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Effects of Iron Deficiency Anemia on Functional Status of Patients of Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Objective: To evaluate effects of iron deficiency anaemia on functional status of patients with heart failure with reduced ejection fraction (HfrEF).

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital, Multan Pakistan, from Dec 2024 to Sep 2025.

Methodology: A total of 320 adult patients with chronic HFrEF were enrolled through consecutive sampling. Functional status was assessed by New York Heart Association (NYHA) class, six-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ). Iron deficiency was defined as serum ferritin <100 μg/L or 100–299 μg/L with transferrin saturation (TSAT) <20%. Haemoglobin, ferritin and TSAT were measured. Comparisons between IDA (Group-A) and non-IDA (Group-B) groups were performed. Multivariable linear regression was applied to identify independent predictors of 6MWT distance.

Results: Iron deficiency was observed in 196(61.3%) patients. Compared to non-deficient patients, those with IDA had lower mean haemoglobin (11.17±0.95 vs. 13.54±0.87 g/dL, p<0.001), ferritin (63.95 vs. 170.70 μg/L, p<0.001), TSAT (15.65% vs. 28.35%, p<0.001), 6MWT distance (280.98±44.56 vs. 303.32±42.51 m, p<0.001), and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores (42.72±8.91 vs. 47.28±8.76, p<0.001). Regression analysis showed transferrin saturation (β=0.18, p=0.015) and haemoglobin (β=0.23, p=0.011) as independent predictors of six-minute walk test (6MWT) distance.

Conclusion: IDA significantly impairs functional capacity and quality of life in patients with HFrEF. Routine screening and correction of iron deficiency should be integrated into heart failure management to improve outcomes.

Keywords: Anemia, Ejection Fraction, Exercise Test, Iron-Deficiency, Quality of Life.

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INTRODUCTION

Iron deficiency remains the leading cause of anaemia affecting nearly one-third of the global population.[1] The World Health Organization (WHO) estimates that approximately two billion individuals, accounting for nearly 25% of the world's population are affected, with iron deficiency anaemia (IDA) contributing to nearly half of these cases.[2] In 2016, WHO further reported that anaemia was present in 42% of children under five years of age and 40% of women of reproductive age across the globe.[3]

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome characterized by impaired ventricular contractility, resulting in reduced cardiac output and inadequate tissue perfusion.[4] Patients typically present with exertional dyspnoea, fatigue and fluid retention, leading to repeated hospitalizations and diminished quality of life.[5] Despite advances in pharmacological and device-based therapies, HFrEF continues to carry significant morbidity and mortality worldwide, particularly in low and middle-income countries.[6]

IDA is increasingly recognized as a frequent comorbidity in HFrEF, even in the absence of overt anaemia.[7] Iron plays a central role in oxygen transport and cellular energy metabolism; its deficiency aggravates fatigue, exercise intolerance and impaired functional capacity.[8] Several studies suggest that IDA negatively influences exercise performance, symptom burden and health-related quality of life.[9] However, evidence remains limited regarding its exact contribution to functional status, particularly in patients managed in resource-constrained settings, highlighting a gap in the literature.[10]

This study was conducted to evaluate the effects of iron deficiency anaemia on functional status among patients with HFrEF. Understanding this relationship may provide insights into early identification of at-risk individuals and guide targeted interventions. Such

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findings could help improve clinical outcomes, reduce hospitalizations and inform evidence-based management strategies in populations where the burden of both heart failure and IDA is high.

METHODOLOGY

This analytical cross-sectional study was carried out in the Department of Medicine, Combined Military Hospital Multan, Pakistan from December 2024 to September 2025 after obtaining approval from the Institutional Review Board (ERC No 111/2024 dated 03 Dec 2024).

Inclusion Criteria: Patients of either gender aged 18 years and above with a documented diagnosis of chronic HFrEF (LVEF <40%) who were clinically stable for at least two weeks and were able to perform the six-minute walk test were included.

Exclusion Criteria: Patients with acute decompensated heart failure, recent (<3 months) blood transfusion or iron therapy, end-stage renal disease requiring dialysis, active infection, chronic inflammatory disease, haematological disorders or malignancy, pregnant women and those unable to perform functional assessments were excluded.

Sample size was calculated using G*Power 3.1. A mean difference of 40 metres in six-minute walk test distance and a standard deviation of 74 metres, were assumed, yielding an effect size of 0.54.[11] The minimum required sample size was 182 participants. Given the expected iron-deficiency prevalence of 49.6% among patients with HFrEF, the final sample size was increased to 320 to ensure adequate representation of both IDA and non-IDA subgroups and to maintain sufficient power for subgroup analyses.[12]

Adult patients with a prior diagnosis of HFrEF were recruited through consecutive sampling. A formal written informed consent was obtained from each participant before enrolment.

