



Prevalence of Iron Deficiency in Patients of Heart Failure with Reduced Ejection Fraction and Response to Injectable Iron Therapy- A Hospital Based Observational Study

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| Article History | Abstract |
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| Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 25 Nov 2023 | <p>Aim of the Study: To estimate the prevalence of iron deficiency in patients of heart failure with reduced ejection fraction & response to injectable iron therapy in patients with iron deficiency anemia in heart failure with reduced ejection fraction. Materials and Methods: 1000 patients with heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction <40%) who met the prespecified inclusion and exclusion criteria were chosen. A detailed history was taken and clinical examination was performed. Peripheral venous blood was drawn, and a complete hemogram along with iron studies (iron, ferritin, transferrin saturation and total iron binding capacity) were performed. Results: Prevalence of iron deficiency among patients of heart failure with reduced ejection fraction was 63%. Most of the patients (71.42%) had absolute iron deficiency whereas 28.57% cases had functional iron deficiency status. 520(82.53%) patients were found to be anemic and 110(17.46%) patients were non anemic which was statistically significant, suggesting that the prevalence of iron deficiency was higher among all anaemic patients with heart failure with reduced ejection fraction, as compared to non-anaemic individuals. The use of injectable iron therapy significantly improved the NYHA functional status among all the patients of heart failure with reduced ejection fraction. Conclusion: Our study showed that there is a large burden of iron deficiency in patients of heart failure with reduced ejection fraction irrespective of anemia status. The correction of iron deficiency, irrespective of the presence or absence of concomitant anemia, improves the NYHA functional status and quality of life. It may therefore be prudent to assess and use iron status as a therapeutic target in all patients with heart failure even with normal hemoglobin levels.</p> |
| CC License CC-BY-NC-SA 4.0 | Keywords: Iron deficiency, Heart failure with reduced ejection fraction |

1. Introduction

Heart failure (HF) is a prevalent issue that affects 1–2% of the population and is a leading cause of death, illness, and poor quality of life (QoL).^(1,2) Anemia is a common comorbid condition in stable HF patients, and it worsens morbidity by causing regular hospitalizations, reduced exercise ability, poor quality of life, and increased death.⁽³⁾ Anaemia is coexisting in about 20% of HF patients and is an established contributing factor in predicting poor outcomes and hospitalisations in patients with HF.⁽⁴⁾ HF is frequently accompanied with iron deficiency (ID) with or without anemia.⁽⁵⁾ Despite the fact that ID is the most prevalent nutritional deficit in the world, impacting more than 1/3rd of the total population its link to HF with or without anemia is gaining attention. It needs to be emphasized that ID can occur without decreased hemoglobin. However, measurement of iron stores still does not form a routine place in the evaluation of patients of HF, thus making it a generally underdiagnosed entity in this subset of patients. Studies, performed in patients with HF, have proven that iron deficiency is associated with decreased overall exercise capacity and more severe HF symptoms such as fatigue and exertional dyspnea.⁽⁶⁾ Clinical benefits of iron therapy in iron-deficient patients with HF are therefore

expected to result not only from the increase in haemoglobin concentration, but also from an improvement in the functioning of nonhematopoietic tissues, such as skeletal muscles.⁽⁷⁾ ID is an appealing therapeutic target since replacement therapy improves outcome in individuals with HF - a notion that has been verified in clinical research recently.⁽⁸⁾ The European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute and chronic HF for the first time identified ID as a comorbidity in HF in 2012, and suggested identification of ID based on iron values in all individuals with suspected HF.⁽⁹⁾ A recent randomized, double-blind research shown that intravenous iron improved functional outcomes and standard of living in ID individuals with or without anemia and heart failure (HF).⁽¹⁰⁾ As a result, ID has recently taken on a distinctive function in the area of HF and is the topic of new research.

