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# IRON PROFILE IN HEART FAILURE PATIENTS – A HOSPITAL BASED CROSS-SECTIONAL STUDY IN NORTH-EASTERN PART OF INDIA

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## Abstract

**Background:** Iron deficiency (ID) is a major co-morbidity occurring in about 50% of patients with heart failure (HF) and in an even higher proportion of patients with acutely decompensated HF, ranging from 72% to 83%. The presence of ID in HF patients has clinical implications independently from the presence of anemia. ID contributes to maintain and worsen symptoms of HF such as reduced exercise tolerance and limitations in daily living activities and concurs to impair quality of life. ID also increases patient mortality and morbidity, leading to a greater risk for early hospital readmission and prolonged hospitalization. There is scarce of data regarding iron profile in heart failure patients in Manipur, India. The present study aimed to determine the serum iron, iron binding capacity and ferritin level among the patients with HF and its correlation with the severity of HF. **Materials and Methods:** A cross-sectional study conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, India from January 1, 2021, to December 31, 2022, among heart failure patients admitted in Medicine ward and Intensive coronary care unit (ICCU). Routine hematological, radiological investigation and biochemical parameters including serum iron, serum ferritin, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC) were done. Statistical Package for Social Sciences (SPSS) 21.0 was used for statistical analysis. ANOVA test and Student's t test were performed. A p-value < 0.05 was considered as statistically significant. **Result:** A total of 149 heart failure patients were reported with a mean age of 59.38(± 11.7) years, with majority females (78, 52.4%) and most patients 53 (35.8%), belonging to obese category I for Body mass index. According to NYHA classification, majority of the patients belonged to class IV (63, 42.4%) followed by class III (33, 22.1%). Twenty-one(30%) male patients had low serum total iron (<60µg/dl) and 24 (30.7%) female patients had low serum total iron (<35µg/dl) , 36(24.1%) patients had high TIBC >425 µg/dl and 59(39.8%) patients had high UIBC >360 µg/dl.The mean serum ferritin of male patients was 390.85 ng/ml and that of female was 365ng/ml. Serum iron (p value 0.03) and serum ferritin (p value 0.03) shows statistically significant differences in relation to the severity of the heart failure while TIBC and UIBC did not have significant differences with the severity of heart failure (p value 0.05).**Conclusion:** The serum iron levels, serum ferritin, serum total iron binding capacity were significantly deranged in heart failure cases, moreover when severity of heart failure increases. Iron profile screening in HF cases and further multicentric study is needed to find out the causal association are highly recommended.

## INTRODUCTION

Heart failure (HF) is an increasing public health concern and a leading cause of morbidity and death globally. In the general population, the incidence of HF with reduced ejection fraction ranges from 1-2 percent, but in the over-65 age group, it can reach up to 10%.[1] Heart failure (HF) is a serious illness with a dismal prognosis. Its outcome depends on the severity of the heart disease and co-morbidities.


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Among these co-morbidities, iron deficiency (ID) is present in 30-50% of patients with chronic HF, and an even larger percentage of patients with acutely decompensated HF (72%–83%). ID in HF results due to depletion of iron stores, defective iron absorption and reduced availability of iron recycled in the reticuloendothelial system.[2] In addition to being essential for oxygen transport and erythropoiesis, iron is also needed for the mitochondrial level of energy production and other cellular functions. Iron has a role both in providing oxygen to the body fuel and enhancing the oxidative capacity of energy manufacturing factory of the myocytes.[3] Iron deficiency is associated with worse symptoms and unfavourable clinical outcomes, regardless of left ventricular ejection fraction (LVEF).[4] When ferritin <100 μg/L or ferritin 100–300 μg/L and transferrin saturation (TSAT) <20% it leads to the following conditions- Decrease oxygen storage in myoglobin, Mitochondrial dysfunction, Oxidative stress, Cellular apoptosis, Reduced myocardial function and Reduced oxygen transport in hemoglobin.[2]With the above condition it leads to reports of fatigue, exercise intolerance, increased hospitalization and increased mortality and hence leads to heart failure.[5-9] Many previous literature had shown different findings on the role of iron ferritin as a risk factors in causing heart failure.[10-16] For these reasons, the 2021 European Society of Cardiology (ESC) guidelines recommend to assess the iron status as part of examinations to be performed in HF patients in order to identify their needs. Making a diagnosis of ID has important practical implications: according to recent trials enrolling patients with HF with reduced ejection fraction (HFrEF), the correction of ID improved symptoms and quality of life of these patients, with preliminary data showing a positive impact on the risk of hospitalizations.[17]Hence, this study was conducted to determine serum iron, iron binding capacity and ferritin level among the patients with heart failure.

