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Brief Report

Prevalence and Implications of Iron Deficiency in Non-Anemic Female Heart Failure Patients in India

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ABSTRACT

Background and Aims: Heart failure (HF) is a growing health challenge in India, with emerging evidence linking iron deficiency to HF-related morbidity. This study assessed iron deficiency prevalence in non-anemic female HF patients in India and explored its clinical implications.

Methods: A single-center cross-sectional study was conducted at IMS & SUM Hospital, Odisha, from January to December 2022. Forty-seven non-anemic female HF patients meeting specific criteria were included. Clinical assessments, hematological investigations, and 2D-Echo were performed, evaluating iron status, hemoglobin, ferritin, transferrin saturation, and NT-PRO BNP levels. Statistical analysis used SPSS software.

Results: Iron deficiency was prevalent in 57% of patients, including absolute (32%) and functional (25%) types. Common comorbidities were Type 2 diabetes mellitus and hypertension (47%). Severe symptoms (NYHA Class IV) were associated with higher iron deficiency prevalence, but no significant link was found with systolic or diastolic dysfunction. The iron-deficiency group exhibited lower hemoglobin, ferritin, and transferrin saturation levels.

Conclusion: This study underscores the under-recognized impact of iron deficiency in non-anemic female HF patients in India. While preliminary data hint at potential cardiac function effects, larger-scale research is needed. Routine iron status testing should be considered in national recommendations to enhance HF management and patient outcomes in India.

Keywords: Iron Deficiency, Non-Anemic, Female Heart Failure Patients, Ferritin, Transferrin Saturation.

INTRODUCTION

Heart failure (HF) is a burgeoning global health crisis, imposing significant burdens on morbidity and mortality worldwide (1). India, too, grapples with a rising prevalence of HF, necessitating a thorough exploration of its multifaceted origins, risk factors, and potential modifiers (2). Among the myriad contributing factors, iron deficiency has emerged as a crucial yet often overlooked determinant in the pathophysiology of HF (3).

Iron, an essential micronutrient, plays pivotal roles in various cellular processes, including oxygen transport, energy metabolism, and cardiac function (4). In HF, iron deficiency can result from a complex interplay of factors such as reduced dietary intake, impaired absorption, chronic inflammation, and occult blood loss (5). While iron deficiency anemia (IDA) in HF has been extensively studied, growing recognition of the non-anemic state, wherein patients exhibit depleted iron stores without reduced hemoglobin levels, has delineated a distinct clinical entity (6).

The pathophysiological mechanisms underlying iron deficiency in non-anemic HF patients are multifaceted. Even in the absence of anemia, iron deficiency has been associated with impaired myocardial contractility, reduced exercise capacity, and an increased risk of hospitalization (7). Furthermore, iron deficiency is linked to elevated proinflammatory cytokines and oxidative stress, further exacerbating HF progression (8).

Given the complexity of these interactions, a comprehensive exploration of iron status in non-anemic female HF patients in the Indian context is warranted.

Understanding the prevalence and clinical implications of iron deficiency in this specific population is critical, as it can inform tailored diagnostic and therapeutic strategies (9). Existing studies, predominantly conducted in Western populations, may not accurately represent the Indian scenario due to potential disparities in dietary habits, genetic factors, and comorbid conditions (10). Additionally, gender-specific differences in iron metabolism and HF manifestation necessitate dedicated investigation into non-anemic female HF patients (11).

This article aims to address this critical knowledge gap by assessing the prevalence of iron deficiency in non-anemic female HF patients in India and delineating its clinical significance. We hypothesize that iron deficiency is an under-recognized yet prevalent condition in this patient cohort, with implications for symptom burden, hospitalizations, and long-term outcomes (12). Our study adopts a comprehensive approach, encompassing clinical assessments, iron status biomarkers, and patient-reported outcomes, to elucidate the intricate relationship between iron deficiency and HF in non-anemic females (13). By shedding light on the prevalence and clinical relevance of iron deficiency in this specific context, our research seeks to enhance our understanding of HF pathophysiology and optimize patient care strategies, ultimately improving the quality of life and prognosis of this vulnerable patient population (14).

