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Retrospective Study on Iron Deficiency in Patients with Heart Failure in a Tertiary Care Hospital

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ABSTRACT
Background: Iron deficiency is highly prevalent in patients with heart failure. It may be an absolute or functional iron deficiency. Because iron is an essential cofactor for enzymes involved in cellular respiration and oxidative phosphorylation, iron deficiency is associated with poor prognosis. The present study was conducted to assess the impact of iron deficiency in patients with heart failure.
Methods: This retrospective study was conducted from July 2024 to December 2025 on 125 patients with heart failure. Demographic details, relevant histories and laboratory findings were noted. The patients were categorized as having absolute or functional iron deficiency according to standard guidelines. Any major adverse cardiovascular event (MACE) was noted.
Results: There was a male preponderance (58.40%), with a mean age of 61.30 ± 12.31 years. The prevalence of iron deficiency was 84.80%. Absolute iron deficiency was more prevalent than functional iron deficiency (72.64% vs 27.36%). The presence of iron deficiency was associated with higher New York Heart Association (NYHA) class, severe left ventricular (LV) dysfunction and mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels ($p<0.05$). The outcome in terms of MACE was poor in patients with iron deficiency compared with those without ($p=0.01$) and in patients with absolute iron deficiency compared with those with functional iron deficiency ($p<0.01$).
Conclusion: It can be effectively concluded that presence of iron deficiency in heart failure is associated with poor exercise tolerance (higher NYHA class), increased hospitalization and poor outcome. The presence of absolute iron deficiency has more significant impact on outcome as compared to functional iron deficiency.

Key-words: : Absolute iron deficiency, Anemia, Ejection fraction, Functional iron deficiency, Heart failure

INTRODUCTION
Heart failure denotes a condition wherein there is failure of heart to circulate the amount of blood and nutrients as per body's demands [1]. It is a huge public health burden with high mortality (75% at 5 years) [2]. It leads to frequent outpatient visits and admissions. Iron deficiency is prevalent and a commonly associated comorbidity [3].

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Iron deficiency is when iron stores are not sufficient to meet the demands of the body or to cover the physiological or pathological loss of iron [4]. Iron deficiency may occur even without anemia.

In the physiological state, iron is an important cofactor of the enzymes involved in the oxidative metabolism, the Krebs cycle and the electron transport chain. In addition to erythropoiesis, it is involved in oxygen uptake, transport and storage [5]. Thus, a deficiency of iron leads to impaired cellular oxidation and production of energy. Traditionally, anemia has been considered the result and hallmark of iron deficiency. However, even in the presence of erythropoiesis, it may severely affect the

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aerobic performance impairing exercise tolerance, leading to fatigue and causing symptoms [6].

Iron deficiency has been thought to have a bidirectional relationship with heart failure. Heart failure patients may be prone to iron deficiency due to low intake of food or decreased gastrointestinal absorption of iron [7]. There is also decreased availability of iron as it is being recycled in the reticuloendothelial system [8].

Iron deficiency may be either absolute or functional. Absolute iron deficiency is due to low or depleted total body iron stores that causes iron deficient erythropoiesis. It suppresses hepcidin production and ferroportin degradation, upregulating iron absorption at the gastroduodenal junction using divalent meta-transporter 1 and iron export from macrophages and hepatocytes into the circulation [4,9]. Functional iron deficiency is often associated with adequate iron stores in the body and results in iron-deficient erythropoiesis due to a mismatch in demand and supply [4,9]. In functional iron deficiency, inflammatory cytokines such as interleukin (IL)-6, IL-1β, and lipopolysaccharide induce hepcidin production, leading to ferroportin degradation, iron retention in macrophages of the RES, decreased iron absorption at the gastroduodenal junction, and decreased plasma iron bioavailability, ultimately resulting in iron-restricted erythropoiesis [4,10].

Irrespective of the type, iron deficiency has been linked to poor exercise tolerance, poor quality of life and worse prognosis. Therefore, it is crucial to understand the impact of iron deficiency on patients with heart failure. As studies regarding this are scarce, the present study was conducted.

MATERIALS AND METHODS

Study Design and Setting- This retrospective study was conducted in a tertiary care hospital from July 2024 to December 2025. As this is a retrospective study, ethics approval was not taken. The records of all patients diagnosed with heart failure based on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels [11,12] and admitted to the ward were included in the study.

Inclusion criteria

- Records of patients of either gender.
- Records of patients aged more than 18 years.
- Records of patients diagnosed with heart failure.

Exclusion criteria

- Records of patients having comorbidities causing iron deficiency (malignancy, hemorrhoids).
- Records of patients having comorbid conditions leading to fluid overload (end stage renal disease).
- Records of patients on iron replacement therapy at the time of admission.
- Records of patients having a history of blood transfusion or erythropoietin injection within the last 3 months.
- Records of patients wherein baseline iron study data was not available.
- Records of pregnant and breast-feeding female patients.