2. Materials And Methods

This was a prospective observational analytical study conducted in a tertiary care hospital in India. The patients who were admitted having clinical heart failure with NYHA functional class II- IV were taken under consideration at the time of enrolment after obtaining written informed consent were included in the study. Data were collected using a standard questionnaire and answers were recorded. Any personal history of hypertension, dyslipidemia, diabetes mellitus and CAD were noted. Tobacco consumption in any form was asked about. All patients underwent detailed evaluation including clinical, biochemical (including complete blood counts, serum iron profile and NTPROBNP levels), electrocardiography and echocardiography evaluation.

Inclusion criteria

- Written informed consent must be obtained prior to any screening procedures
- Patient having clinical criteria for heart failure
- NYHA functional class II- IV was taken under consideration at the time of enrolment
- Ejection fraction on echocardiography $\leq 40\%$

Exclusion Criteria

- Patient who had acute coronary syndrome with heart failure
- Patient who had myocardial infarction in the last three months
- Patients of severe comorbidities like chronic kidney disease, chronic lung disease, chronic liver disease
- Red blood cells (or other blood component) transfusions or erythropoietin therapy within 3 months prior to enrolment.

3. Results and Discussion

Observation

A total of 1000 patients of heart failure with reduced ejection fraction were enrolled in the study. All the Heart failure cases with reduced ejection fraction were evaluated to observe the serum Iron status. Mean age of all patients enrolled in this study was 56.54 ± 8.56 years

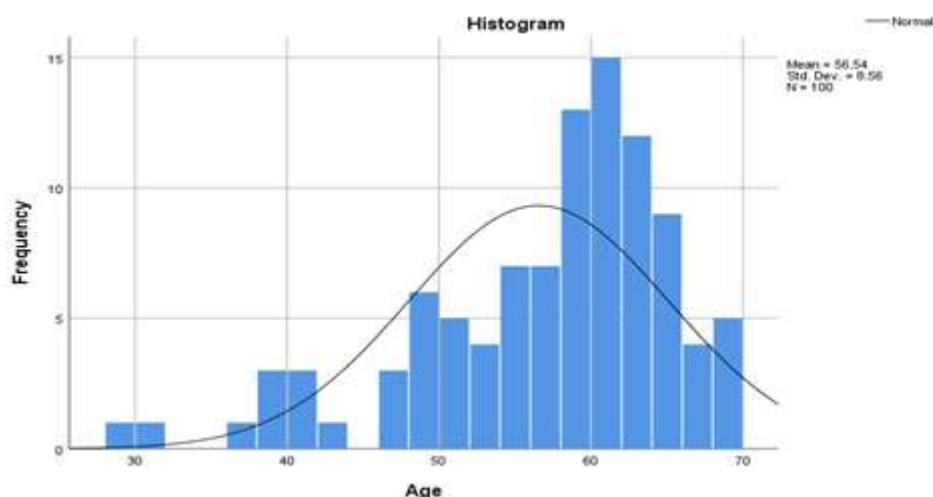


Fig 1: Histogram showing normal distribution of age among HFrEF patients (n=1000)

with a range from minimum 29 years to 69 years (Fig 1). Most of the patients were belonging to above 50 years age group and only 2% patients belonged to age group 18 to 30 years of age ((Fig 2).

