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Beyond the Guidelines: The Critical Role of Type 1 Iron Deficiency in Predicting Mortality in Patients with Heart Failure

Kılavuzların Ötesinde: Kalp Yetersizliği Olan Hastalarda Mortaliteyi Tahmin Etmede Tip 1 Demir Eksikliğinin Kritik Rolü

ABSTRACT

Objective: The criteria for iron deficiency (ID) may encompass depleted iron stores alongside unmet iron demands by cardiomyocytes, potentially serving as predictors of adverse outcomes in patients with heart failure (HF).

Method: We included 570 patients with HF. Based on newly proposed definitions of ID, patients were categorized into three groups: Type 1 (transferrin saturation [TSAT] < ≈15–16% with anemia), Type 2 or 3 (TSAT < ≈20% with no or mild anemia) and those meeting HF guideline-defined ID criteria. Binary logistic regression was used to identify independent predictors of one-year all-cause mortality in patients with HF. Cox proportional hazard regression was performed to assess the impact of Type 1 ID on mortality.

Results: Among the 570 HF patients, 175 (30.7%) had Type 1 ID, 250 (43.9%) had Type 2 or 3 ID, and 415 (72.8%) met the guideline-defined criteria for ID. One-year all-cause mortality rates were 38.3% in patients with Type 1 ID, 22.7% in those with Type 2 or 3 ID, and 26.0% in those meeting guideline ID criteria. Increased age (odds ratio [OR]: 1.054, 95% confidence interval [CI]: 1.025–1.084) and Type 1 ID (OR: 1.830, 95% CI: 1.044–3.208) were independent predictors of one-year all-cause mortality. Cox regression analysis demonstrated an increased risk of mortality in HF patients with Type 1 ID compared to those without, in both unadjusted (hazard ratio [HR]: 2.289, 95% CI: 1.644–3.186, P < 0.001) and adjusted (HR: 1.543, 95% CI: 1.070–2.225, P = 0.020) models.

Conclusion: Type 1 ID was an independent predictor of one-year all-cause mortality in patients with HF, unlike Type 2 or 3 ID and guideline-defined ID. Patients with Type 1 ID with HF had a higher overall mortality risk compared to those without Type 1 ID.

Keywords: Guideline-defined iron deficiency, heart failure, iron deficiency type, mechanistic pathway, mortality

ÖZET

Amaç: Demir eksikliği (DE) kriterleri, kalp yetersizliği (KY) olan hastalarda olumsuz sonuçların öngörücüsü olarak karşılanmamış kardiyomiyosit demir talepleri ile tükenmiş demir depolarını içerebilir.

Yöntem: Çalışmaya 570 KY hastası dahil edilmiştir. DE açısından önerilen yeni tanımlamaya göre hastaları üç gruba ayırdık: tip 1 (TSAT≤≈%15-16 ve anemi varlığı), tip 2 veya 3 (TSAT<≈20% ve hafif anemi valığı veya anemi olmaması) ve KY kılavuzuna göre DE kriterleri. Binary lojistik regresyon analizi, KY hastalarında 1 yıllık tüm nedenlere bağlı mortalite için bağımsız öngörücüleri tanımlamak için kullanıldı. Tip 1 DE'nin mortalite üzerindeki etkisini belirlemek için Cox orantılı hazard regresyon modelleri uygulandı.

Bulgular: Kalp yetersizliği olan 570 hastanın, 175'inde (%30,7) tip 1 DE, 250'sinde (%43,9) tip 2 veya 3 DE ve 415'inde (%72,8) kılavuzların önerdiği DE kriterleri mevcuttu. 1 yıllık tüm nedenlere bağlı mortalite sırasıyla tip 1 DE için %38,3, tip 2 veya 3 DE için %22,7 ve kılavuzların önerdiği DE kriterlerini karşılayanlar için %26,0 olarak gözlenmiştir. Artmış yaş (OR: 1.054, %95CI:1.025-1.084) ve tip 1 DE varlığı (OR:1.830, %95CI:1.044-3.208) 1 yıllık tüm nedenlere bağlı mortalite için bağımsız belirleyiciler olarak tespit edilmiştir. Cox regresyon analizi, hem düzeltilmemiş (HR:2.289, %95CI:1.644-3.186, P < 0.001) hem de düzeltilmiş (HR:1.543, %95CI:1.070-2.225, P = 0.020) analizlerde tip 1 DE olan KY hastalarında tip 1 DE olmayanlara kıyasla artmış mortalite riski olduğunu göstermiştir.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Sonuç: Tip 1 DE, tip 2 veya 3 DE ve kılavuzlarda tanımlanan DE'den farklı olarak KY hastalarında 1 yıllık tüm nedenlere bağlı mortalite için bağımsız bir belirleyici olmuştur. KY hastalarında tip 1 DE, tip 1 DE olmayan KY hastalarına kıyasla artmış genel mortalite riski ile karakterize olarak bulunmuştur.

