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INCIDENCE OF ANEMIA IN HEART FAILURE AND RESPONSE TO IRON THERAPY

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ABSTRACT

Introduction: Anemia is a frequent comorbidity in patients with chronic heart failure (CHF), contributing to worsening symptoms, reduced exercise tolerance, and poor prognosis. Iron deficiency, whether absolute or functional, plays a significant role in its pathogenesis. Correction of anemia with iron supplementation has been shown to improve functional status, quality of life, and clinical outcomes. This study was undertaken to evaluate the incidence of anemia in heart failure patients and assess the hematological and clinical response to iron therapy. **Material and Methods:** A prospective observational study was conducted on 102 patients diagnosed with chronic heart failure admitted to a tertiary care hospital. Detailed clinical history, physical examination, and laboratory investigations including hemoglobin, hematocrit, serum ferritin, serum iron, and transferrin saturation were performed. Patients with confirmed anemia were treated with iron therapy and monitored for hematological and symptomatic improvement over a follow-up period. Data were analyzed using appropriate statistical tools. **Results:** Anemia was found in a substantial proportion of heart failure patients, highlighting its strong association with disease severity. Hematological parameters including hemoglobin and serum ferritin improved significantly following iron supplementation. Patients reported marked improvement in exercise tolerance, reduced fatigue, and better functional capacity. Statistical analysis confirmed the beneficial role of iron therapy in correcting anemia and alleviating symptoms, thereby improving overall quality of life in heart failure patients. **Conclusion:** Anemia is highly prevalent in patients with chronic heart failure and is frequently linked to iron deficiency. Timely detection and management with iron therapy lead to significant improvement in hematological indices and clinical status. Screening for anemia and iron deficiency should be incorporated into routine evaluation of CHF patients, and iron supplementation should be considered an integral part of comprehensive management.

Keywords: Heart failure, Anemia, Iron deficiency, Intravenous iron therapy

INTRODUCTION

Heart failure (HF) is a complex condition in which the heart fails to pump enough blood to meet the body's demands, emerging as a major global health problem. It affects millions worldwide, with an estimated prevalence of 2% in adults and more than 10% in people over 70 years. Advances in

cardiovascular care have prolonged life expectancy, but this has increased the number of people at risk of developing HF. Lifestyle factors, including smoking, poor diet, alcohol use, and physical inactivity, also contribute significantly. Additionally, hypertension, diabetes, and coronary artery disease are major causes. Socioeconomic disparities further influence disease outcomes, as patients in low- and middle-income countries face limited access to timely diagnosis and advanced therapies. The burden on healthcare systems is substantial, with HF costing billions annually, driven by hospitalizations and recurrent admissions. Prognosis remains poor, with about half of patients dying within five years of diagnosis. Beyond mortality, patients struggle with debilitating symptoms such as breathlessness, fatigue, and edema, leading to reduced quality of life and high disability rates. Addressing HF requires preventive strategies, early diagnosis, lifestyle modification, multidisciplinary care, and broader access to treatment to improve outcomes [1,2].

Anemia is one of the most important comorbidities in HF, affecting up to half of hospitalized patients and worsening prognosis. It contributes to greater functional decline, frequent hospitalizations, and reduced quality of life. Causes of anemia in HF are multifactorial, with iron deficiency being most prominent. This may result from poor intake, absorption problems, or impaired utilization of iron stores. Chronic inflammation suppresses red blood cell production, while coexisting chronic kidney disease reduces erythropoietin levels, worsening anemia. Dilutional effects from fluid overload and adverse effects of medications also contribute. Anemia aggravates HF by reducing oxygen delivery, forcing the heart to work harder, which accelerates disease progression. Symptoms such as fatigue and dyspnea become more severe, limiting daily activities. Management typically focuses on iron replacement, with intravenous iron being superior to oral supplements due to poor absorption and side effects with oral therapy. Erythropoiesis-stimulating agents are less favored due to safety concerns and limited outcome benefits. Addressing HF through optimized treatment and novel agents such as SGLT2 inhibitors can also indirectly improve anemia. Nutritional support to correct deficiencies in iron, folate, or vitamin B12 plays a complementary role [3-5].

