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Prevalence of iron deficiency in non-anemic heart failure patients

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ABSTRACT

Background: To study the prevalence of iron deficiency in non-anemic heart failure patients.

Materials and methods: This is a single-center cross-sectional study done in the Department of General Medicine at the Institute of Medical Sciences and SUM Hospital, Odisha, between November 2020 and June 2022. The selection of participants was made based on Framingham criteria. An iron profile was used to detect iron deficiency anemia during the study period. According to the WHO, Anemia is defined as having a hemoglobin (Hb) level below 12 gm/dL in females and 13 gm/dL in males. Serum ferritin below 100 ng/mL is considered an absolute iron deficiency, and serum ferritin between 100 and 300 ng/mL with low transferrin saturation (TSAT <20%) is regarded as functional Iron deficiency.

Results: A total of 100 individuals with non-anemic heart failure (53% men and 47% women) were included in the study. Most of the individuals were of class IV New York Heart Association (NYHA) (N=39). Iron deficiency was present in 60% of individuals, with 32% having absolute iron deficiency and 28% having functional iron deficiency. Men and women had almost the same prevalence of iron deficiency (62.2% vs 57.44%). The levels of mean Hb, ferritin, and transferrin saturation in the iron deficiency group (i.e., 13.2 gm/dL, 139.7 ng/mL, and 14.4%) were less when compared to the non-iron deficiency group (i.e., 13.3 gm/dL, 391.35 ng/mL and 36.1%).

Conclusion: Our research emphasizes the impact of iron deficiency on heart failure patients in India, which is still underappreciated and ignored. This study recommends more in-depth analysis to define this manageable illness correctly and explore habitual testing in upcoming national recommendations.

Introduction

Heart failure is a prevalent issue that affects 1-2% of people and is a leading reason of death, illness, and poor quality of life (QoL).[1,2] Anemia is a common co-morbid condition in stable heart failure candidates, and it worsens morbidity by causing regular hospitalizations, reduced exercise ability, poor quality of life, and increased death.[3] Heart failure is frequently accompanied by iron deficiency with or without anemia. Even though iron deficiency is the

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most prevalent nutritional deficit globally, impacting more than one-third of the total population, its link to heart failure with or without anemia is gaining attention.[4,5-7]

Iron deficiency is an appealing therapeutic target since replacement therapy improves outcomes in individuals with heart failure-a notion verified in many recent research studies.[8,9] Diagnosis and management of heart failure guidelines from the European Society of Cardiology (ESC), for the first time, iron deficiency was identified as a co-morbidity in heart failure in 2012. It was also suggested that the identification of iron deficiency depends on the iron values in all individuals with suspected heart failure.

It has recently been identified that individuals with heart failure are more likely to acquire iron deficiency as a consequence of depleted iron reserves or processes evident in anemia or chronic disease.[10,11] Advanced age, renal disease, female sex, malnutrition, chronic inflammation, decreased iron absorption, increased iron loss, and the severity of heart failure have all been found to be independently linked with ID in HF. It should be noted that many of the risk variables listed above are hypothesized based on observational research and have not yet been shown to cause HF in patients, therefore they are still uncertain.[12,13]

Iron deficiency, whether with or without anemia, reduces working capacity, causes tiredness and activity intolerance, and exacerbates the clinical manifestations of heart failure individuals.[14] A recent randomized, double-blind research has shown that intravenous iron supplementation improved functional outcomes and living standards in Iron deficiency individuals with or without anemia and heart failure.[15]As a result, Iron deficiency has recently taken on a distinctive function in heart failure and is the topic of new research.

Most of the research on the prevalence of iron deficiency in people with heart failure came from foreign countries. The study conducted by Chobufo *et.al* in the USA concluded that anemia should not be considered a prerequisite for screening for iron deficiency in patients with heart failure.[16] Very few studies have looked into this link in Asian people.[17,18] However, there are presently no data from India that can be used to estimate the prevalence of iron deficiency in people with non-anemic heart failure. This study aims to determine the prevalence of iron deficiency in non-anemic heart failure patients. It may aid in formulating potential recommendations for regular iron deficiency evaluation in heart failure individuals in India.

Materials and methods

This is a single-center cross-sectional study done in the Department of General Medicine at IMS and SUM Hospital, Odisha, between November 2020 and June 2022. In this research, 100 non-anemic heart failure patients of IMS & SUM Hospital satisfying the inclusion criteria were included based on guidelines from the ESC and the Framingham criteria heart failure is diagnosed.

Inclusion criteria

1. Patients with symptoms of heart failure confirmed by 2d-echo showing systolic and diastolic dysfunction with raised NT- PROBNP levels.
2. Patients with heart failure having hemoglobin levels of more than 13 (gm/dL) in males and 12 (gm/dL) in females.