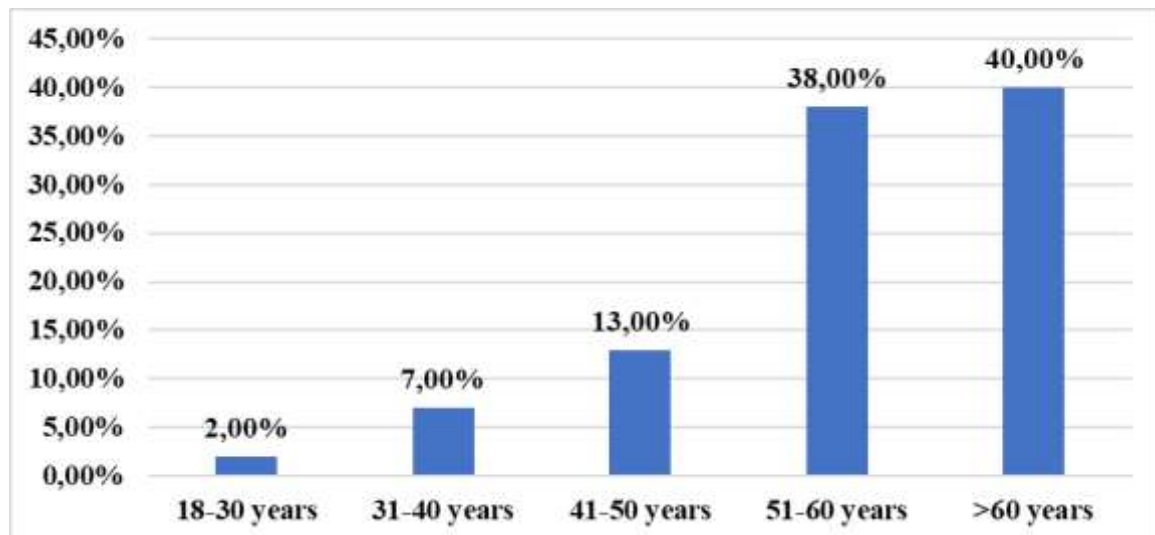


Fig 2: Age distribution as per different age groups among HFrEF patients (n=1000)

Our study showed **male** preponderance with 57% males and 43% females with Heart failure and reduced ejection fraction. (**Fig 3**)

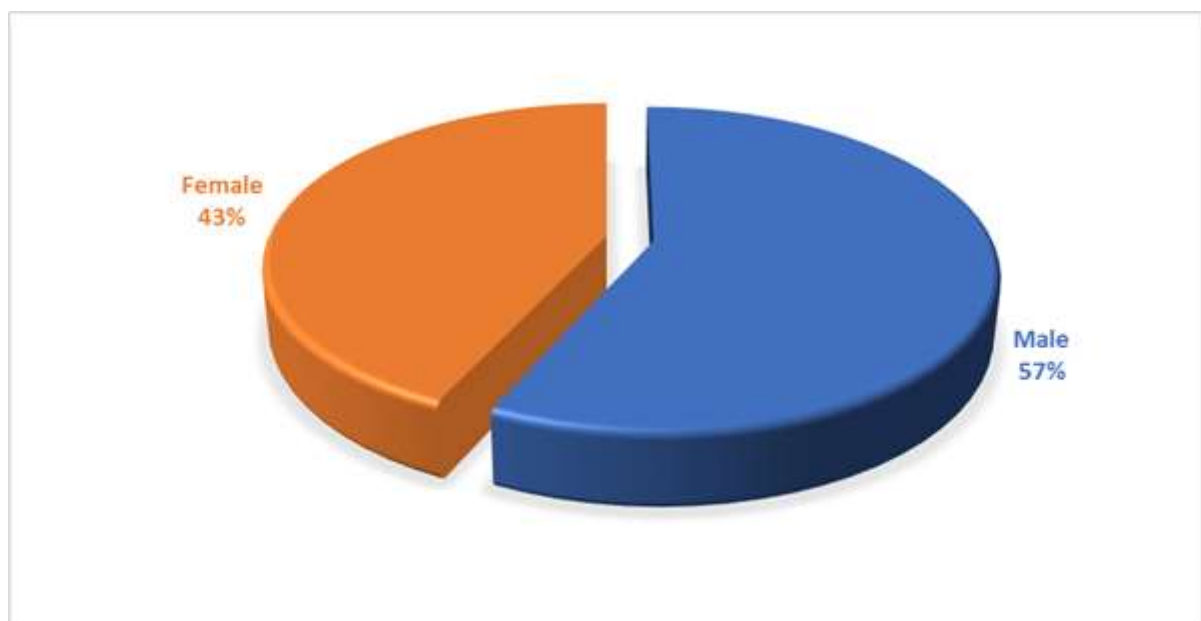


Fig 3: Pie diagram showing gender distribution of HFrEF patients(n=1000)