MATERIALS AND METHODS

This single-center cross-sectional study took place in the Department of General Medicine at IMS and SUM Hospital, Odisha, from January to December 2022. The study involved 47 non-anemic female heart failure patients selected from IMS & SUM Hospital based on specific criteria. Patients with heart failure symptoms confirmed by 2D-echo, demonstrating systolic and diastolic dysfunction along with elevated NT-PROBNP levels, were included. Additionally, female patients with heart failure and hemoglobin levels above 12 gm/dl were considered. Patients with heart failure and chronic kidney disease, those with a recent history of blood transfusions, and pregnant females with heart failure were excluded. Purposive sampling was used to select participants meeting the predefined inclusion and exclusion criteria. The study adhered to ethical guidelines and received approval from the institutional ethics committee. Informed consent was obtained from all participants. Heart failure diagnosis followed European Society of Cardiology (ESC) and Framingham criteria. Participants had symptoms of heart failure confirmed by 2D-echo, systolic and diastolic dysfunction, and elevated NT-PROBNP levels. Hemoglobin levels exceeding 12 gm/dl were also required for inclusion. Comprehensive assessments included clinical examinations, routine hematological investigations, and 2D-Echo. Participants were categorized based on ejection fraction into heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), or heart failure with preserved ejection fraction (HFpEF). Iron status and complete iron profiles were evaluated, alongside standard hemograms and NT-PRO BNP levels. Statistical analysis was performed using SPSS software version 20.0, employing chi-square tests and Student's t-tests to calculate p-values. A p-value of <0.05 indicated statistical significance.

RESULTS

During the study period, 47 female individuals with heart failure (HF) were admitted to IMS & SUM Hospital. Of these, 18 (38%) were classified as Class IV according to the New York Heart Association (NYHA) classification. Iron deficiency was identified in 57% of the individuals (n=27), comprising 32% with absolute iron deficiency and 25% with functional iron deficiency. Co-morbidities, such as Type 2 diabetes mellitus and hypertension, were present in 47% (n=22) of the patients for each condition. Acute pulmonary edema was observed in 42% (n=20) of the individuals, and 13% (n=6) had atrial fibrillation. The mean ejection fraction (EF) was 42.63%, and mean NT-PRO BNP levels were 1688.4 ng/L. The baseline characteristics were categorized into Iron-deficient and Non-Iron-deficient groups (Table 1).

Table 1: Illustration of Baseline Characteristics of the Study Participants.

Feature	Iron deficient heart failure patients	Non Iron deficient heart failure patients	P-Value
History of Previous Myocardial Infarction	8	8	0.46
History of Hypertension	13	9	0.83
History of Type 2 Diabetes Mellitus	13	9	0.83
History of Use of Angiotensin converting enzyme inhibitors	14	10	0.90
Orthopnoea	12	11	0.47
Crepitations	26	15	**0.03**
Gallop	6	2	0.27
Elevated Jugular venous pressure	22	11	**0.04**
Pedal Edema	18	11	0.41
Atrial Fibrillation	4	2	0.62
Chest X Ray Showing Heart Enlargement	7	7	0.50
Pulmonary Edema	13	7	0.36

Table 2: Comparison of mean values between Iron deficient and non - Iron deficient Groups.

Parameter (Mean±SD)	In total study individuals	Iron deficient heart failure patients	Non Iron deficient heart failure patients
Hb (gm/dl)	12.26±0.48	12.2±0.31	12.3±0.22
Ferritin (ng/ml)	239.4±102	138.7±66.5	390.35±190.7
Transferrin Saturation (%)	22.9±10.8	14.3±5.8	35.9±15.6

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	3	1(33.3)	2(66.7)	0.17	0.01	**0.03**
2	12	4(33.3)	8(66.7)	0.40	0.13	
3	14	7(50)	7(50)	0.44	0.17	
4	18	15(83.3)	3(16.7)	0.53	0.24	

In the Iron-deficiency group, there was a higher prevalence of heart failure features, including Crepitations (p-value=0.03) and raised jugular venous pressure (JVP) (p-value=0.04). More individuals in the Iron-deficiency group used ACE-inhibitors (n=14). Mean hemoglobin (Hb), ferritin, and transferrin saturation levels were lower in the Iron-deficiency group (Table 2).

Absolute Iron deficiency was found in 15 (32%) individuals, while functional Iron deficiency was seen in 12 (25%) individuals. In total, Iron deficiency (including both types) was identified in 27 (57%) individuals.

Patients were categorized by NYHA functional class, revealing a statistically significant positive association between NYHA class and iron deficiency. The prevalence of iron deficiency increased with the severity of dyspnea (p-value=0.03) (Table 3).

Further categorization based on left ventricular systolic and diastolic function showed that, among those with systolic dysfunction, 69.3% had iron deficiency (p-value=0.06), and among those with diastolic dysfunction, 60% had iron deficiency (p-value=0.39). However, no statistically significant association was found between systolic and diastolic dysfunction and the presence of iron deficiency, both collectively and within subgroups (Table 4 and 5).

These results underscore the prevalence of iron deficiency in HF, its association with symptom severity and its potential impact on heart failure features.

