.g. haemorrhoids, malignancy, etc.) or
- confounding assignment of etiology for fluid overload (e.g. end-stage renal diaease).

All participants then underwent thorough history (including dietary history) and clinical evaluation, blood sampling, and comprehensive transthoracic echocardiography using standardized equipment.

Patients were characterized as having heart failure with preserved ejection fraction HfpEF (EF 45-50%), mid-range HfmrEF (EF 31-44%), or reduced HfrEF (EF ≤30%). Apart from routine haemogram, 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). Anaemia was defined as haemoglobin (Hb) <13 g/dl for males and <12 g/dl for females, based on World Health Organization definition. Although generally accepted serum ferritin cut-off level to diagnose absolute ID is 30 mg/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 mg/L). Absolute ID was taken as serum ferritin <100 mg/L and functional ID was defined as normal serum ferritin (100-300 mg/L) with low TSAT (<20%).

Statistical analysis

Continuous variables with normal and non-normal distribution were expressed as Mean (SD) and Median (Range), respectively, while categorical variables were presented as count (%). Proportions and mean were compared using Chi- square and ANOVA respectively, p - values <0.05 were considered statistically significant and collected data were analysed by SPSS software version 20.0 with application of appropriate statistical methods.

RESULTS

During the period of study, 120 patients admitted to hospital with clinical diagnosis of Heart Failure were studied, out of which64 (53.7%) were males and 56 (46.7%) were females. Mean age of the study subjects was 62.817±12.3 years, with maximum patients of NYHA class IV i.e. 45 (37%). Risk factors like diabetes mellitus, hypertension, CAD and smoking were found in 46.63% (n= 56), 75.83% (n= 91), 44.6% (n= 53) and 20% (n= 24) patients respectively. Out of 120 patients ,76.67% (n= 92) patients were diagnosed based on Framingham Clinical Criteria for heart failure. Out of 120 patients, 40% (n=48) patients presented with Acute Pulmonary edema.AF was found to be present in 15.8% (n=19) patients. Mean haemoglobin levels, mean iron levels, mean ferritin levels and mean Transferrin saturation were calculated and were found to be 9.82±1.23 g/dl, 55.789 mcg/dl, 307.87±362.95 mcg/L and 15±10 % respectively. Mean Ejection Fraction (EF) in this study was 42±12%. Mean BNP levels were calculated to be 1048.54 ng/L.

Baseline characteristics of these patients, grouped in two groups Iron Deficit and Non - Iron Deficit group, are shown in (Table 1). As shown in the table, prevalence of various HF characteristics were higher in patients in iron deficit group-Rales (n= 70; p value=0.0001), Gallop (n=16; p-value=0.001) and raised JVP (n=59; p-value=0.001); in comparison to non-iron deficit where presence of Rales (n=36), Gallop (n=5) and raised JVP (n=26) were lower. Also, there is a significant difference found in the prevalence of risk factors like use of ACE-inhibitors, between iron deficit and non-iron deficit group; with more patients in iron deficit group using Ace-inhibitors (n=37; p-value<0.0001). The mean Hemoglobin levels, Ferritin and Transferrin saturation in Iron deficit group were found to be less i.e. 9.69±2.52 g/dl, 228.6±306.27µg/L and 13.44±7.9% respectively, as

compared to Non-iron deficit group i.e. 10.03±2.01 g/dl, 424.8±410.25 µg/L and 27.2±14.8% respectively. These were found to be statistically significant with p - values to be0.0025, 0.003, 0.0001.

It was also found that mean BNP levels were higher in patients with iron deficiency i.e. 1163.9±946.2 pg/ml but were lower in non-iron deficit patients i.e. 875.4±953.5 pg/ml, however this correlation was not found to be statistically significant (p value 0.105).

Table 1: Baseline characteristics of study population.