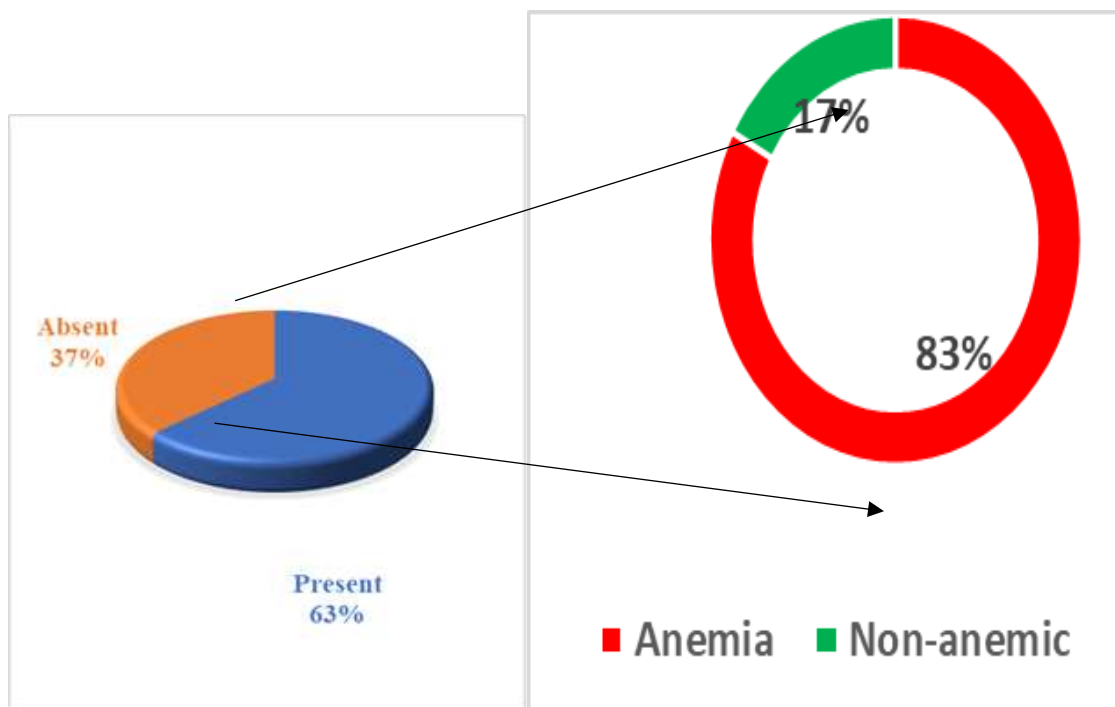
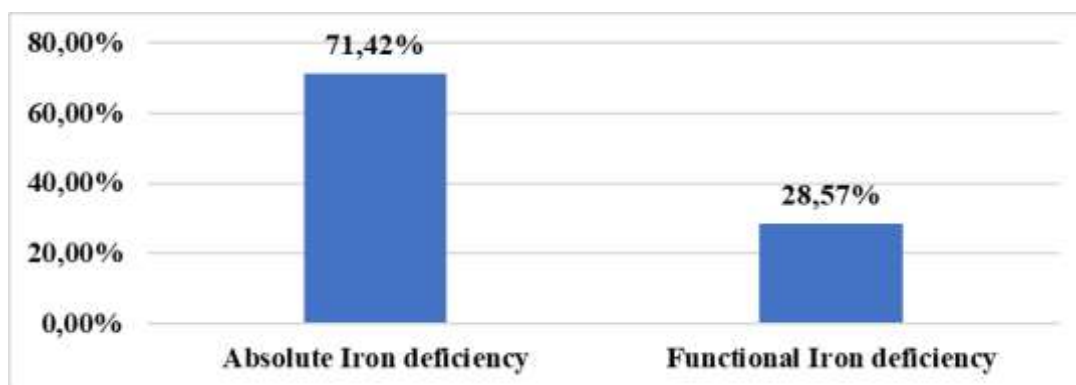