## MATERIALS AND METHODS

A hospital based cross-sectional study was conducted among the patients with heart failure admitted in Intensive Coronary care Unit (ICCU) and Medicine ward of Regional Institute of Medical Sciences, Imphal, Manipur, India, from January 1, 2021, to December 31, 2022, in collaboration of Biochemistry Department, RIMS, Imphal. The severity of heart disease was taken as per New York Heart Association (NYHA).[18 ]

**Inclusion criteria**

Included all diagnosed heart failure persons aged above 18 years of both sexes.

**Exclusion criteria**

Included patients with known case of chronic kidney disease, history of acute blood loss, iron supplementation in last 3 months, having hemolytic diseases, pregnancy issue and neoplastic disease.

**Sample Size:** Sample size was calculated by using the formula: n = 4PQ d 2 where,

P = Prevalence (from a previous study conducted by Sharma SK et al [15] the value was found to be 76%)

Q = 100-P

d = absolute allowable error (5-10% of P) = 7 = 4 × 76(100-76) 7 2 = 148.89

Required sample size (n) = 149

**Study Tools**

1. Estimation of serum iron: measured by Photocolorimetric method.
2. Estimation of serum ferritin measured by enzyme linked immunosorbent assay.

**Operational definitions:**

Iron profile such as total iron binding capacity, serum ferritin and serum iron level were taken as per World Health Organisation (WHO) guideline.[19]

1. Normal Serum Iron Level. a. Male: 60 – 160 μg/dl b. Female: 35 – 145 μg/dl

2. Total iron binding capacity: 250 – 425 μg/dl.

3. Unsaturated iron binding capacity: 160 – 360 μg/dl.

4. Serum ferritin a. Men: 60-400 ng/ml b. Cyclic women: 10-150 ng/ml c. Menopausal women: 24-280 ng/ml

5. New York Heart Association (NYHA) Classification of severity of Heart Failure [20]

NYHA Class I: No symptoms* with normal physical activity. Normal functional status.

NYHA Class II: Mild symptoms* with normal physical activity. Comfortable at rest. Slight limitation of functional status.

NYHA Class III: Moderate symptoms* with less than normal physical activity. Comfortable only at rest. Marked limitation of functional status.

NYHA Class IV: Severe symptoms* with features of heart failure with minimal physical activity and even at rest. Severe limitation of functional status

**Study procedure:** The sociodemographic and clinical history of the patients using a predefined proforma and clinical examinations, routine hematological, radiological investigation and biochemical parameters including serum iron, serum ferritin, total iron binding capacity, unsaturated iron binding capacity were recorded.

**Statistical Analysis:** Collected data were tabulated and analyzed accordingly using Statistical Package for Social Sciences (SPSS) 21.0 (IBM Corp., Armonk, NY, United States) and expressed as descriptive statistics such as mean (SD) used for continuous variables and frequency, percentages were used for categorical variables. ANOVA test and Student's t test were used to compare the means and a p-value < 0.05 was considered as statistically significant.

Ethical clearance was obtained from the Research Ethics Board (Ref.No.A/206/REB-Comm(SP)/RIMS/2015/707/49/2020). Informed consent was obtained from the study participants


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before data collection, and confidentiality was maintained by limiting the identifying variables to a minimum.

## RESULTS

A total of 149 patients with heart failure were included in the study with the mean (+SD) age 59.38 (+11.7) years and majority were below age group of 60 years (52.4%). The baseline characteristics of the participants were given in [Table 1]. Most of them were females (78, 52.4%) while males were 71(47.6%). Majority patients, 53(35.8%) belonged to Obese I category of the body mass index (BMI) class. According to NYHA classification, majority of the patients belonged to class IV which is severe limitation of functional status (63,42.4%). The iron profile in heart failure cases were shown in [Table 2]. Majority of the male patients (36,50%) had S. iron (µg/dl) of 60 to 160 µg/dl with the mean (+SD) S. iron of 144.61 (+ 47.25) µg/dl. While majority females (39, 50%) had S. iron (µg/dl) of 35 to 145 µg/dl with the mean (+ SD) S. iron of 166.17 (+ 59.68) µg/dl. The study showed that most of the participants (73, 49%) had TIBC of 250 to 425 µg/dl with mean (+SD) of 333.80 (+83.68) µg/dl. Majority of the male patients (65, 91.5%) had serum ferritin >60 to 400 ng/dl with the mean(+SD) of 390.85 (+95.93) ng/dl while none of them had serum ferritin <60 ng/dl. Majority of the cyclic women patients (18, 90%) had serum ferritin,10 to 150 ng/dl while most of the menopausal women (40, 69%) have serum ferritin 24 to 280 ng/dl. The mean (+SD) S. ferritin of the overall female patients with heart failure was 365.31 (+136.98) ng/dl. Maximum participants had UIBC (59, 39.8%) of more than 360 µg/dl with the mean (+SD) serum UIBC of 300.56 (+138.60) µg/dl. Association between iron profile and severity of heart failure were shown in [Table 3].The study finding of ANOVA test shows that the serum iron and serum ferritin were found to be lower as the severity of heart failure increases according to NYHA classification which were statistically significance (p value = 0.03). There was no significant difference between serum TIBC, serum UIBC with the severity of heart failure according to NYHA classification (p value 0.05). Post hoc analysis showed significant difference for serum iron between the class I and class IV which is shown in [Table 3].

