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THE BURDEN OF IRON DEFICIENCY IN INDIAN PATIENTS WITH HEART FAILURE: TIME TO STEP-UP

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ABSTRACT

Background: Heart failure (HF) is a leading global disease and iron deficiency (ID) in HF carries significant health ramifications such as worsened exercise capacity, poor quality of life and negative prognosis. The present multi-centric observational, data collection study was conducted across various HF clinics in India with an objective to determine the nationwide frequency of ID in Indian patients with HF. **Methods:** Patients ≥ 18 years of age who had visited the HF clinic and provided their consent for the future usage of their anonymized data were included in the study. **Results:** ID was observed in 68.80% of HF patients in the study. **Conclusion:** This study emphasises the need of screening and monitoring HF patients for ID.

KEYWORDS: Heart failure; Iron deficiency; Absolute iron deficiency; Ferritin; Screening of iron deficiency.

INTRODUCTION

Heart failure (HF) is a chronic, progressive and heterogeneous clinical syndrome resulting from cardiac overload and damage.[1] It is a leading global challenge representing a major cause of frequent hospitalizations, morbidity and mortality.[2] Globally, around 64.3 million

people are living with HF, with nearly half of them having HF with reduced ejection fraction (HFrEF).[3] The reported prevalence of HF was 1.2/1000 in India. The prevalence of HF in Indian population was estimated to be approximately 1% of the total population.[4]

HF is exacerbated by comorbidities that have a detrimental effect on patients. Iron deficiency (ID) in HF carries significant health ramifications such as worsened exercise capacity, poor quality of life and negative prognosis.[5] Reported evidence from a small single-center regional study highlighted prevalence of ID was 76% in Indian patients with chronic HF with a higher rate in women than in men.[6]

Absolute ID is identified by depleted iron stores. International guidelines on HF characterize ID as a serum ferritin <100 µg/L [absolute ID].[8]

The European Society of Cardiology (ESC) 2021 HF guidelines and 2022 ACC/AHA HF guidelines recommend the optimal management of underlying diseases and co-morbidities, including ID, in HF. In keeping with the importance of the optimal management of co-morbidities, the ESC HF guidelines recommend that 'all patients with HF should be routinely screened for anemia and iron deficiency with a complete blood count, serum ferritin concentration, and TSAT.[9] Unfortunately, there is no recent large nationwide epidemiological data from India, to recognize the true burden of ID in HF.

Majority of the prevalence studies of ID in HF are from the western world. Few studies evaluating this association for the Asian population are available however studies targeting Indian patient population are lacking.[8] Limited data from India proves to be a challenge for developing the appropriate management strategies for ID in HF leading to delay in diagnosis and poor prognosis. The present multi-centric study was planned with an objective to determine the nationwide frequency of ID in Indian patients with HF visiting HF clinics and also to assess the gender and age wise association of absolute ID.

MATERIALS AND METHODS

Study Design

STEP UP (Study To Evaluate Presence of Underlying Iron Deficiency in Indian Patients with Heart Failure) was a multi-center, retrospective, observational, data collection study across various HF clinics located at multiple geographic locations in India. Data of HF patients visiting these centers and evaluated for iron profile tests performed by the National

Accreditation Board for Testing and Calibration Laboratories(NABL) accredited laboratories in past was collected.

Patient Characteristics

Patients ≥ 18 years of age who had visited the HF clinic and provided their consent for the future usage of their anonymized data were included in the study. Patient data for whom iron profile tests were performed in past with NABL accredited laboratories was retrieved and analyzed. Patients were excluded from the study if the investigator was not willing to share anonymized data of such patients and iron profile tests were performed by non NABL accredited laboratories.

Sample size

Convenience sampling was used as a practical strategy to obtain the required patient sample by using the clinical record form (CRF) of the patients meeting the inclusion/exclusion criteria available from the various centers included in the study within the stipulated study period.[10]

Outcome measures

The primary outcome measure of this study was the frequency of absolute ID in HF patients. The secondary outcome measures were the gender and age distribution of absolute ID in these patients.