Iron therapy has emerged as a promising treatment strategy in HF patients with anemia. Iron deficiency is present in nearly half of these patients and contributes substantially to symptoms and disease progression. Intravenous formulations, particularly ferric carboxymaltose, are widely studied and shown to improve exercise tolerance, quality of life, and reduce HF-related hospitalizations. These benefits are attributed to correction of iron deficiency, which improves oxygen utilization and reduces symptom burden. However, studies have not consistently demonstrated a mortality benefit, suggesting that while IV iron improves functional outcomes, it may not alter long-term survival. Current guidelines recommend IV iron supplementation in patients with symptomatic HF and documented iron deficiency, defined by low ferritin or reduced transferrin saturation. Oral iron, though convenient, remains ineffective due to poor absorption, especially in the setting of inflammation. Safety profiles of IV iron are favorable, with most side effects being mild and transient. Hypersensitivity reactions are rare, while hypophosphatemia is occasionally seen but usually manageable [6-8].

The incidence of anemia in HF varies between 10% and 50%, influenced by diagnostic criteria and patient characteristics. Older adults and those with advanced disease have higher risk. Mechanisms involve a complex interplay of iron deficiency, chronic inflammation, renal dysfunction, and medication effects. Clinically, anemia worsens fatigue, dyspnea, and exercise intolerance, directly reducing quality of life. It is also linked to increased hospitalizations and mortality, marking it as a strong predictor of poor prognosis. Evaluation includes hemoglobin measurement, iron studies, and assessment of comorbid conditions. Early identification and treatment, often with intravenous iron, can improve outcomes significantly [9,10].

The effect of iron therapy in HF is well established in terms of reducing hospitalizations and improving exercise capacity and patient-reported well-being. Meta-analyses confirm reductions in HF-related admissions and symptomatic improvements with IV iron therapy. Although mortality benefits are less clear, its ability to ease the burden of symptoms makes it an essential therapy. Oral iron is less effective due to absorption barriers, reinforcing the role of IV supplementation as the

preferred strategy. Safety remains favorable, with no significant increase in adverse events. Thus, IV iron therapy is a valuable adjunct in managing HF patients with anemia, offering significant improvements in functional capacity, quality of life, and reduced hospitalization, even if survival rates remain unchanged [11,12].

This study investigates the incidence and prevalence of anemia in heart failure patients, analyzing its severity and relationship with clinical outcomes, while also evaluating the efficacy and safety of iron therapy as a treatment strategy. It focuses on improvements in hemoglobin levels, functional capacity, and quality of life, along with examining the therapy's impact on heart failure progression through measures such as exercise tolerance, left ventricular function, hospitalization rates, and mortality. The findings aim to provide meaningful insights into the role of iron therapy as a therapeutic intervention in the management of anemia associated with heart failure.

MATERIAL AND METHODS

This prospective observational study was conducted at the Department of General Medicine, G.R. Medical College & J.A. Group of Hospitals, Gwalior (M.P.) from April 2023 to April 2025. Ethical approval has been obtained from the Ethical Approval Committee of G.R. Medical College & J.A. Group of Hospitals, Gwalior (M.P.).

Study Population

The study population comprised hospitalized patients aged 18 years and above with a confirmed clinical diagnosis of heart failure, representing both genders and varying severities with diverse ejection fraction profiles. A calculated sample size of 102 patients was determined to allow adequate representation. Inclusion criteria ensured enrollment of patients with diagnostic confirmation through clinical, electrocardiographic, echocardiographic, or radiological evidence, while exclusions eliminated confounders such as CKD, cancer, congenital heart disease, prior anemia, chronic iron therapy, transfusion, pregnancy, or lactation.

Data Analysis

Data were analyzed using IBM SPSS version 20.0, with graphs and charts generated through Microsoft Excel and Word. Descriptive statistics including mean, standard deviation, and percentages summarized continuous and categorical variables. Associations such as anemia with gender or symptoms were tested using Chi-square, while paired t-test or Wilcoxon signed-rank test compared laboratory values before and after treatment. ANOVA evaluated differences across EF groups. A p-value <0.05 indicated statistical significance, with data accuracy ensured by double entry, cross-verification, and anonymized records.

RESULTS

The analysis of anemia among 102 heart failure patients revealed a clear age-related pattern, with the highest prevalence occurring in the 51–70 age group (55.88%), followed by 31–50 years (25.49%) and those over 70 years (14.71%), while the youngest group (18–30 years) showed minimal involvement (3.92%). Statistical analysis confirmed a highly significant deviation from uniform distribution ($\chi^2 = 61.37$, $p = 2.99 \times 10^{-13}$), establishing age as a key factor in anemia occurrence. Gender-wise, anemia was more common in males (58.9%) than females (41.1%), with both sexes most affected in the 51–70 age range; however, no significant association was found between age and gender ($\chi^2 = 0.51$, $p = 0.917$), suggesting that anemia risk spans both sexes equally in middle-aged and older patients.