Methodology- The demographic details and relevant details were noted. The New York Heart Association (NYHA) class was recorded [11]. The results of laboratory findings were recorded. Anemia was defined as a hemoglobin level less than 13 g/dL in males and 12 g/dL in females. Absolute iron deficiency was defined as patients having serum ferritin levels less than 100 mcg/L [13]. Functional iron deficiency was defined as patients with ferritin levels greater than 100 mcg/L and transferrin saturation less than 20% [11,14].

2D echocardiography was done. Left ventricular (LV) dysfunction was noted and patients were diagnosed based on ejection fraction (EF) as [11,12]:

- Heart failure with preserved EF (HFpEF): EF≥50%,
- Heart failure with mildly reduced EF (HFmrEF): EF=41% to 49%, and
- Heart failure with reduced EF (HFrEF): EF≤40%.

The details of hospitalization were noted. Major adverse cardiovascular event (MACE) was defined as nonfatal stroke or myocardial infarction, prolonged hospitalization related to HF of more than 14 days and cardiovascular death [15].

Statistical Analysis- The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 22.0. All qualitative data were expressed as percentages, while quantitative data were expressed as mean±standard deviation. For analytical statistics, qualitative data were analyzed using the chi-square test, and quantitative data were analyzed using the Student's t-test. Statistical significance was considered by $p<0.05$.

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RESULTS

There were 52 females (41.60%) and 73 males (58.40%). The mean age of the study population was 61.30 ± 12.31 years. There were no differences in age and gender distribution when assessed by NYHA classification, severe LV dysfunction, type of heart failure, NT-proBNP, duration of hospitalization, and MACE (p>0.05).

A total of 106 patients (84.80%) had iron deficiency. 27 patients (25.72%) had iron deficiency without anemia. Among patients with iron deficiency, 77 (72.64%) had absolute iron deficiency, while 29 (27.36%) had functional iron deficiency. When analyzed by iron deficiency status, patients with iron deficiency had significantly higher NYHA class, severe LV dysfunction, heart failure (HFrEF), higher mean NT-proBNP levels, longer mean duration of hospitalization, and a higher rate of MACE (p<0.05; Table 1).

Table 1: Distribution of the parameters according to the presence of iron deficiency

Parameter	No iron deficiency		Iron deficiency		p-value
NYHA class					
II	5	26.32%	10	9.43%	0.03*
III	7	36.84%	26	24.53%	
IV	7	36.84%	70	66.04%	
Severe LV dysfunction	7	36.84%	71	66.98%	0.01*
Heart failure					
HFpEF	8	42.11%	21	19.81%	0.025*
HFmrEF	7	36.84%	29	27.36%	
HFrEF	4	21.0	56	52.83%	
Mean NT-proBNP (pg/mL)	7438	3562	12138	8061	<0.01*
Mean duration of hospitalization (days)	11.89	2.45	14.12	4.87	<0.01*
MACE	8	42.11%	76	71.70%	0.01*

*NYHA: New York Heart Association; LV: left ventricular, HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; HFrEF: Heart failure with reduced ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; MACE: Major Adverse Cardiovascular Event; *indicates statistically significant p-value.*

When analyzed by type of iron deficiency, no effect was observed on NYHA class or hospitalization duration (p>0.05). However, severe LV dysfunction, HFrEF and MACE were significantly more in patients with absolute iron deficiency than in those with functional iron deficiency; p<0.05, while NT-proBNP levels were higher in patients with functional iron deficiency than with absolute iron deficiency; p<0.01 (Table 2).

Table 2: Distribution of the parameters according to the absolute or functional iron deficiency

Parameter	Absolute iron deficiency		Functional iron deficiency		p-value
NYHA class					
II	8	10.39%	2	6.90%	0.33
III	16	20.78%	10	34.48%	
IV	53	68.83%	17	58.62%	
Severe LV dysfunction	56	72.73%	15	51.72%	0.04*
Heart failure					
HFpEF	10	12.99%	11	37.93%	0.02*
HFmrEF	23	29.87%	6	20.69%	
HFrEF	44	57.14%	12	41.38%	
Mean NT-proBNP (pg/mL)	8145	2858	14085	6843	<0.01*

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Mean duration of hospitalization (days)	13.86	3.27	15.13	6.67	0.58
MACE	63	81.82%	13	44.83%	<0.01*

*NYHA: New York Heart Association; LV: left ventricular, HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; HFrEF: Heart failure with reduced ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; MACE: Major Adverse Cardiovascular Event; *indicates statistically significant p-value.*

DISCUSSION

In the present study, 25.72% of patients had iron deficiency without anemia. The presence of iron deficiency had a significant impact on the NYHA class, presence of severe LV dysfunction, type of heart failure and mean NT-proBNP. NYHA class was not affected by iron deficiency type, whereas the latter three were significantly higher in patients with absolute iron deficiency than in those with functional iron deficiency. Patients with iron deficiency had significantly longer hospitalization and a higher rate of adverse outcomes (MACE). The mean duration of hospitalization was not affected by the type of iron deficiency, whereas patients with absolute iron deficiency had a higher incidence of MACE than those with functional iron deficiency.