Anonymized data of patients matching the inclusion and exclusion criteria was retrieved and filled in the clinical record form (CRF). Data of these patients was electronically stored and used for research. The following laboratory values were considered as per 2021 ESC HF guidelines on ID in HF: serum ferritin <100 µg/L [absolute ID].[8]

Statistical analysis

De-identified data obtained from the respective centers was entered in a Microsoft Excel Sheet and analyzed using suitable statistical method. Descriptive statistics was used for analysis and categorical data was represented as frequencies and percentages. Quantitative data was described as Mean ± standard deviation (SD).

Ethical Considerations

This study was approved by the Independent Ethics Committee, Dhanashree Hospital, Pune. The study was registered with the Clinical Trial Registry of India (CTRI) with a registration number CTRI/2022/12/048457.

RESULTS

De-identified data of 545 patients with HF from 61 HF clinics across India from March 2021 to March 2022 was retrieved and analyzed. Frequency of Absolute Iron Deficiency have been shown in Table 1.

Table 1: Frequency of Absolute Iron Deficiency (n=545).

Gender	Absolute ID (n=375) [Serum Ferritin< 100 µg / L]	No ID (n=169)
Male	91 (16.69%)	99 (18.16%)
Female	284 (52.11%)	70 (12.84%)

*The data is represented as frequency (%).

ID- Iron Deficiency; n-sample size; TSAT- Transferrin saturation

Female predominance in ID with HF (52.29% vs 16.69%) was noted. Approximately 69% population of HF reported ID. Absolute ID (75.73% vs 24.26%) was more common in females than males. The study involved wide variety of patients with different age groups [(18-20 years) to >80 years].

Table 2: Prevalence and mean age of the patients according to iron deficiency (n=545).

Iron Deficiency	Frequency (%)	Age (Years) (Mean ± SD)
Absolute ID (n=375)	68.80	41.10 ± 16.21
No ID (n=169)	31.20	53.58 ± 15.96
Total (n=545)	**100**	44.98 ± 17.12

ID- Iron Deficiency; n-sample size; SD- Standard Deviation

Absolute ID was more common in the second, third and fourth decades of life (Table 3) and it was also more common in females between 21-30 years and in males between 51-60 years (Table 4).

Table 3: Age-wise prevalence of iron deficiency (n= 545).

Age (Years)	Absolute ID (n= 375) Frequency (%)	No ID (n=170) Frequency (%)
18-20	11 (2.01%)	2 (0.36%)
21-30	117 (21.47%)	17 (3.11%)
31-40	78 (14.31%)	19 (3.48%)
41-50	68 (12.47%)	35 (6.42%)
51-60	48 (8.8%)	34 (6.23%)
61-70	31 (5.68%)	41 (7.52%)
71-80	17 (3.12%)	17 (3.11%)
81-90	5 (0.91%)	6 (1.1%)
91-100	0	0

ID- Iron Deficiency; n-sample size

Table 4: Age and gender wise prevalence of iron deficiency (n= 545).

Age (Years)	Gender	Absolute ID (n=375) Frequency (%)	No ID (n=169) Frequency (%)
18-20	M	4 (0.73%)	1 (0.18%)
	F	7 (1.28%)	1 (0.18%)
21-30	M	11 (2.01%)	12 (2.2%)
	F	106 (19.44%)	5 (0.91%)
31-40	M	13 (2.38%)	11 (2.01%)
	F	65 (11.92%)	8 (1.46%)
41-50	M	18 (3.3%)	16 (2.93%)
	F	50 (9.17%)	19 (3.48%)
51-60	M	19 (3.48%)	21 (3.85%)
	F	29 (5.32%)	13 (2.38%)
61-70	M	14 (2.56%)	26 (4.77%)
	F	17 (3.11%)	15 (2.75%)
71-80	M	9 (1.65%)	10 (1.83%)
	F	8 (1.46%)	7 (1.28%)
81-90	M	3 (0.55%)	2 (0.36%)
	F	2 (0.36%)	4 (0.73%)
91-100	M	0 (0%)	0 (0%)
	F	0 (0%)	0 (0%)