Exclusion criteria

1. Heart failure patients with chronic kidney disease.
2. Heart failure patients with recent blood transfusions history.
3. Pregnant females with heart failure.

All the study individuals underwent clinical examination, routine hematological investigations, and 2D-Echo using standard instruments. Participants were classified as having heart failure with reduced ejection fraction (HfrEF) (EF <40%); heart failure with mid-range ejection fraction (HfmrEF) (EF 41-50%); or heart failure with preserved ejection fraction(HfpEF) (EF>50%).

These individuals' iron status was evaluated in addition to standard hemograms by assessing their complete iron profile. Hemoglobin concentrations (gm/dL) were measured using an automatic system Coulter LH 750 Hematology Analyzer (Beckman Coulter, Krefeld), Serum iron measurement was performed with calorimetric assay, and transferrin was assessed using an immune-turbidimetric assay on a modular automated clinical chemistry analyzer. Serum ferritin was measured using an immunoassay based on electrochemiluminescence. All measurements were performed with Modular E170 (Roche/Hitachi). Plasma concentration NT-PRO BNP (ng/l) was measured using an immunoassay based on electrochemiluminescence on the Modular system.

According to the WHO, anemia is defined as having a Hb level of less than 12 gm/dL for females and less than 13 gm/dL for males. Serum ferritin of 30 ng/mL is a typical cut-off level for diagnosing absolute Iron deficiency. Still, in heart failure, as there is both increased iron buildup intracellularly and ferritin tissue overexpression (driven by inflammation), there will be a generalized rise in its level in the blood. In these circumstances, a serum ferritin level of 100 ng/mL is used as a cut-off value to diagnose absolute Iron deficiency. Functional Iron deficiency was described as serum ferritin between 100-300 ng/mL with low TSAT (<20%), whereas absolute Iron deficiency was considered serum ferritin <100 ng/mL.[19]

Statistical analysis

The chi-square test and Student's t-test were used to calculate the *p* value. Using SPSS software version 20.0, collected data were evaluated with the application of appropriate statistical methods, and $p<0.05$ were considered statistically significant.

Results

During the study timeframe, 100 individuals admitted to IMS & SUM Hospital with a clinical diagnosis of HF were included, out of which 53 (53%) were men and 47 (47%) were women, with a greater number of individuals in class IV NYHA, i.e., 39 (39%). Iron deficiency was seen in 60% of individuals (N=60), with absolute iron deficiency in 32% and functional Iron deficiency in 28%. Co-morbidities like Type 2 diabetes mellitus and hypertension were present in 46% (N=46) and 46% (N=46) patients. Out of 100 individuals, 41% (N=41) came to the hospital with features of acute pulmonary edema, and 15% (N=15) with atrial fibrillation. Mean ejection fraction (EF) and NT-PRO BNP levels were 43.64%, and 1699.5 ng/L respectively. The baseline features of all study individuals grouped into Iron deficient and non-iron deficient groups are depicted in Table 1.

As depicted in the above table, the prevalence of multiple heart failure features was higher in individuals in the Iron deficiency group compared to the Non-iron deficiency group (Rales, p=0.002, Raised jugular venous pressure (JVP), p=0.003). Also, there is a considerable difference in the use of ACE- inhibitors, with more individuals in the Iron deficiency group using them (N=31). The levels of mean Hb, Ferritin and Transferrin saturation in the Iron deficiency group were less when compared to the non-iron deficient group (Table 2).

Men and women had almost the exact prevalence of ID (62.2% vs 57.44%). Absolute iron deficiency was seen in 32 (32%) individuals. Functional Iron deficiency was seen in 28 (28%) individuals. Thus, Iron deficiency was seen in 60 (60%) individuals including both absolute and functional Iron deficiency.

Based on New York Heart Association (NYHA) functional class, patients were further categorized into Iron Deficit and Non-iron deficiency groups (Table 3). This study showed a statistically significant positive association between NYHA class and iron deficiency. The prevalence of iron deficiency increased with the class of dyspnea with a p value of 0.0001.

Table 1 Baseline characteristics of the study population.

Feature	Iron deficient heart failure patients	Non-iron deficient heart failure patients	*p* value
History Of Previous MI	18	15	0.5
History Of Hypertension	29	17	0.6
History Of Diabetes Mellitus	29	17	0.6
History Of Use OfACEi's	31	19	0.8
Orthopnea	26	22	0.3
Rales	58	30	**0.002**
Gallop	13	4	0.1
Elevated JVP	49	22	**0.003**
Pedal Edema	40	23	0.3
Atrial Fibrillation	10	5	0 .5
Chest X Ray Showing Heart Enlargement	16	14	0.3
Pulmonary Edema	28	13	0 .1

Table 2 Comparison of mean values between Iron deficient and non-iron deficient groups.