	Iron deficient HF patients (n1)	Non deficient HF patients (n2)	p-value
Age	63.1±11.4	62.4±13.6	0.76#
History			
Previous MI	22	18	0.429*
Hypertension	35	20	0.04*
Diabetes Mellitus	35	20	0.45*
Use of ACE inhibitors	37	23	<0.0001**
Signs			
Orthopnoea	31	26	0.23**
Rales	70	36	<0.0001*
Gallop	16	5	0.01*
Elevated JVP	59	26	<0.001*
Pedal Edema	48	27	0.24*
ECG and chest X ray			
Atrial fibrillation	12	6	0.53*
X Ray s/o Heart enlargement	19	17	0.29*
X Ray s/o Pulmonary Edema	33	16	0.17*
Iron parameters			
Mean Hb (g/dl)	9.69±2.52	11.03±2.01	0.0025***
Mean Ferritin (mcg /l)	228.6±306.27	424.8±410.25	0.0033***
Mean TSAT (%)	13.44±7.9	27.2±14.8	0.0001***
Mean BNP Levels (pg/ml)	1163.9±946.2	875.4± 953.5	0.105*

* Fisher's exact test, ** Chi square test, #ANOVA, ***unpaired t-Test.

Patients with ID with or without anemia were stratified (Table 2).With 72.5% (n = 87) prevalence of anemia in 120 heart failure patients, it was found that iron deficiency as a cause of anemia was found in 41.6 % (n=50).and the rest 30.8% (n=37) had anemia due to some other causes. It was also found that amongst non-anemic patients (n=33), 22 patients (18.35%) were found to have iron deficiency, signifying the importance of getting iron profile amongst non - anaemic patients.

Table 2: Characteristics of anemia in patients with/ without ID.

Total patients 120		
Characteristics	Anaemic (N=87)	Non anaemic (N=33)
Iron deficit	50 (41.6%)	22(18.3%)
Non-iron deficit	37 (30.8%)	11(9.1%)

Males and females had almost equal prevalence of ID (60.93% vs 58.92%). Absolute ID (serum ferritin <100 mg/L) was present in 38 (31.66%) patients. Absolute ID with anemia (Hb<13 g% for male and <12 g% for females) was present in 25 (20.83%) patients. Functional ID (serum ferritin 100-300 mg/L with TSAT <20%) was present in 34 (28.33%) patients and functional ID with anemia was present in 25 (29.16%) patients. Thus ID (either absolute or functional) was found in 72 (60%) patients and ID with anemia was present in 50 (41.6%) patients (Table 3).

Patients with ID were further categorized as per their NYHA functional class and Left ventricular systolic & diastolic function (Table 4).

Iron deficiency was present in 40 (88.9%) patients out of 45 patients of Class IV dyspnea; 17 out of 34 patients with Class III dyspnea (50%); 11 out of 29 patients with Class II dyspnea (38%); and 2 out of 6 patients with Class I dyspnea (33.3%).

This correlation shows a significant positive relationship i.e. as the class of dyspnea increases , the prevalence of iron deficiency increases with p-value = 0.017.

It was observed that out of 66 patients having systolic dysfunction, iron deficiency was present in 46 patients i.e. 69.6% patients (p value= 0.03). It was also found that out of 103 patients with diastolic dysfunction , iron deficiency was found in 65 patients i.e. 63.1 % (p value = 0.001)This shows a significant statistical relationship; but individually there is no correlation found within further

subgroups of systolic and diastolic dysfunction with presence of iron deficiency.

Table 3: Status of Iron Deficiency (ID) of study population.

	Males (*n* = 64)	Females (*n* = 56)	Total (*n* = 120)
Absolute ID	20(16.66%)	18 (15.14%)	38(31.66%)
With anemia	15	10	25(20.83%)
Without anemia	5	8	13(10.83%)
Functional ID	19(15.83%)	15 (12.5%)	34(28.33%)
With anemia	14	11	25(29.16%)
Without anemia	5	4	9(7.5%)
Absolute or functional ID	39(32.5%)	33 (27.5%)	72(60%)
With anemia	29	21	50(41.6%)
Without anemia	10	12	22(18.3%)

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

	Total number of patients	Iron Deficiency	Percentage (%)	p- value
NYHA class				
I	6	2	33.3	
II	29	11	37.9	
III	34	17	50	0.017
IV	45	40	88.9	
LV dysfunction	66	46	69.6	0.03
EF <30%	33	23	13	
31-44%	33	23	16	0.092
>45%	54	26	2	
Diastolic dysfunction	103	65	54.16	<0.001
Type I	41	28	23.33	
Type II	38	22	18.33	0.585
Type III	24	13	10.83	