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

Left Ventricle	Dysfunction	Total	Iron deficient Heart failure patient's n (%)	Non iron deficient heart failure patient's-n (%)	95 % CI		P-VALUE
					Upper	Lower	
SYSTOLIC	Present	26	18(69.3)	8(30.7)	0.69	0.40	0.06
	Absent	21	9(42.8)	12(57.2)	0.59	0.30	
DIASTOLIC	Present	40	24(60)	16(40)	0.93	0.71	0.39
	Absent	7	3(42.8)	4(57.2)	0.28	0.06	

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	13	9(69.2)	4(30.8)	0.42	0.15	0.19
	HFmrEF	13	9(69.2)	4(30.8)	0.42	0.15	
	HFpEF	21	9(42.8)	12(57.2)	0.59	0.30	
DIASTOLIC	Type 1	16	11(68.75)	5(31.25)	0.56	0.24	0.49
	Type 2	15	9(60)	6(40)	0.54	0.22	
	Type 3	9	4(44.4)	5(55.6)	0.38	0.10	

Heart failure with reduced ejection fraction (HFrEF)- EF less than or equal to 40%,
Heart failure with midrange ejection fraction (HFmrEF)- EF of between 40% and 49%,
Heart failure with preserved EF (HFpEF)- EF is greater than or equal to 50%.

DISCUSSION

Our study focused on assessing the prevalence of iron deficiency in non-anemic female heart failure patients and its associations with clinical characteristics. The findings revealed a substantial prevalence of iron deficiency, with 57% of individuals exhibiting either absolute or functional iron deficiency, consistent with previous research in heart failure populations (15).

Notably, the prevalence of iron deficiency was higher in Class IV NYHA patients, highlighting its correlation with the severity of heart failure symptoms, a relationship observed in prior studies. [10] This underscores the clinical significance of addressing iron deficiency as a potential therapeutic target in heart failure management.

Co-morbidities, such as Type 2 diabetes mellitus and hypertension, were common in the heart failure population, affecting 47% of patients. Co-morbidities can complicate heart failure management, emphasizing the need for a multidisciplinary approach to address both heart failure and associated co-morbidities (16).

Additionally, our study noted a higher prevalence of acute pulmonary edema and atrial fibrillation in the cohort, consistent with the clinical profile of heart failure patients, where acute decompensation and arrhythmias are common manifestations (17). Although not directly related to iron deficiency, these observations highlight the complex nature of heart failure and the need for comprehensive management strategies.

Furthermore, individuals in the Iron-deficiency group exhibited a higher prevalence of certain heart failure features, such as Crepitations and raised jugular venous pressure (JVP), suggesting that iron deficiency may contribute to the severity of heart failure symptoms and clinical signs, as supported by previous research. [27] The increased use of ACE-inhibitors in the Iron-deficiency group may reflect healthcare providers' attempts to manage heart failure symptoms and mitigate the effects of iron deficiency (18).

Despite these associations, our study did not find a statistically significant link between iron deficiency and systolic or diastolic dysfunction. This discrepancy with some previous research may be attributed to the relatively small sample size, indicating the need for larger cohort studies to explore this relationship more comprehensively.

In conclusion, our study highlights the high prevalence of iron deficiency in non-anemic female heart failure patients and its association with the severity of heart failure symptoms. Co-morbid conditions and clinical features commonly observed in heart failure patients add complexity to management. While we did not find a significant association between iron deficiency and cardiac dysfunction, ongoing research is crucial to elucidate the intricate relationship between iron status and cardiac function. Identifying and managing iron deficiency in heart failure patients remains integral to comprehensive heart failure care.

LIMITATIONS OF THE STUDY

This single-center study conducted in odisha limits the generalizability of findings to a broader population, potentially not representing the diversity of heart failure patients across various regions and healthcare settings. The relatively small sample size of 47 non-anemic female heart failure patients may impact the robustness and representativeness of results. The cross-sectional design hinders the establishment of causal relationships and tracking of changes over time. Exclusion criteria may have omitted relevant subgroups. Heart failure's complex nature and diverse presentations may not have been fully accounted for. Lack of longitudinal data limits insights into changes in iron deficiency over time. Findings may not apply universally due to variations in healthcare systems, socioeconomic statuses, and ethnic backgrounds.

Recognizing these limitations is crucial for a nuanced interpretation of study results and for guiding future research in this area.

CONCLUSION

This research highlights the significant impact of iron deficiency on heart failure patients in India, an often neglected aspect of their care. While preliminary data

suggest potential effects on cardiac function, extensive research is needed to validate these findings. The study calls for in-depth analysis and routine iron status testing in national recommendations to enhance heart failure management.

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