**Table 1: Baseline characteristics of the participants (N=149).**

| **Socio-demographic characteristics** | **n (%)** |
|---|---|
| Mean Age in years | 59.38 ± 11.7 |
| Age group: (in years)<br><60 years<br>> 60 years | <br>78 (52.4%)<br>71 (47.6%) |
| Sex:<br>Male<br>Female | <br>78 (52.4%)<br>71 (47.6%) |
| Body mass index (WHO Asian):<br>Normal range (18.5-22.9)<br>At risk (23-24.9)<br>Obese I (25-29.9)<br>Obese II (≥30) | <br>32 (21.4%)<br>42 (28.2%)<br>53 (35.8%)<br>22 (14.6%) |
| NYHA classification | |
| Class I: Normal functional status<br>Class II: Slight limitation of functional status<br>Class III: Marked limitation of functional status<br>Class IV: Severe limitation of functional status | 24 (16.1%)<br>29 (19.4%)<br>33 (22.1%)<br>63 (42.4%) |

*NYHA – New York Heart Association

**Table 2: Iron profile of the participants (N=149)**

| **Iron profile** | | **n(%)** |
|---|---|---|
| Serum iron level (µg/dl): | Male (n=71):<br><60<br>60 to 160<br>>160 | <br>21 (30%)<br>36 (50%)<br>14 (20%) |
| | Female (n=78):<br><35<br>35 to 145<br>>145 | <br>24 (30.7%)<br>39 (50%)<br>15 (19.3%) |
| Total iron binding capacity (µg/dl):<br><250<br>250 to 425<br>>425 | | <br>40 (26.9%)<br>73 (49%)<br>36 (24.1%) |
| Serum ferritin (ng/ml) | Male (n=71):<br>60 to 400<br>>400 | <br>65 (91.5%)<br>6 (8.5%) |
| | Female – cyclic (n=20):<br>10 to 150<br>>150 | <br>18 (90%)<br>2 (10%) |


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| | | |
|---|---|---|
| | Female – menopausal (n=58):<br>24 to 280<br>>280 | <br>40 (69%)<br>18 (31%) |
| Undifferentiated iron binding capacity (µg/dl):<br><160<br>160 -360<br>>360 | | <br>43 (29.1%)<br>47 (31.1%)<br>59 (39.8%) |

**Table 3: Association between iron profile and severity of heart failure (N=149)**

| NYHA* classification | Iron profile in heart failure patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Serum iron (mean ± SD) | p value | Serum TIBC(mean ± SD) | p value | Serum ferritin(mean ± SD) | p value | Serum UIBC (mean ± SD) | p value |
| Class I | 172.70 ± 54.18 | 0.03 | 348.11 ± 94.34 | 0.05 | 403.90 ± 115.32 | 0.03 | 284.64 ± 139.96 | 0.48 |
| Class II | 151.74 ± 57.54 | | 332.08 ± 56.54 | | 397.78 ± 93.92 | | 271.0 ± 125.85 | |
| Class III | 146.65 ± 51.30 | | 339.90 ± 43.24 | | 347.50 ± 130.21 | | 333.86 ± 155.21 | |
| Class IV | 130.00 ± 47.51 | | 393.64 ± 54.39 | | 318.35 ± 127.80 | | 302.79 ± 135.20 | |

*NYHA – New York Heart Association, TIBC – Total iron binding capacity, UIBC – Undifferentiated iron binding capacity

## DISCUSSION

The present study showed that the mean (SD) age was 59.38 ±11.7 years with a minimum of 32 years and maximum of 85 years. Also, majority of the patients with Heart failure were female and below 60 years of age. Similar findings were reported in studies conducted by Moliner P et al,[16] and Jain D et al.[21] The present study showed that majority of the patients with HF belong to Obese I category followed by at risk category of the BMI classification while none of them belonged to underweight category, which was similar to the study by Jankowska EA et al,[22] This can be explained by the fact that obesity is a risk factor for the non-communicable diseases like HF. However some published reports showed that anemia is frequently associated with decreased BMI, a finding that suggests that patients with cachexia are at greater risk for anemia.[23] Serum levels of proinflammatory cytokines are increased in cachectic patients with CHF and may contribute to development of anemia by several mechanisms. Proinflammatory cytokines including tumor necrosis factor-(TNF-), interleukin-1, and interleukin-6 have been shown to disrupt multiple aspects of erythropoiesis, including reduction of renal erythropoietin secretion, suppression of erythropoietin activity in red blood cell precursors in the bone marrow level, and reduction of bioavailability of iron stores for hemoglobin synthesis. Proinflammatory cytokines also increase levels of the liver derived peptide hormone, hepcidin. Hepcidin interacts with ferroportin and other iron transport proteins in the enterocyte to inhibit gut iron absorption and thereby reduces iron bioavailability for hemoglobin synthesis.[1]