DISCUSSION

The findings from this study highlight a remarkably high prevalence of anaemia in Heart Failure patients in Indian population. ID as a major cause of anaemia adds to the poor prognosis. Iron deficiency is prevalent even in patients without anaemia, signifying the importance of iron deficiency as a single poor prognostic factor in heart failure patients. In large clinical trials and heart failure registries prevalence of anaemia ranges from 14 to 70% among hospitalised patients. In this study anaemia was found to be prevalent in 72.5% population which is similar to these studies. In USA, a prospective study of community-dwelling adults with self-reported HF revealed a prevalence rate of iron deficiency in 61.3%.[14] In Europe, prevalence rates of iron deficiency ranging from 37% to 50%.[5,15] have been reported. In the study, the prevalence of Iron Deficiency being found was 60%(n=72), which is significantly higher than these studies. This shows the burden of this condition in Indian Heart Failure patients.

On gender-based analysis, it was found that ID was slightly higher in men with HF as compared to women (60.93% vs 58.92%). With a mean age of 62.81±12.5 years, the women in this 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 not in accordance with previous studies that suggested female gender as an independent correlate of ID in HF.[5,12]

In this study, 60% patients were having ID and 41.6% had ID with anemia. A significant number of patients (18.3%) were having ID but no anemia. Thus, if Hemoglobin levels are taken into consideration for workup of Iron Deficiency in HF patients, a significant part of the putative iceberg would have been missed.

With 47.3% prevalence, functional ID is also making a significant part of disease burden. This subset will be missed 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.[16] These findings lay emphasis on getting a complete iron profile (including TSAT) in HF patients.

In comparison to the study by Sharma et al, with 63.3% (n = 95) prevalence of anaemia in 150 heart failure patients , it was found that iron deficiency as a cause of anaemia was found in 51.3% (n=77)and the rest 12% (n=18) had anaemia due to some other causes. It was also found that amongst non-anaemic patients, some patients 37 patients (24.7%) were found to have iron deficiency signifying the importance of getting iron levels in all patients with heart failure, irrespective of Hb status.

In the 2016 ESC Guidelines for the diagnosis and treatment of iron deficiency in acute and chronic HF, the ESC recommended ID testing in HF patients based on the assessments of ferritin(a measure of stored iron) and TSAT(a measure of circulating iron for functional utilization).[10,11] However, ferritin is also an acute-phase protein. It can be falsely elevated if inflammation or subclinical infection is present. A low ferritin level indicates absolute 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 gold standard marker is bone marrow aspiration and specific staining for iron. Recommendations worldwide are being changed to incorporate the need to assess and treat ID in patients with chronic HF.[17] As 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, significant difference was found regarding NYHA functional class among HF patients with or without ID. Prior large-scale studies also have established that ID in HF patients correlates with NYHA functional class and work capacity of patients.[6,13]

Various studies with beneficial effect of Iron supplementation in HF have been published including two open, noncontrolled trials and four randomized, placebo-controlled trials.[18-22] Apart from NYHA class and walking distance, Iron supplementation has been shown to improve echocardiographic parameters of myocardial performance.[23,24] Unfortunately, such trials are lacking in Indian patients. Study tries to lay foundation for future large-scale multicentre observational as well as randomized interventional studies in Indian subjects.

This study is a single-center study conducted at a tertiary care centre in Northern India. In India with different cultures and food habits, it is difficult to generalize the findings necessitating multicentre larger studies. Secondly, the observational character of 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.

CONCLUSION

Study highlights the often-missed burden of ID in HF patients in India. Also, it established a significant relationship between iron deficiency and functional capacity in heart failure patients. It also focuses on positive grounds that some evidence does exists in the effect of iron deficiency on the normal cardiac functioning (i.e. systolic and diastolic function) but need further evidences to generalize the data. This study suggests to consider routine iron parameters testing in future Indian guidelines.

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