Further, iron deficiency was strongly associated with anemia: 69.5% of anemic females and 60.6% of anemic males were iron-deficient, while its prevalence was very low in non-anemic patients (11.11% in females, 10.71% in males). Mean hemoglobin levels were markedly lower in anemic patients compared to non-anemic ones, and statistical validation confirmed a significant association between anemia and iron deficiency ($\chi^2 = 30.43$, $p = 1.12 \times 10^{-6}$). Overall, the findings highlight a

pronounced age-related predisposition to anemia in heart failure, with no gender-based variation in risk across age groups, but a strong link between anemia and iron deficiency, underscoring the importance of routine screening and targeted iron supplementation in improving outcomes for these patients.

In heart failure patients with anemia, clinical evaluation prior to treatment revealed that certain symptoms were markedly more prevalent than others. The most common findings included pedal edema (78.43%), tachycardia (72.55%), dyspnea (68.63%), hepatojugular reflux (69.61%), rales (62.75%), and fatigue (61.76%), while less frequent manifestations included S3 gallop (25.49%), pulmonary edema (6.86%), and pleural effusion (22.55%). Other signs such as pallor (47.06%), hepatomegaly (39.22%), cardiomegaly (40.20%), and elevated jugular venous pressure (39.22%) were also noted. Statistical analysis using chi-square goodness-of-fit demonstrated a highly significant variation in symptom distribution ($\chi^2 = 147.15$, $p = 8.84 \times 10^{-23}$), confirming that specific symptoms occur disproportionately more often. Overall, these findings highlight that anemia in heart failure presents with a distinct clinical profile, with pedal edema, dyspnea, and tachycardia emerging as hallmark indicators, emphasizing the importance of careful symptom assessment for early detection and timely management to improve outcomes.