Parameter	In total individuals (Iron deficient heart failure patients (Mean±SD)	Iron deficient heart failure patients (Mean±SD)	Non-iron deficient heart failure patients (Mean±SD)
Hb (gm/dL)	13.26±0.49	13.2±0.32	13.3±0.23
Ferritin (ng/mL)	240.4±103	139.7±66.6	391.35±191.7
Transferrin saturation (%)	23.1±10.9	14.4±5.9	36.1±15.7

Table 3 Grouping of patients with iron deficiency as per their functional class.

NYHA class	Total number of patients	Iron deficient Heart failure patient's N (%)	Non-iron deficient heart failure patient's N (%)	95% CI		*p* value
				Upper	Lower	
1	6	2(33.3)	4(66.7)	0.12	0.02	**0.0001**
2	25	9(36)	16(64)	0.34	0.16	
3	30	15(50)	15(50)	0.39	0.21	
4	39	34(87.1)	5(12.9)	0.49	0.29	

Based on left ventricular systolic & diastolic function, patients were further categorized (Table 4).

It was seen that 55 individuals had systolic dysfunction, out of which 39 had ID (i.e., 70.9% patients, p=0.01); 85 individuals had diastolic dysfunction, out of which 52 had Iron deficiency (i.e., 61.1%, p=0.56). This showed a statistically significant association between systolic dysfunction and the presence of iron deficiency, but no significant association was found between diastolic dysfunction and Iron deficiency. Further, individually within subgroups, a statistically significant association was found in left ventricular systolic function (LVEF), and no significant association was found in the type of diastolic dysfunction with Iron deficiency (Table 5).

Table 4 Grouping of patients with iron deficiency as per their left ventricle function.

Left Ventricle	Dysfunction	Total	Iron deficient heart failure patients N (%)	Non-iron deficient heart failure patients N (%)	95% CI		*p* value
					Upper	Lower	
Systolic	Present	55	39(71)	16(29)	0.64	0.44	0.01
	Absent	45	21(46.66)	24(53.34)	0.55	0.35	
Diastolic	Present	85	52(61.17)	33(38.82)	0.91	0.76	0.56
	Absent	15	8(53.33)	7(46.66)	0.23	0.08	

Table 5 Sub-grouping of patients with Iron deficiency as per their LVEF and type of diastolic dysfunction.

LV dysfunction	Type	Total number of patients	Iron deficiency N (%)	Non-iron deficiency N (%)	95% CI		*p* value
					Upper	Lower	
Systolic	HFrEF	27	19(70.3)	8(29.7)	0.36	0.18	**0.04**
	HFmrEF	28	20(71.4)	8(28.6)	0.37	0.19	
	HFpEF	45	21(46.6)	24(53.4)	0.55	0.35	
Diastolic	Type 1	34	23(67.6)	11(32.4)	0.59	0.21	0.5
	Type 2	31	31	18(58)	13(42)	0.47	
	Type 3	20	20	11(55)	9(45)	0.33	

Discussion

The results of this study show that people with heart failure in the Indian community have an astonishingly high frequency of iron deficiency. The outlook is not good because Iron deficiency is a primary contributor to anemia. Iron deficiency is common even in individuals who do not have anemia, highlighting its significance as a single factor with a lousy prognosis in individuals with heart failure. Anemia prevalence among hospitalized individuals varied from 14 to 70% in extensive clinical studies and heart failure registries.

According to future research, iron insufficiency was prevalent in 61.3% of community-dwelling people in the USA with self-reported heart failure.[20]Iron insufficiency prevalence rates in Europe range from 37 to 50%.[21,22] The prevalence of non-anemic iron deficiency identified in the research was 60% (N=60), much higher than that seen in prior investigations. This demonstrates the severity of this issue among Indian individuals with heart failure.

According to a sex-based assessment, males with heart failure had somewhat higher Iron deficiency rates than women (55% vs 45%). Most of the study's participants were post-menopausal, making menstrual blood loss - a typically prevalent basis of Iron deficiency in females - an extremely improbable reason for Iron deficiency. This result contradicts earlier research that claimed the female gender to be a sovereign indicator of Iron deficiency in heart failure.[21,23]

In this research, 60% of the participants did not have anemia but had Iron deficiency. Therefore, a large portion of the potential iceberg would have been overlooked if hemoglobin values were considered to evaluate Iron deficiency in heart failure individuals. Functional Iron deficiency contributes significantly to the burden of the disease and has a prevalence of 46.6%. If TSAT and serum ferritin is carefully considered throughout the workup, this subgroup will be noticed. In a recent article, Yeo *et al*. emphasized the importance of functional iron deficiency evaluation and linked it to clinical features independent of ejection fraction.[24] These results highlight the need to provide heart failure individuals with a complete iron profile, including TSAT.