Mohan *et al.* conducted an observational study of 120 patients with heart failure [13]. They reported a male preponderance (53%) and iron deficiency in 60% of the total population. They also reported that absolute iron deficiency was more prevalent than functional iron deficiency (31.66% vs 28.33%, respectively). They noted that most patients with NYHA class IV had iron deficiency (88.90%), while among patients with LV dysfunction, 69.60% had iron deficiency. These findings were similar to the present study.

Koblava *et al.* conducted their study on 223 hospitalized patients to assess iron deficiency in patients with decompensated heart failure [16]. They noted that iron deficiency was prevalent in patients with decompensated heart failure (70 to 89%). Patients with iron deficiency were found to have a higher NYHA class than those without iron deficiency; p<0.05. These findings were similar to those of the present study.

Gopinath *et al.* conducted a study on 283 patients [17]. They reported a male preponderance of 63%. They also noted that the prevalence of iron deficiency was 84.70%. Absolute iron deficiency was more prevalent than functional iron deficiency (63.90% vs 20.60%, respectively). 24% patients had iron deficiency without anemia.

When analyzed according to the presence of iron deficiency, they noted that MACE was significantly higher in patients with iron deficiency than in patients without iron deficiency (p<0.01. The categories of NYHA class, heart failure, severe LV dysfunction and NT-proBNP levels were similar in the two groups; p>0.05. When assessed for absolute vs. functional iron deficiency, they reported that MACE was significantly higher in patients with absolute iron deficiency (p<0.01). The NYHA class, heart failure category, and duration of hospitalization were similar in the two groups. NT-proBNP levels were significantly higher in patients with functional iron deficiency (p<0.01). These findings were similar to those of the present study.

Another study demonstrated that both forms of iron deficiency are associated with a higher NYHA class than in non-iron-deficient patients [18]. This may be due to the shared pathophysiological consequence of reduced iron availability, which affects cellular energy production. Iron is an essential cofactor for various enzymes involved in mitochondrial oxidative phosphorylation and the electron transport chain [19]. Thus, iron deficiency reduces final ATP production in myocytes, resulting in dyspnoea, fatigue, and reduced exercise tolerance, and is associated with a higher NYHA class in iron-deficient patients.

The FERIC-RO study was conducted on 163 patients with decompensated heart failure [20]. They noted that patients with iron deficiency had a higher NYHA class and higher NT-proBNP at admission than patients without iron deficiency (p<0.05). They also noted a smaller decrease in NT-proBNP during hospitalization in patients with iron deficiency. NT-proBNP is an indicator of myocardial stress. It is increased in patients with iron deficiency, particularly with functional iron deficiency. Functional iron deficiency is characterized by elevated hepcidin levels driven by inflammatory cytokines, particularly IL-6 [21]. This inflammatory state not only traps iron in reticuloendothelial stores but also directly contributes to myocardial stress and neurohormonal

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activation. It has been demonstrated that functional iron deficiency is associated with elevated high-sensitivity C-reactive protein (hsCRP) and NT-proBNP, indicating a more pronounced inflammatory state [22]. This may contribute to greater myocardial wall stress and consequently higher levels of NT-proBNP.

Functional iron deficiency is driven by inflammation and may result in partially preserved cellular iron delivery to myocytes. On the other hand, absolute iron deficiency is characterized by low iron stores, resulting in reduced iron availability to myocytes for heme synthesis and compromising myoglobin function and mitochondrial respiration. This results in a higher prevalence of HFrEF and severe LV dysfunction in patients with absolute iron deficiency. This also results in a higher incidence of MACE. The present study was a single-center study and was limited by the attendance of the donors. Therefore, the results may not be generalized.

CONCLUSIONS

The present study highlights the burden of iron deficiency in patients with heart failure. Iron deficiency is associated with higher NYHA classes indicating poor exercise tolerance and impaired cellular metabolism. It is also associated with severe LV dysfunction and a higher prevalence of HFrEF. The high NT-proBNP levels are consistent with the high myocardial wall stress as part of an ongoing inflammatory state. Therefore, functional iron deficiency is associated with higher NT-proBNP levels than absolute iron deficiency. Iron deficiency, particularly absolute iron deficiency, is associated with poor outcomes in heart failure. Therefore, it is recommended that an iron profile assessment be included as a baseline parameter for patients with heart failure. The categorization of iron deficiency as absolute and functional becomes imperative for prognosis. However, large-scale multicenter studies are needed to determine the exact underlying pathophysiology of iron deficiency in heart failure patients.

CONTRIBUTION OF AUTHORS

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