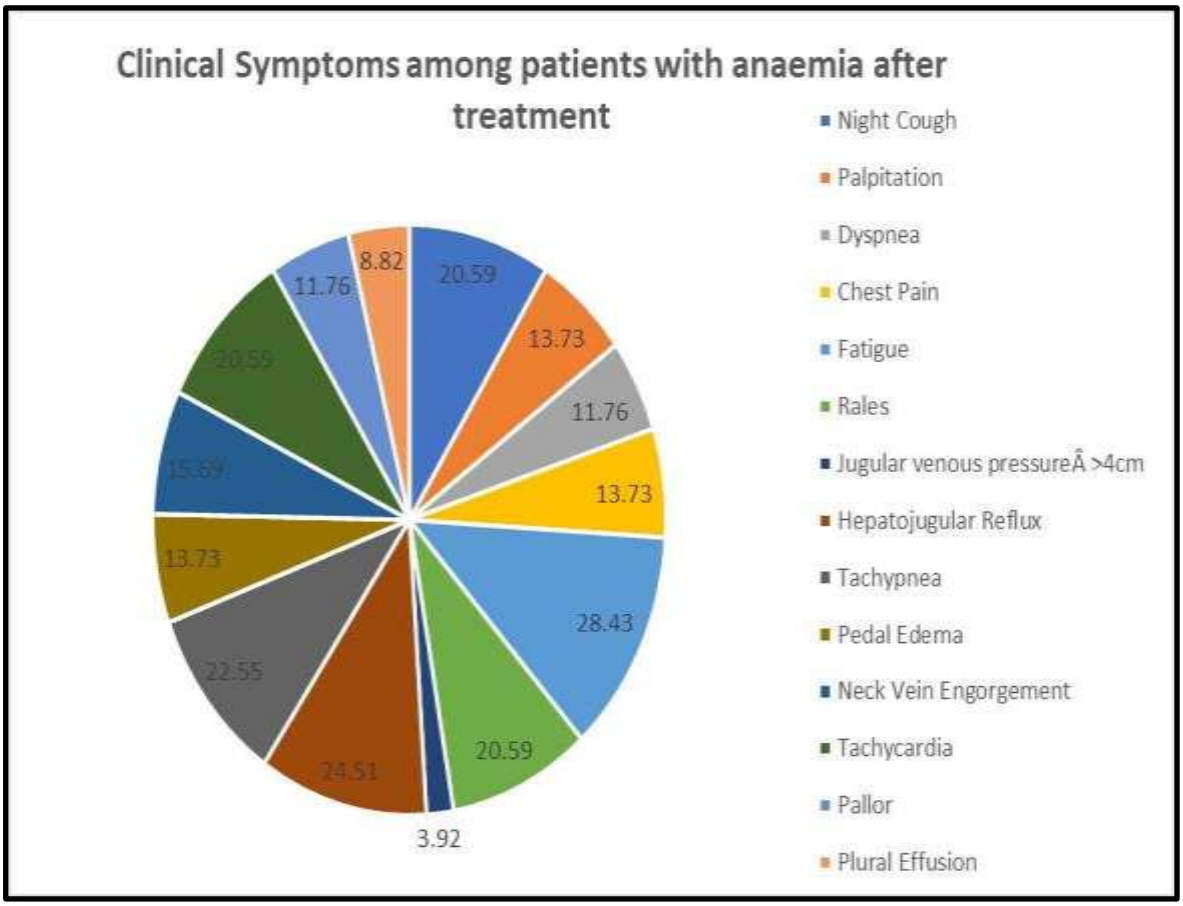

Figure 1: Clinical Signs and Symptoms among patients with anemia after treatment with Ferric Carboxymaltose

Post-treatment with Ferric Carboxymaltose, heart failure patients with anemia showed a marked reduction in major symptoms such as pedal edema, dyspnea, tachycardia, and fatigue, with statistically significant improvement ($\chi^2 = 113.28$, $p < 0.001$), confirming substantial therapeutic benefit and meaningful clinical improvement.