Patients were evaluated in the outpatient department and relevant demographic, clinical and laboratory data were recorded on a predesigned proforma. Diagnosis of HFrEF had been confirmed on transthoracic echocardiography using the Simpson biplane method, with a left ventricular ejection fraction (LVEF) less than 40%. The functional status of patients was assessed using standardized tools. The New York Heart Association (NYHA) functional class was assigned by a consultant medical specialist with atleast more than 5 years clinical experience. NYHA class was assigned on the basis of symptoms and physical activity tolerance.

Exercise capacity was further quantified using the six-minute walk test (6MWT), performed according to American Thoracic Society guidelines, with distance covered in metres recorded as an objective measure. The 6MWT was performed on a 60m long flat, hard-surfaced indoor corridor. The patients had taken their medications, were counselled in detail about the nature of test and wore comfortable clothing and shoes during the test. A trainee of medicine recorded baseline vitals and the Borg scale rating for dyspnea and fatigue. At every 3m, the walking track was marked and cones were placed at the turnarounds. All the participants walked at a rate as per their own desire and condition. They were told that they can stop whenever they get tired and resume walking when possible. At the end of the test the trainee medicine again recorded vitals and the Borg scale for dyspnea and fatigue The distance covered was calculated in meters and recorded. Health-related quality of life was evaluated using the validated Kansas City Cardiomyopathy Questionnaire (KCCQ). KCCQ scores of all patients scaled from 0 to 100 and scores represented health status as follows: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.[13]

Laboratory investigations were performed at the time of enrolment. Blood samples were drawn for serum Hb level (in g/dl), serum ferritin (in ug/L) and transferrin saturation in % (TSAT). Anaemia was defined as haemoglobin less than 13 g/dL in men and less than 12g/dL in women according to World Health Organization criteria.[14] Iron deficiency was categorised as serum ferritin below 100 µg/L or as ferritin between 100–299 µg/L with TSAT less than 20%.[15]

Data was analyzed using Statistical package for Social Sciences (SPSS) version 25. Continuous variables such as age, haemoglobin, ferritin, TSAT and 6MWT distance were expressed as Mean ± Standard Deviation or median with interquartile range, depending on data distribution assessed by the Shapiro–Wilk test. Those who had IDA were considered as Group-A, and those without IDA were in Group-B. Categorical variables such as gender, NYHA class and anaemia status were presented as frequencies and percentages. Comparisons between patients with and without iron deficiency were made using independent-samples t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Pearson or Spearman correlation was employed to assess the relationship between haemoglobin, ferritin and functional outcomes. To adjust for potential confounders, multivariable linear regression was applied with six-minute walk distance as the dependent variable while independent variables included iron deficiency status, age, sex, left ventricular ejection fraction (LVEF), haemoglobin level and relevant comorbidities. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 320 patients with HFrEF were included in the final analysis. The mean age was 65.38±8.87 years. Iron deficiency was identified in 196(61.3%) patients, being more prevalent among males compared to females with 178(55.6%) males and 142(44.4%) females. The median (IQR) of left ventricular ejection fraction (LVEF) was 35.20% (3.9), with all patients having values below 40%. Regarding functional class, 7(2.2%) patients were in NYHA class I, 145(45.3%) in class II and 168(52.5%) in class III, as shown in Table-I.

Table-I: Baseline Demographic and Clinical Characteristics of Study Participants (n=320)

Variable		Group-A (n=196) n(%)	Group-B (n=124) n(%)	*p*-value
Age in years (Mean±SD)		65.28±8.81	65.55±8.98	0.793
Gender	Males	107(54.6%)	71(57.3%)	0.640
	Females	89(45.4%)	53(42.7%)	
LVEF, Median (IQR)		35.10(3.5)	35.45(4.7)	0.715
NYHA Class	Class-I	3(1.5%)	4(3.2%)	0.501
	Class-II	92(47.0%)	53(42.8%)	
	Class-III	101(51.5%)	67(54.0%)	

**LVEF: Left Ventricular Ejection Fraction (%), NYHA: New York Heart Association*

Table-II: Iron Deficiency and Functional Capacity Characteristics of Study Participants (n=320)