ID- Iron Deficiency; n-sample size; M- male; F- female

DISCUSSION

STEP-UP was conducted with an objective to determine the nationwide frequency of ID in Indian patients with HF. This will establish true burden of ID in HF as this data is lacking for Indian population. Data of 545 patients were collected and analyzed from 61 HF clinics across India from March 2021 to March 2022.

In recent years, there is increasing recognition of the burden of ID in patients of HF which is evidenced by the incorporation of management of ID in the 2021 ESC HF guidelines.[5] In the USA, a prospective study evaluating ID in HF identified a prevalence of 61.3%.[11] Similarly, a study from Europe reported a prevalence rate of ID in HF ranging from 37% to 50%.[6,12] Studies assessing HF patients in Asian population demonstrated that Indian patients had high rates of ID.[13,14] Reported evidence from a small single-center regional study highlighted prevalence of ID was 76% in Indian patients with chronic HF with a higher rate in women than in men.[6] Additionally, Trivandrum Heart Failure registry and National Heart Failure registry reported that HF was more common in the younger Indian population which was a decade younger than the evidence from the international registries.[15-17]

In the present study, we found the frequency of ID as 68.80% which is at par with the reported studies. The gender-based analysis of present study demonstrated a significant higher frequency of ID in females than males (52.29% vs 16.69%). Absolute ID was found to be more common in the younger population (21-50 years). These findings highlight on periodically screening of all HF patients for ID irrespective of age.

In this study, more than half of the total study population 68.80% had absolute ID. These findings emphasize on evaluation of complete iron profile in the routine screening of HF patients, a practice still unpopular in countries like India.

The findings from our study emphasize on a remarkably high prevalence of ID in Indian HF patients. ID in HF represents an independent predictor of poor prognosis.[18] Besides adding burden of decreased exercise capacity and quality of life, ID has been associated with increased hospitalization and mortality rates as well.[19] The published evidence highlights that ID correction is beneficial in patients with HF and coexisting ID in terms of improvement in NYHA functional class, quality of life, exercise capacity and reduced hospitalizations for HF.[20-23] Evidence for iron replacement in acute decompensated heart failure and heart failure with preserved ejection fraction (HFpEF) is currently limited.[18,25] Intravenous iron does not yet report strong benefits in terms of reducing mortality.[26]

Guidelines worldwide are highlighting evaluation and treatment of ID in HF patients. As our study implies that approximately three-fourths of Indian HF patients have ID, there is an important clinical need for incorporation of routine screening of ID in the Indian management protocol.

To best of our knowledge, this is the largest multi-centric study in the recent past evaluating the frequency of ID across all geographic Indian population of ambulatory HF patients. However, the study is limited by its retrospective design and missing data. Many important and relevant biochemical and clinical data points were missing. This is solely due to unavailability of data in the selected patient. Biomarkers of interest such as serum iron, soluble transferrin receptor or hepcidin were not available as they are not routinely assessed in clinical practice. Haemoglobin levels were not included in the study; hence the presence or absence of iron deficiency anemia could not be analysed. Ejection fraction was not included in the data collection. Therefore, all types of HF were included in the study without any separate analysis for the different types of HF.

CONCLUSION

Our study emphasizes on a remarkably high burden of ID in Indian HF patients as approximately three-fourths of HF patients in the study had ID. This study highlights frequency of absolute ID of 68.80% (with female predominance) in Indian patients of HF. Absolute ID was more frequent in 21-50 years' age group. This study further emphasizes the need for routine screening of ID in patients of HF. Evaluation and optimal management of ID in HF could effectively reduce the disease burden and improve HF outcomes.

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