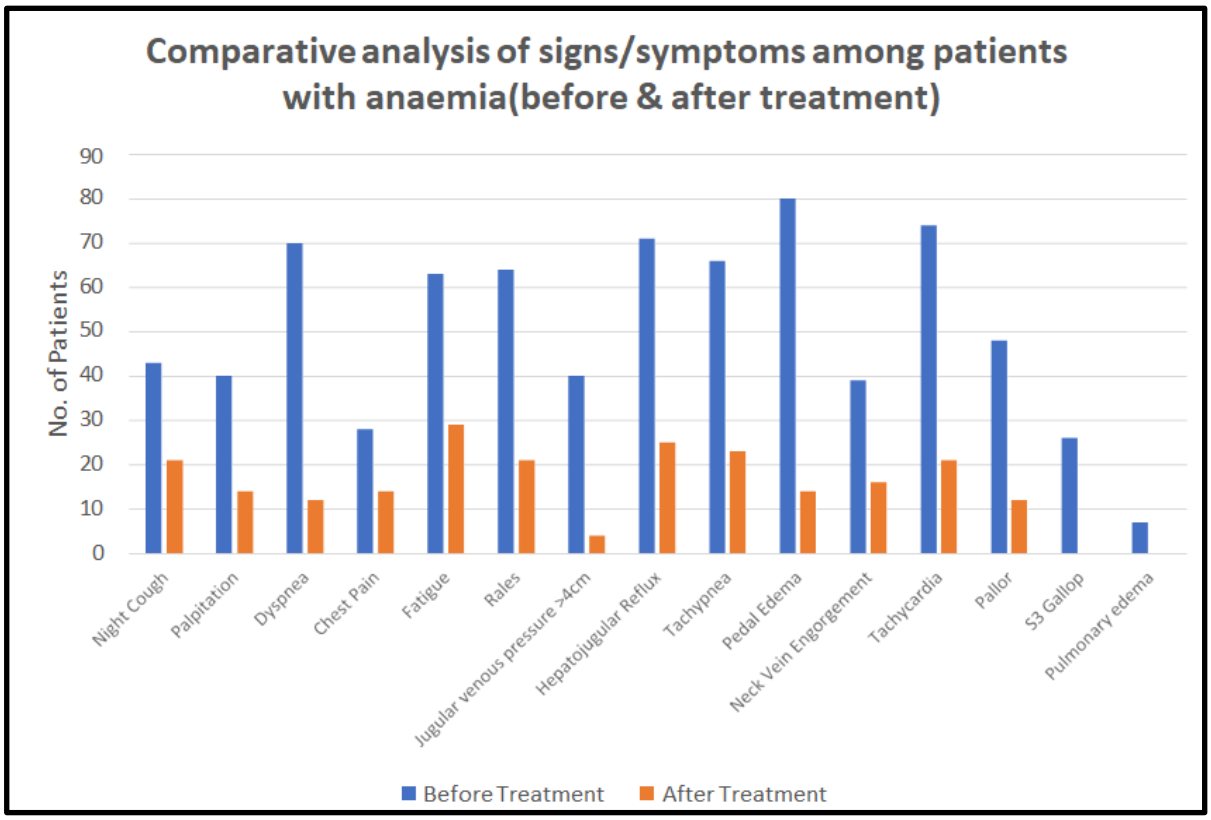

Figure 2: Comparative analysis of signs/symptoms among patients with anemia before and after treatment with Ferric Carboxymaltose

Iron therapy with Ferric Carboxymaltose led to highly significant reductions in major symptoms of anemic heart failure, including dyspnea (82.9%), pedal edema (82.5%), tachycardia (71.6%), and fatigue (54%), with complete resolution of S3 gallop and pulmonary edema, confirming its strong therapeutic impact on symptom burden and overall clinical outcomes ($p < 0.00001$).

Table 1: Patients with associated comorbidities

Comorbidities	Male	Female	Total	Total %
Hypertension	39	5	44	43.14
Diabetes	48	8	56	54.90
Both Hypertension &Diabetes	9	3	12	11.76
Total	96	41	137	134.31
Chi-square value (χ^2) =5.78, p-value = 0.05				

Among anemic heart failure patients, hypertension, diabetes, or both were more frequent in males than females, but the chi-square test ($\chi^2 = 5.78$, $p = 0.055$) showed the gender difference was not statistically significant, though it suggested a possible trend requiring larger studies for confirmation.

The analysis of left ventricular ejection fraction (EF) in heart failure patients with and without anemia showed that among the anemic group, reduced EF was most common (28 of 56), followed by preserved EF (15) and mid-range EF (13), while in non-anemic patients, reduced EF (18 of 46) and preserved EF (19) were nearly equal, with mid-range EF being least frequent (9). Although a greater proportion of anemic patients fell into the reduced EF category, statistical testing ($\chi^2 = 2.41$, $p = 0.299$) revealed no significant association between anemia and EF status, suggesting that anemia does not directly influence EF distribution and that other cardiac factors are likely responsible for EF variation. In addition, lifestyle factors such as alcohol consumption were

examined, revealing that 37 of 56 anemic patients (66%) reported a history of alcohol use, with a striking gender disparity—35 males and only 2 females. This association was highly significant ($\chi^2 = 42.10$, $p = 8.68 \times 10^{-11}$), indicating that male anemic patients were far more likely to have alcohol exposure. Since chronic alcohol intake impairs hematopoiesis and iron metabolism, it may contribute to the development or worsening of anemia in heart failure. These findings emphasize that while EF distribution does not significantly differ by anemia status, lifestyle factors like alcohol use—particularly in males—play an important role in anemia risk, underscoring the need for holistic management that combines iron therapy with lifestyle modifications for optimal patient outcomes.

Table 2: Laboratory parameters of patients with anemia

Parameter	Mean (Before Treatment)	SD (Before Treatment)	Coefficient of Variation (CV)
RBC Count (million/uL)	3.73	1.06	0.28
Hemoglobin (g/dL)	9.30	3.24	0.34
Hematocrit (%)	32.51	7.63	0.23
Reticulocyte Count (%)	1.44	0.64	0.44
Serum Iron (mcg/dL)	48.06	22.62	0.47
Ferritin (ng/mL)	62.36	55.07	0.88
Serum Albumin (g/dL)	3.15	0.59	0.18
Total Protein (g/dL)	6.20	0.47	0.08
Direct Bilirubin (mg/dL)	0.41	0.16	0.39
ALT (U/L)	34.28	10.82	0.31
AST (U/L)	36.06	11.43	0.31
Serum Creatinine (mg/dL)	0.98	0.18	0.18
Blood Urea Nitrogen(mg/dL)	14.48	3.95	0.27

Baseline labs in anemic heart failure patients showed low hemoglobin (9.3 g/dL), reduced RBC count, and deficient iron indices (serum iron 48.06 mcg/dL, ferritin 62.36 ng/mL) with high variability, especially in ferritin (CV 0.88), indicating heterogeneous iron deficiency and erythropoietic activity, thereby underscoring the need for individualized iron therapy and routine biochemical monitoring.