Variable	Group-A (n=196)	Group-B (n=124)	*p*-value
Hb in g/dl (Mean±SD)	11.17±0.95	13.54±0.87	<0.001
Ferritin in µg/L, Median (IQR)	63.95 (37.4)	170.70 (79)	<0.001
TSAT, Median (IQR)	15.65 (5.0)	28.35 (10.8)	<0.001
6MWT, Mean±SD	280.98±44.56	303.32±42.51	<0.001
KCCQ Scores, Mean±SD	42.72±8.91	47.28±8.76	<0.001

** TSAT: Transferrin Saturation (%), 6MWT: 6-Minute Walk Test (metres), KCCQ: Kansas City Cardiomyopathy Questionnaire*

Mean haemoglobin in iron-deficient patients was 11.64±0.79 g/dL in males and 10.61±0.81 g/dL in females, while in those without iron deficiency it was 13.95±0.65 g/dL in males and 12.98±0.83 g/dL in females. Patients with anaemia consistently demonstrated serum ferritin <100 µg/L while those with normal haemoglobin exhibited ferritin >100 µg/L and TSAT >20%. In terms of functional outcomes, patients with iron deficiency had a significantly lower mean six-minute walk test (6MWT) distance compared to non-deficient patients (280.98±44.56 m vs. 303.32±42.51 m, *p*<0.01). Similarly, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were lower among iron-deficient patients, reflecting poorer quality of life (42.72±8.91 vs. 47.28±8.76, *p*<0.01) as shown in Table-II.

In the multivariable linear regression model adjusted for age, sex, haemoglobin, LVEF, and NYHA functional class, transferrin saturation (TSAT) showed a significant positive association with six-minute walk test (6MWT) distance (β = 0.18, *p*=0.015). This indicates that higher TSAT levels were independently associated with better exercise capacity. In contrast, serum ferritin did not demonstrate a significant relationship with 6MWT distance (*p*=0.995). Among the covariates, haemoglobin (β = 0.23, *p*=0.011) and age (β = 0.11, *p*=0.046) also emerged as significant predictors of functional performance as shown in Table-III.

Table-III: Multivariable Linear Regression Analysis of Predictors of 6-Minute Walk Test (6MWT) Distance (n=320)

Variable	B (Unstandardized)	β (Standardized)	*p*-value
Age	0.54	0.11	0.046
Sex	7.08	0.08	0.190
Haemoglobin	7.15	0.23	0.011
Serum Ferritin	0.00	0.00	0.995
TSAT	0.95	0.18	0.015
LVEF	−0.37	−0.02	0.667
NYHA Class	4.79	0.06	0.277

**LVEF: Left Ventricular Ejection Fraction (%), NYHA: New York Heart Association, TSAT: Transferrin Saturation.*
Dependent variable: 6MWT. Adjusted R^2: 0.13

DISCUSSION

In our study TSAT levels, not ferritin levels, were independently associated with better exercise capacity. Singer *et al.,* in their study mentioned that iron deficiency in the context of chronic heart failure is associated with adverse outcomes, including reduced exercise capacity and increased healthcare expenses through recurrent hospitalizations.[16] Intravenous iron supplementation remains the only established therapeutic strategy that has demonstrated improvement in functional performance and quality of life among these patients. A study by Masini *et al.,* found that the likelihood of iron deficiency was higher among female patients, those experiencing more severe clinical symptoms, individuals with anaemia, and those with preserved ejection fraction.[17] A serum iron concentration of ≤13 µmol/L together with TSAT below 20% was strongly associated with elevated five-year mortality. In contrast, patients with serum ferritin levels under 100 ng/mL tended to exhibit comparatively lower mortality rates. A similar study established that serum ferritin concentrations below 100 µg/L alone are insufficient to identify patients who would derive the greatest benefit from intravenous iron therapy.[18] In contrast, individuals with transferrin saturation under 20%, most of whom also present with anaemia, are more likely to experience favourable outcomes with intravenous iron supplementation.

A study by Ebner *et al.,* demonstrated a significant association between reduced haemoglobin levels and diminished exercise capacity (r=0.24, p<0.001).[19] Patients with concurrent iron deficiency and anaemia exhibited markedly lower functional performance compared to those with either condition alone. Multivariate regression analysis further identified anaemia as independent predictors of mortality in patients with heart failure, even after adjusting for NYHA class. Evidence from a review indicates that iron deficiency in heart failure with reduced ejection fraction adversely influences functional status, exercise tolerance, quality of life and both cardiac structure and function, while also increasing the risk of hospitalisation for decompensated heart failure.[20] Mechanistic studies further suggest that iron deficiency exacerbates impaired cardiac energetics by disrupting mitochondrial activity, thereby contributing to disease progression.[16,17]