Fig 4: Prevalence of Iron deficiency among all HFrEF patients (n=1000)

The prevalence of Iron deficiency in our study was found to be 63% among them 83% were anemic and 17% non-anemic in all the heart failure with reduced ejection fraction patients which was depicted in (Fig 4)

Fig 5: Distribution of Iron deficiency proportion having absolute and functional iron deficiency among HFrEF patients (n= 630)



Our study shows 71.42% patients (450 out of 630) had absolute Iron deficiency whereas 28.57% had Functional Iron deficiency (fig 5).

Fig 6: NYHA Class at baseline among Iron deficient patients of HFrEF (n=630)

| | | Frequency (n) | Percentage (%) |
|------------|-------|---------------|----------------|
| NYHA Class | 2 | 218 | 34.61% |
| | 3 | 97 | 15.38% |
| | 4 | 315 | 50% |
| | Total | 630 | 100% |

In our study 50% patients were in NYHA class 4 where as 15% and 34.61% patients were in class 3 and class 2 respectively. (Fig 6)

Fig 7: Change in NYHA functional status after injectable Iron therapy among Iron deficient patients of HFrEF (n=630)

| | | Frequency (n) | Percentage (%) |
|------------|-------|---------------|----------------|
| NYHA Class | 1 | 303 | 48.07% |
| | 2 | 254 | 40.38% |
| | 3 | 73 | 11.53% |
| | Total | 630 | 100% |

Fig 8: NYHA functional class of HFrEF patients at six month of iron therapy (n= 630)