In contrast, the Sharma *et al.* study indicated that anemia affected 63.3% (N=95) of the 150 individuals with heart failure.[25] It was discovered that 51.3% (N=77) of these individuals had iron deficiency. In comparison, the other 12% (N=18) had anemia for various other reasons. Additionally, it was shown that among non-anemic individuals, 37 (24.7%) had an iron shortage, highlighting the need to check the iron profile in all heart failure individuals, regardless of Hb status.

Based on analyses of ferritin (a metric of deposited iron) and TSAT, the ESC suggested Iron deficiency evaluation in heart failure individuals in its 2016 Recommendations.[26,27] Ferritin is an acute-phase reactant, however. It may be artificially increased if there is an

underlying infection. Absolute Iron deficiency is shown by a low ferritin level. TSAT (<20%) can be used to diagnose Iron deficiency if ferritin levels are elevated (functional). Since the estimated result depends on the serum iron, TSAT's sole drawback is the diurnal variations. The combination of these two measures' thresholds, like in the FAIR-HF research (ferritin <100 ng/mL or ferritin 100-300 ng/mL if TSAT <20%), is advised due to their inherent limitations. The ideal indicator is aspiration from bone marrow and concrete iron staining. The necessity to diagnose and manage Iron deficiency in individuals with chronic heart Failure is being incorporated into global recommendations.[28] According to the study, Iron deficiency is a frequently overlooked burden among Indian patients with heart failure, necessitating more regular testing in upcoming Indian offers.

In this research, heart failure individuals with or without Iron deficiency differed significantly regarding their NYHA functional class. Prior extensive research has also demonstrated a relationship between heart failure with Iron deficiency, NYHA functional class, and job capability.[29,30]

Four randomized, placebo-controlled trials and two open, noncontrolled studies with positive results for iron supplementation in heart failure have all been reported. Supplementing with iron has been established to enhance echocardiographic markers of cardiac muscle function in addition to NYHA class and walking distance.[31,32] Unfortunately, Indian patients lack participation in these studies. This study aims to build the groundwork for future massive multicenter observational research in Indian participants and randomized interventional investigations. Absolute iron deficiency in heart failure can be brought on by lower intake as a result of anorexia, cardiac cachexia, poor iron absorption brought on by intestinal edema, and hepcidin-induced downregulation of iron transporters such as ferroportin. The functional iron deficit in HF is caused by processes related to those that cause anemia of chronic diseases or inflammatory conditions. HF is associated with higher amounts of inflammatory cytokines that promote hepatic hepcidin production which binds, internalizes, and degrades ferroportin. This leads to impairment of iron absorption into the blood from enterocytes and entrapment of iron in the storage pool (liver and reticuloendothelial cells). Together, these effects result in relative iron depletion.[33]

This study was done at a tertiary care facility in eastern India as a single-center study. It is challenging to generalize the results in India due to the many cultures and eating customs, needing multicenter, more extensive investigations. Second, it's essential to realize that research is observational. This research article has yet to be framed to explain the underlying pathogenesis of Iron deficiency in individuals with non-anemic heart failure. There were no controls obtained to analyze Iron deficiency in participants with or without heart failure.

Limitations of the study

1. This investigation was carried out at a tertiary care facility in Odisha as a single-center study. Given the size of India and its many cultures and eating customs, it is challenging to generalize the results, needing much bigger investigations.
2. It is essential to recognize that our study was observational.
3. The research needs to frame to clarify the underlying processes of Iron deficiency in heart failure individuals.
4. There were no controls obtained to assess Iron deficiency in participants with or without heart failure.
5. Without a detailed assessment of the three patients with HFrEF, HFmrEF and HFpEF were included.

Conclusion

Our research emphasizes the impact of Iron deficiency on heart failure patients in India, which is still underappreciated and ignored. It also stresses that some data supports the effects of iron deficiency on healthy heart function (including both systolic and diastolic); however, extensive research is required to generalize the findings. This article recommends more in-depth analysis to correctly define this manageable illness and explore routine testing in upcoming national recommendations.

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Conflict of interest

None declared.

Ethical approval

The study was approved by the Institutional Ethics Committee, Institute of Medical Sciences, and SUM hospital (ECR/627/Inst/OR/2014/RR-20).

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