Packer *et al.,* proposed redefining iron deficiency in heart failure by prioritizing hypoferremia, defined as transferrin saturation (TSAT) below 20%, rather than relying solely on ferritin-based criteria.[21] In a study involving 760 participants, the mean 6MWT distance was reported as 281±103 meters.[22] Among patients with HFrEF and iron deficiency, the minimal clinically important difference (MCID) for improvement in exercise capacity was estimated at 14–15 meters, which provide a useful benchmark for the clinical interpretation of trial outcomes. Alcaide et al. conducted a study on 447 patients with heart failure and preserved ejection fraction, demonstrating that those with iron deficiency performed significantly worse on the six-minute walk test compared to individuals with normal iron status.[23] They also reported higher scores on the Minnesota Living with Heart Failure Questionnaire, reflecting poorer quality of life. Among biomarkers of iron metabolism, serum soluble transferrin receptor (sTfR) emerged as the strongest independent predictor of both functional capacity (β = –63, p<0.0001, R^2 =0.39) and quality of life (β = 7.95, p<0.0001, R^2 =0.14) in multivariate analyses.

LIMITATION OF STUDY

This study has certain limitations. Being an analytical cross-sectional design, causal relationships between iron deficiency anaemia and functional outcomes could not be established. The study was conducted at a single tertiary-care centre, which may limit the generalizability of the results to other settings. Potential residual confounding from unmeasured variables such as nutritional status, medication adherence and socioeconomic factors cannot be excluded. Despite these limitations, the study provides valuable local data on the burden and clinical impact of iron deficiency anaemia in patients with HFrEF.

CONCLUSION

Iron deficiency anaemia was found to significantly impair functional status in patients with heart failure with reduced ejection fraction. Patients with iron deficiency demonstrated reduced six-minute walk distance, poorer symptom burden as reflected by NYHA class and lower health-related quality of life scores. These findings highlight the clinical relevance of screening for iron deficiency in this high-risk population, as timely recognition and correction may improve exercise tolerance and overall outcomes. Integration of iron profile assessment into the routine evaluation of heart failure patients could therefore play a vital role in optimizing management strategies, particularly in resource-limited settings where both conditions are highly prevalent.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AUH & FS: Data acquisition, data analysis, critical review, approval of the final version to be published.