Anahtar Kelimeler: Kılavuzun önerdiği demir eksikliği, kalp yetersizliği, demir eksikliği tipi, mekanistik yolak, ölüm

Iron deficiency (ID) is increasingly recognized as a critical comorbidity in heart failure (HF), significantly contributing to impaired clinical status and adverse outcomes.[1,2] While the association between ID and poor prognosis in HF is well established, the impact of correcting ID on improving clinical endpoints remains uncertain. Current guideline definitions of ID primarily rely on blood-based biomarkers such as ferritin, transferrin saturation (TSAT), and serum iron levels, criteria largely extrapolated from studies in chronic kidney disease and inflammatory bowel disease.[3-5] These definitions emphasize the role of erythroid precursors, focusing on the correction of anemia rather than targeting meaningful reductions in clinical endpoints, such as mortality, or addressing ID at the cardiomyocyte level.[5] Moreover, ferritin levels can be significantly elevated in patients with chronic HF due to systemic inflammation, irrespective of actual iron status within cardiomyocytes.[6] In chronic HF, a patient's status plays a critical role in the development of functional ID, which in turn impairs the effective utilization of iron by cardiomyocytes.[7] Consequently, the reliability of circulating biomarkers as surrogates for intracellular iron content, particularly within cardiomyocytes, remains a topic of ongoing debate. Although correcting ID with intravenous iron supplementation has shown promise in improving functional status and quality of life in HF patients, its impact on mortality is inconclusive.[8,9] Recent insights by Packer et al.[5] have introduced novel mechanistic pathways of ID in HF, with a focus on elucidating cardiomyocyte iron concentration. These pathways classify ID into three distinct subtypes: Type 1 ID, characterized by a TSAT ≤ 15-16% accompanied by anemia; and Types 2 and 3 ID, characterized by TSAT ≤ 20% with mild or no anemia. Type 1 ID reflects reduced systemic iron availability, significantly contributing to anemia and further exacerbating heart failure. Type 2 ID is associated with systemic inflammation, while deconditioning increases the vulnerability of skeletal muscle to iron depletion, leading to worsening symptoms and reduced exercise tolerance. Type 3 ID, on the other hand, reflects disproportionate cardiomyocyte iron depletion as cardiomyopathy progresses. In this study, we aimed to evaluate one-year all-cause mortality in patients with HF in relation to the newly defined mechanistic pathways of ID. Additionally, we compared the prognostic implication of this new classification with the guideline-based criteria for ID.

Materials and Methods

This research was a retrospective, single-center observational study. This study was approved by Karabük University Rectorate Non-Interventional Clinical Research Ethics Committee (Approval Number: 2024/1862, Date: 10.09.2024). All procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

ABBREVIATIONS

HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ID	Iron deficiency
IQR	Interquartile range
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
TSAT	Transferrin saturation
WHO	World Health Organization

We included 651 adult patients diagnosed with HF who had available iron parameters, including serum ferritin, serum iron, and TSAT, and who were admitted to the cardiology outpatient clinic between January 1, 2023 and October 1, 2023. None of the patients with HF had received intravenous or oral iron therapy. Patients with hemoglobin levels below 9.0 g/dL (n = 53) or above 15.0 g/dL (n = 28) were excluded. Ultimately, 570 patients met the inclusion criteria and were included in the final analysis.

The diagnosis of HF was confirmed through a review of patients' epicrisis reports, cross-checked with HF-specific medical therapy and International Classification of Diseases, 10th Revision (ICD-10) codes (I50.0, I50.1, I50.9, I11.0, I13.0, I13.2, I42.0). Comorbidities were identified based on ICD-10 codes in combination with relevant medications (Table 1, Appendix Table 1). Variables, including age, sex, comorbidities, medications, and laboratory results were extracted from the hospital's electronic information management system. Mortality data were also obtained from this system.