Table 3: Laboratory parameters of patients with anemia after treatment with Ferric Carboxymaltose

Parameter	Mean (After Treatment)	SD (After Treatment)	Coefficient of Variation (CV)
Hemoglobin (g/dL)	11.83	2.00	0.16
Reticulocyte Count (%)	1.65	0.74	0.44
Serum Iron (mcg/dL)	81.29	23.26	0.28
Ferritin (ng/mL)	127.04	54.89	0.43
Serum Albumin (g/dL)	3.45	0.60	0.17
ALT (U/L)	31.59	11.57	0.36
AST (U/L)	35.58	11.52	0.32

After Ferric Carboxymaltose therapy, hemoglobin rose to 11.83 g/dL with marked improvements in serum iron (81.29 mcg/dL), ferritin (127.04 ng/mL), and albumin, while variability in most parameters stabilized, confirming effective anemia correction and consistent hematologic recovery in heart failure patients.

Table 4: Multivariate analysis of laboratory parameters among patients with anemia

Parameter	Mean Before Treatment	Mean After Treatment	p-value
Ferritin (ng/mL)	63.82	127.04	1.39×10^{-13}
ALT (U/L)	33.65	31.59	0.182348
AST (U/L)	36.18	35.58	0.712479
Serum Albumin (g/dL)	3.16	3.45	0.001057
Reticulocyte Count(%)	1.43	1.65	0.028455
Haemoglobin (g/dL)	9.52	11.83	4.64×10^{-10}
Serum Iron (mcg/dL)	49.13	81.29	6.97×10^{-17}

Multivariate analysis showed significant post-treatment improvements with Ferric Carboxymaltose, as hemoglobin rose from 9.52 to 11.83 g/dL, ferritin doubled, serum iron increased markedly, albumin improved, and reticulocyte count rose, while ALT and AST changes were nonsignificant, confirming effective anemia correction without hepatic toxicity.

Table 5: Mortality among patients with anemia

	Anaemic		Non-anaemic	
	Female	**Male**	**Female**	**Male**
18-30	0	0	0	0.00
31-50	0	1	0	1.00
51-70	1	1	0	0
>70	1	2	0	0
Total	2	4	0	1
Total %	1.96	3.92	0.00	0.98
Chi-square value (χ^2) =1.70, p-value = 0.192				

Mortality was higher in anemic heart failure patients (10.7%) compared to non-anemic patients (2.2%), but the difference was not statistically significant ($\chi^2 = 1.70$, $p = 0.192$), suggesting a possible trend that may require larger studies for confirmation.

Table 6: Etiology of Heart Failure among patients

Category	Count	Percentage
Ischemic Heart Disease		**33.3%**
Dilated Cardiomyopathy	19	**18.6%**
Valvular Heart Disease	23	**22.5%**
Mycarditis	06	**5.9%**
High Output Heart Failure	17	**16.7%**
Others		**2.9%**

Ischemic heart disease (33.3%) was the leading cause of heart failure, followed by valvular disease (22.5%) and dilated cardiomyopathy (18.6%), with the chi-square test ($\chi^2 = 21.74$, $p = 0.00059$) confirming a statistically significant distribution of etiologies.

DISCUSSION

Heart failure (HF) is a complex clinical syndrome in which the heart fails to pump blood adequately to meet the metabolic demands of the body. It is a major global health burden, associated with high morbidity, mortality, and healthcare costs, especially in aging populations. Despite advances in

pharmacological and device-based therapies, HF continues to present considerable therapeutic challenges. Anemia is an important yet under-recognized comorbidity in HF, significantly worsening prognosis, reducing quality of life, and increasing hospitalization rates [13].

Anemia, defined by reduced hemoglobin levels, is reported in 30–50% of HF patients, depending on diagnostic criteria and population studied. Its etiology is multifactorial, involving chronic inflammation, renal dysfunction, hemodilution, nutritional deficiencies (iron, folate, vitamin B12), and bone marrow suppression. Among these, iron deficiency is particularly important, as iron plays a crucial role in erythropoiesis, cellular metabolism, and mitochondrial function. Deficiency therefore impairs both hematologic and cardiac performance [14].