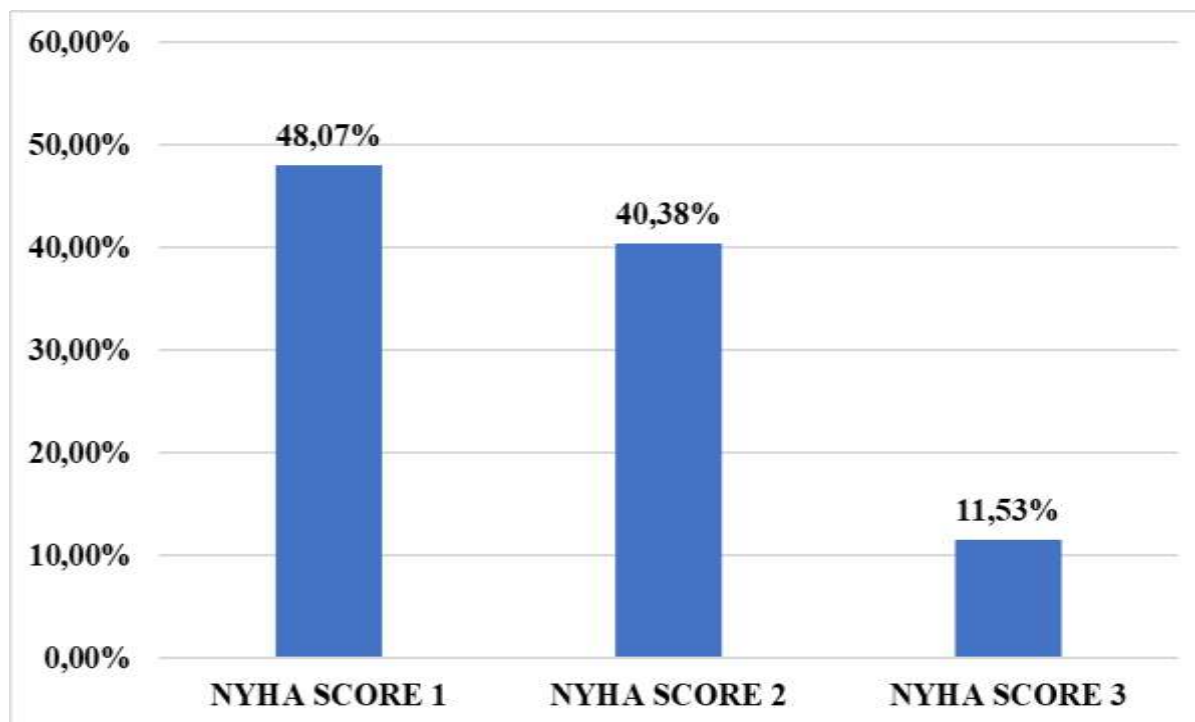


Fig 9: Comparing NYHA class among Iron deficient patients before and at six month of Iron therapy (n= 630)

| NYHA class Baseline * NYHA class Follow up Cross tabulation | | | | | |
|---|---|-----------------------------|-----|----|-------|
| | | NYHA Score during follow up | | | Total |
| | | 1 | 2 | 3 | |
| NYHA Score at Baseline | 2 | 157 | 40 | 21 | 218 |
| | 3 | 39 | 41 | 17 | 97 |
| | 4 | 107 | 173 | 35 | 315 |
| Total | | 303 | 254 | 73 | 630 |
| P-value | | <0.001 | | | |

During follow up after the intervention at 6 months of giving injectable iron therapy to all iron deficiency patients, NYHA class was again accessed and found to be improved in all patients. Around 48.07% patients score was improved to NYHA class 1, 40.38% patients' score was improved to NYHA class 2 and only 11.53% patients had NYHA class 3 after 6 months of intervention. The association between improvement in NYHA class at 6 month and administration of injectable iron therapy at presentation was found to be statically significant in our study (p – value <0.001) (Fig 8 & 9)

Fig 10: Comparison between baseline Ejection fraction and EF at 6 month of Injectable iron therapy

| | Mean | Std. Deviation | Std. Error Mean | P-value |
|-------------------|---------|----------------|-----------------|---------|
| Ejection fraction | 34.30 | 4.312 | 0.431 | 0.071 |
| Follow up EF | 34.6300 | 4.30329 | 0.43033 | |

The mean Ejection fraction improved among patients after 6 months of injectable iron therapy but is not statistically significant (p-value>0.05). (Fig 10)

In this study, 1000 patients with heart failure with reduced ejection fraction who met the prespecified inclusion and exclusion criteria were chosen. A detailed history was taken and clinical examination was performed. A complete hemogram along with iron studies (iron, ferritin, transferrin saturation and total iron binding capacity) were performed. The study was conducted with an aim to estimate the prevalence of Iron deficiency in all patients of heart failure with reduced ejection fraction and to observe the response of injectable iron therapy in these patients.

The mean age of all patients enrolled as cases in this study was 56.54 ± 8.56 years with a range from minimum 29 years to 69 years. Studies by Tee Joo Yeo et al⁽¹¹⁾ and John G. F. Cleland et al⁽¹²⁾ in their study found similar age distribution with a higher prevalence in fifth and sixth decade. Our study showed male preponderance similar to previous studies. The higher risk of heart failure with reduced ejection fraction in men compared to women has been attributed to their predisposition to macrovascular coronary artery disease and myocardial infarction—a well-known antecedent to heart failure with reduced ejection fraction.

The total number of iron deficient individuals was 630 (63.0%). Among them 520(82.53%) patients found to be anaemic and 110(17.46%) patients were non anaemic which was statistically significant, suggesting that the prevalence of iron deficiency was higher among all anaemic patients with heart failure with reduced ejection fraction, as compared to non-anaemic individuals. Out of total iron deficiency patients 450(71.42%) had absolute iron deficiency and 180(28.57%) had functional iron deficiency. However, the identification of iron deficiency in patients with normal hemoglobin levels emphasizes the incorporation of iron level assessment in all patients of heart failure.