AAS & WA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

HMAA & MA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Gardner W, Razo C, McHugh T. Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990–2021: findings from the Global Burden of Disease Study 2021. Lancet Haematol 2023; 10(9): 713-734. https://dx.doi.org/10.1016/S2352-3026(23)00160-6
2. Sharma J, Sriram D, Sengupta A, Rajeshwari PN. Assessing the prevalence of iron deficiency anemia and risk factors among children and women: A case study of rural uttar pradesh. Clin Epidemiol Glob Health 2024; 26: 101545. https://doi.org/10.1016/j.cegh.2024.101545
3. Sun J, Wu H, Zhao M, Magnussen CG, Xi B. Prevalence and changes of anemia among young children and women in 47 low- and middle-income countries, 2000-2018. EClinicalMedicine 2021; 41(1): 101136. https://dx.doi.org/10.1016/j.eclinm.2021.101136
4. Rashid AM, Khan MS, Fudim M, DeWald TA, DeVore A, Butler J. Management of Heart Failure with Reduced Ejection Fraction. Curr Probl Cardiol 2023; 48(5): 101596. https://doi.org/10.1016/j.cpcardiol.2023.101596
5. Jishnu M, Wilde MI, Rocca HPBL, Emans ME, De A, Siegers CEP, et al. Newly diagnosed heart failure with reduced ejection fraction: timing, sequencing, and titration of guideline-recommended medical therapy. Eur Heart J 2025; 46(25): 2394-2405. https://doi.org/10.1093/eurheartj/ehaf244
6. Jishnu M, Clephas BRD, La Rocca BL, Brugts JJ. Guideline-directed medical therapy for HFrEF: sequencing strategies and barriers for life-saving drug therapy. Heart Fail Rev 2023; 28(5): 1221-1234. https://dx.doi.org/10.1007/s10741-023-10325-2
7. Clephas PR, Malgie J, Schaap J, Koudstaal S, Emans M, Linssen GC, et al. Guideline implementation, drug sequencing, and quality of care in heart failure: design and rationale of TITRATE-HF. ESC Heart Fail 2023; 11(1): 550–559. https://dx.doi.org/10.1002/ehf2.14604
8. Özmen M. Iron Deficiency Anemia and Mortality Rate in Heart Failure with Reduced Ejection Fraction. J Updates Cardiovasc Med 2025; 13(2): 72–80. https://dx.doi.org/10.32596/jucvm.galenos.2025.2024-27-94
9. Solberg A, Reikvam H. Iron Status and Physical Performance in Athletes. Life 2023; 13(10): 2007. https://dx.doi.org/10.3390/life13102007
10. Keller K, Friedrich O, Treiber J, Quermann A, Friedmann-Bette B. Iron deficiency in athletes: prevalence and impact on VO2 peak. Nutrition 2024; 126: 112516. https://doi.org/10.1016/j.nut.2024.112516
11. Myhre PL, Øyunn K, Berge, Morten G, Lars G, Stein Ø. Changes in 6-min walk test is an independent predictor of death in chronic heart failure with reduced ejection fraction. Eur J Heart Fail 2024; 26(12): 2608–2615. https://dx.doi.org/10.1002/ejhf.3391
12. Mir A, Hafeez I, Ahmad N, Rashid A, Gull MM, Rather JI. Prevalence Of Iron Deficiency Anemia In Heart Failure In A Tertiary Care Hospital Of North India. J Popul Ther Clin Pharmacol 2024; 31(7): 1–10. https://doi.org/10.53555/z8pj2645
13. Spertus J, Jones P, Sandhu A. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 76(20): 2379–2390. https://doi.org/10.1016/j.jacc.2020.09.542
14. Akbarpour E, Paridar Y, Mohammadi Z, Mard A, Danehchin L, Abolnezhadian F, et al. Anemia prevalence, severity, types, and correlates among adult women and men in a multiethnic Iranian population: the Khuzestan Comprehensive Health Study. BMC Public Health 2022; 22(1): 1-13. https://doi.org/10.1186/s12889-022-12512-6
15. Von Haehling S. Iron deficiency in heart failure: Epidemiology, diagnostic criteria and treatment modalities. ESC Heart Fail 2024; 12(2): 723–726. https://dx.doi.org/10.1002/ehf2.15157
16. Singer CE, Vasile CM, Popescu M, Popescu AIS, Marginean IC, Iacob GA, et al. Role of Iron Deficiency in Heart Failure—Clinical and Treatment Approach: An Overview. Diagnostics 2023; 13(2): 304. https://dx.doi.org/10.3390/diagnostics13020304
17. Masini G, Graham F, Pellicori P, Cleland J, Cuthbert J, Kazmi S, et al. Criteria for Iron Deficiency in Patients With Heart Failure. JACC 2022; 79(4): 341–351. https://doi.org/10.1016/j.jacc.2021.11.039
18. Graham FJ, Guha K, Cleland JG, Kalra PR. Treating iron deficiency in patients with heart failure: what, why, when, how, where and who. Heart 2024; 110(20): 1201–1207. https://doi.org/10.1136/heartjnl-2022-322030
19. Ebner N, Jankowska EA, Ponikowski P, Lainscak M, Elsner S, Sliziuk V, et al. The impact of iron deficiency and anaemia on exercise capacity and outcomes in patients with chronic heart failure. Results from the Studies Investigating Co-morbidities Aggravating Heart Failure. Int J Cardiol 2016; 205: 6–12. https://doi.org/10.1016/j.ijcard.2015.11.178
20. Martens P. The Effect of Iron Deficiency on Cardiac Function and Structure in Heart Failure with Reduced Ejection Fraction. Card Fail Rev 2022; 8(6): 1-7. https://dx.doi.org/10.15420/cfr.2021.26
21. Packer M, Anker SD, Butler J, John GF, Cleland PR, Mentz RJ, et al. Redefining Iron Deficiency in Patients With Chronic Heart Failure. Circulation 2024; 150(2): 151-161. https://doi.org/10.1161/CIRCULATIONAHA.124.068883
22. Khan MS, Anker SD, Friede T, Jankowska EA, Metra M, Piña IL, et al. Minimal Clinically Important Differences in 6-Minute Walk Test in Patients With HFrEF and Iron Deficiency. J Card Fail 2022; 29(5): 760–770. https://doi.org/10.1016/j.cardfail.2022.10.423
23. Alcaide A, Garay A, L Alcoberro, Jiménez-Marrero S, Yun S, Tajes M, et al. Iron Deficiency: Impact on Functional Capacity and Quality of Life in Heart Failure with Preserved Ejection Fraction. J Clin Med 2020; 9(4): 1199. https://dx.doi.org/10.3390/jcm9041199

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