The pathophysiological interplay between anemia and HF involves reduced oxygen delivery, which aggravates myocardial hypoxia, increases cardiac workload, accelerates ventricular remodeling, and activates neurohormonal pathways. Anemia thus not only reflects disease severity but also directly contributes to disease progression. **Ebner N, et. al; 2016,** highlighted that even iron deficiency without anemia impairs exercise capacity and overall health status. Consequently, therapeutic correction of iron deficiency in HF has gained increasing attention [15].

Avni T, et. al; 2012, randomized trials such as FAIR-HF, CONFIRM-HF, and AFFIRM-AHF have shown that intravenous (IV) iron, particularly ferric carboxymaltose, improves exercise capacity, symptoms, and quality of life in HF patients with iron deficiency. IV iron is preferred over oral formulations due to better absorption and faster replenishment. Importantly, the benefits of iron therapy extend beyond hemoglobin correction, reflecting improved myocardial energy metabolism and skeletal muscle function. Although mortality benefits remain uncertain, reductions in HF-related hospitalizations are consistently reported, and guidelines recommend screening and treatment of iron deficiency in patients with HF with reduced ejection fraction (HFrEF) regardless of anemia status [16].

Loncar G, et. al; 2021, despite these advances, several uncertainties persist. The optimal dosing, timing, and long-term effects of iron therapy remain under investigation. Iron metabolism is also influenced by inflammatory cytokines such as hepcidin, which limit absorption and mobilization, complicating management. Oral iron remains controversial due to poor absorption and limited clinical benefit in HF [17].

In the present study, anemia was most common in patients aged 51–70 years (55.88%), followed by 31–50 years (25.49%), with a significant association between age and anemia incidence ($\chi^2 = 61.37$, $p < 0.001$). **Ponikowski P, et. al; 2014,** studies reported higher anemia prevalence in older HF patients, attributed to comorbidities, inflammation, and declining renal function. Gender distribution showed slightly higher anemia in males (32.35%) than females (22.55%), though not statistically significant, aligning with earlier work suggesting no strong gender predilection [1].

Iron deficiency was significantly more prevalent in anemic females (69.5%) than males (60.6%) ($\chi^2 = 30.43$, $p = 1.12 \times 10^{-6}$). **Goddard AF, et. al; 2011,** reported with women showing greater susceptibility to iron deficiency due to physiological factors [27][28]. Clinical signs such as pedal edema (78.43%), tachycardia (72.55%), and dyspnea (68.63%) were common, consistent with reports linking anemia to worse HF symptoms [18].

Following treatment with ferric carboxymaltose, there was marked improvement in clinical symptoms including dyspnea, edema, and fatigue, consistent with large international trials [19]. Laboratory markers also showed significant improvement: hemoglobin rose from 9.30 g/dL to 11.83 g/dL, serum iron from 48.06 to 81.29 mcg/dL, and ferritin from 62.36 to 127.04 ng/mL. These improvements align with global evidence supporting IV iron as an effective therapy in HF patients with anemia [20].

Comorbid conditions such as diabetes (54.9%) and hypertension (43.14%) were frequently observed, reflecting similar patterns in other cohorts. Anemia was present across all HF phenotypes—reduced, preserved, and mid-range ejection fraction—supporting evidence that anemia adversely affects outcomes regardless of EF classification. Alcohol use was significantly more prevalent among anemic male HF patients, highlighting its role in disrupting iron metabolism and erythropoiesis [21].

The study reinforces that anemia, particularly iron deficiency anemia, is highly prevalent among HF patients, significantly worsens symptoms, and increases morbidity. Intravenous ferric carboxymaltose therapy resulted in substantial clinical and biochemical improvement, consistent with international data. These findings underscore the importance of routine anemia screening and early iron supplementation in HF management to improve functional capacity, reduce hospitalizations, and enhance quality of life [22].

CONCLUSION

This prospective study highlights the high incidence of anemia in heart failure patients, predominantly aged 51–70 years, with iron deficiency as the leading cause. Males were slightly more affected, and alcohol use was a notable risk factor. Anemia manifested with pedal edema, fatigue, tachycardia, and dyspnea, impairing quality of life. Intravenous Ferric Carboxymaltose markedly improved hemoglobin, ferritin, serum iron, albumin, and symptoms, without hepatic toxicity. Pulmonary edema and S3 gallop resolved completely. Mortality was higher but not statistically significant, while ejection fraction distribution remained unaffected, indicating anemia's impact across all heart failure phenotypes.

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