Among the patients who had heart failure with reduced ejection fraction during baseline assessment most cases (53%) were found as NYHA class 4 followed by 31% with NYHA class 2 and then 16% were under NYHA class 3. Among iron deficient patient (63%), during baseline 34.61% had NYHA class 2, 15.38% had NYHA class 3, 50% had NYHA class 4. However, after 6 month of injectable iron therapy the NYHA score was significantly improved ($p < 0.001$). After intervention around 48.07% patients reported with NYHA class 1 followed by 40.38% with NYHA class 2 and only 11.53% with NYHA class 1 category. No significant differences were found between anemic and non-anemic patients. The variations between iron deficiency status and NYHA scoring were not found to be statistically significant in our study. Ghali et al⁽¹³⁾ found among 71% heart failure cases had experienced improvement in their NYHA scoring with minor improvement in iron levels. But another study where palazzuoli A et al⁽¹⁴⁾ gave 12 weeks of darbepoietin therapy found no change in baseline and after intervention NYHA scoring.

Two larger-scale clinical trials which reported the beneficial effects of IV iron therapy in CHF patients with iron deficiency. The FAIR-HF trial⁽¹⁵⁾ showed that among the patients who were given IV Iron, 50% reported being much or moderately improved, and 47% were in NYHA functional class I or II. No significant differences were found between anemic and nonanemic patients. The second study CONFIRM-HF trial⁽¹⁶⁾ showed after IV iron therapy in iron-deficient heart failure patients, there was significantly greater improvement in 6MWT distance at week 24. The beneficial effects of iron therapy were sustained throughout the period of study. Recent meta-analysis by Jankowska et al⁽¹⁶⁾ showed the risk of cardiovascular hospitalization, heart failure hospitalization, NYHA class appeared to be significantly reduced by IV iron therapy.

Numerous mechanisms unrelated to hemodynamic dysfunction may underlie impaired exercise tolerance in patients with heart failure. Among them, inadequate oxygen supply and impaired oxygen use by skeletal muscle during exercise contribute to poor clinical status^(17,18). In addition, anemia may aggravate symptoms in patients with heart failure⁽¹⁹⁾. Targeting these abnormalities may confer functional benefits to such patients. Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; it also is involved in erythropoiesis^(20,21). Traditionally, iron deficiency has been considered to have clinical consequences only in the presence of anemia. Alternatively, a reduced hemoglobin level can be viewed as the result of a process beginning with the gradual depletion of iron stores^(22,23). Iron deficiency in patients with or without anemia attenuates aerobic performance and is accompanied by reports of fatigue and exercise intolerance⁽²⁴⁾. The repletion of iron in patients who have iron deficiency without heart failure improves cognitive, symptomatic, and exercise performance^(25,26). Recently, it has been recognized that patients with heart failure may be prone to the development of iron deficiency because of a depletion of iron stores or defective iron absorption and the reduced availability of iron recycled in the reticuloendothelial system^(27,28). Four small studies showed that the correction of iron deficiency with the use of intravenous iron

in patients with chronic heart failure may result in clinical benefits. ⁽²⁶⁻²⁹⁾ In one of these studies, the symptomatic benefit was similar in patients with anemia and those without anemia⁽²⁹⁾.

4. Conclusion

Our study showed that there is a large burden of iron deficiency in patients of heart failure with reduced ejection fraction irrespective of anemia status. Similar to previous trials our study confirms that correction of iron deficiency, irrespective of the presence or absence of concomitant anemia, improves the NYHA functional status and quality of life. It may therefore, be prudent to assess and use iron status as a therapeutic target in all patients with heart failure even with normal hemoglobin levels. This is especially true for a country like India where a significant proportion of the population are iron deficient.

Limitations Of the Study

1. Iron supplementation and re-assessment for symptomatic improvement may have subjective and observer bias.
2. Follow-up and evaluation of the effects of iron deficiency on mortality and re-hospitalization was not done.

Conflict Of Interest: Nil

Source Of Funding: Self

Ethical Clearance: Ethical Clearance was obtained from the Institutional Ethics Committee prior to the commencement of the study

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