Our study found that according to NYHA classification, majority of the patients with Heart failure belonged to class IV i.e severe limitation of functional status. This might be explained by the fact that in our study, the setting being a tertiary care centre, most of the serious patients are admitted.18 Our findings showed that majority of the male patients with HF have S. iron (µg/dl) of 60 to 160 µg/dl followed by less than 60 µg/dl. The mean (SD) S. iron of the patients with HF was 144.61 (47.25) µg/dl. Among the female patients with HF majority have S. iron (µg/dl) of 35 to 145 µg/dl followed by less than 35 µg/dl. The mean (SD) S. iron of the female patients with heart failure was 166.17 (59.68) µg/dl. Also, serum iron was found to be lower as the severity of heart failure increases according to NYHA classification and was found to be statistically significant (p value < 0.03). This can be explained by the mechanism that Heart failure leads to Iron deficiency anemia. The mean (SD) serum ferritin level of male patients with HF and overall female patients was 390.85 (95.93) ng/dl and 365.31 (136.98) ng/dl respectively. Anemia occurs when there is a deficiency in new erythrocyte production relative to the rate of removal of aged erythrocytes. Erythropoietin,30.4-kDa glycoprotein growth factor produced primarily by kidney, is the key component of the homeostatic system for regulation of red blood cell mass and tissue oxygen delivery as per Bauer C et al,[24]Jelkmann W et al,[25] and Donnelly Set al.[26] Erythropoietin prevents the programmed cell death of erythrocyte progenitor cells and thereby stimulates their proliferation, maturation, and terminal differentiation.[22] Any abnormality that reduces renal secretion or bone marrow response to erythropoietin may result in anemia. Iron deficiency is present in 30% of anaemic patients with CHF, so the majority of observed anemia is normocytic, often classified as anemia of chronic disease. Although risk factors for anemia identified in cross-sectional studies do not provide evidence of a causal link, these observations suggest that several distinct mechanisms may commonly contribute to anemia in patients with CHF.[27]


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Abnormal or deranged iron profile (total serum iron, iron binding capacity and serum ferritin) among heart failure patients had shown significant relation in terms of the severity of the condition. These findings are similar to the study conducted Yeo TJ et al,[28] Parikh A et al and Bolger AP et al.[29,30] As the severity of the heart failure increases, the serum iron profile also showed abnormal ranges, however, the causal relationship could not be established from this study.

Heart Failure (HF) is a global pandemic with rapidly increasing prevalence. In an attempt to maintain patients well being, the therapeutic interest has expanded to the vicious cycles that confer to HF mortality and morbidity and a number of co-morbidities have been targeted. Iron deficiency represents a common co-morbid condition that affects outcomes in HF. The treatment of iron deficiency is strongly supported by the cardiologic societies all over the world. Intravenous iron, primarily Ferric carboxymaltose, has shown clinical benefit in this setting, irrespective of the anemia status.[19]

A representative sample for the heart failure has been included in this study so the result can be generalizable to the population of similar settings. Since, serum ferritin is considered to be a specific marker for the iron profile so by measuring the serum ferritin, serves its purpose on the study. Serum ferritin is also an acute phase reactant it tends to rise in acute inflammatory reaction but by measurement of TIBC, UIBC, serum iron, the rise of serum ferritin due to acute phase reactant is countered. It is noteworthy to mention that the measurement of serum ferritin was measured only once, the results could have been underestimated or overestimated. So, repetitive measurements of serum ferritin over time could have increased the robustness of our study more. As with all cross-sectional study the temporal association could not be ascertained in our study.

## CONCLUSION

The study finding shows that serum iron level, serum ferritin and serum total iron binding capacity were significantly deranged in heart failure cases, moreover so when severity of HF increases. Therefore, iron deficiency screening is highly recommended in all heart failure patients and correction of iron deficiency status may help in improving functional capacity, and to reduce re-hospitalization after discharge in patients with acute HF.

**Limitations:** A longitudinal study on a multicentric level with higher sample size need to be conducted to find the temporal association in this kind of setting. The hemoglobin and severity of anemia were not included in the present study.

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