Anemia was classified according to World Health Organization (WHO) criteria: mild anemia (hemoglobin [Hb]: 10-10.9 g/dL), moderate anemia (Hb: 7-9.9 g/dL), and severe anemia (Hb: < 7 g/dL).[10] Iron deficiency was categorized into three distinct subgroups, based on definitions from the European Society of Cardiology, the American College of Cardiology, and criteria proposed by Packer et al.[3-5]

1. Type 1 ID: TSAT ≤ 16% with anemia
2. Type 2 or 3 ID: TSAT ≤ 20% with no anemia or mild anemia
3. Guideline-defined ID: Serum ferritin < 100 µg/L, or ferritin 100-299 µg/L with TSAT < 20%.

An echocardiography database was used to identify different HF phenotypes based on clinically reported left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction was defined as LVEF ≤ 40%, heart failure with mildly reduced ejection fraction as LVEF 41-49%, and heart failure with preserved ejection fraction as LVEF ≥ 50%.[4]

Table 1. Baseline Characteristics of the Study Population

	Study Population (n = 570)
Age (years)	73 (64–79)
Sex (female/male)	300/270
LVEF (%)	50 (35–55)
Hypertension (n, %)	494 (86.7)
Diabetes mellitus (n, %)	275 (48.2)
Hyperlipidemia (n, %)	289 (50.7)
Atrial fibrillation (n, %)	296 (51.9)
Previous myocardial infarction (n, %)	165 (28.9)
CKD (n, %)	244 (42.8)
History of anemia (n, %)	247 (43.3)
COPD (n, %)	122 (21.4)
Cerebrovascular event (n, %)	86 (15.1)
Types of iron deficiency	
Type 1 ID (n, %)	175 (30.7)
Type 2 or 3 ID (n, %)	250 (43.9)
Guideline-defined ID (n, %)	415 (72.8)
Medical therapy	
Beta-blockers (n, %)	479 (84.0)
RASi (n, %)	407 (71.4)
MRA (n, %)	309 (54.2)
SGLT2i (n, %)	122 (21.4)
Furosemide (n, %)	325 (57.0)
Torasemide (n, %)	76 (13.3)
Laboratory variables	
BNP (pg/mL)	387.21 (172.76–1006.62)
eGFR (mL/min/1.73 m^2)	64.00 (45.25–84.00)
Hemoglobin (g/dL)	12.20 (10.30–13.50)
Ferritin (ng/mL)	47.60 (22.34–110.72)
TSAT (%)	14.48 (8.80–22.84)
Serum iron (mcg/dL)	42.55 (25.47–64.25)
TSH (mIU/L)	1.53 (0.83–2.71)

BNP, Brain Natriuretic Peptide; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; eGFR, Estimated Glomerular Filtration Rate; HFmrEF, Heart Failure with Mildly Reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; ID, Iron Deficiency; LVEF, Left Ventricular Ejection Fraction; MRA, Mineralocorticoid Receptor Antagonists; RASi, Renin-Angiotensin-Aldosterone System Inhibitors; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitors; TSAT, Transferrin Saturation; TSH, Thyroid-Stimulating Hormone.

The primary endpoint was one-year all-cause mortality.

Statistical Analysis

Categorical variables were summarized using counts and proportions, while continuous variables were summarized using the median and interquartile range (IQR). Binary logistic regression analysis was performed to identify independent predictors of one-year all-cause mortality. The model included the following variables for binary logistic regression analysis: age, sex, B-type natriuretic peptide (BNP), heart failure phenotype, hypertension, diabetes mellitus, prior history of myocardial infarction, atrial fibrillation, chronic kidney disease, use of beta-blockers, mineralocorticoid receptor antagonists, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors, Type 1 ID, Type 2 or 3 ID, and guideline-defined ID criteria. Patients were divided into two groups based on the results of the binary logistic regression analysis: those with Type 1 ID and those without. Cross-tabulations were generated to compare categorical patient characteristics based on the presence of Type 1 ID. The Mann-Whitney U test was used to assess differences in continuous variables between the two groups (Type 1 ID present vs. absent). Kaplan-Meier analysis was conducted to estimate the mean survival rate for the overall population. Univariable and multivariable Cox regression analyses were performed to evaluate the predictive value of Type 1 ID for all patients with HF and within each HF phenotype subgroup. The multivariable model was adjusted for age, sex, BNP, ferritin, hyperlipidemia, previous history of myocardial infarction, chronic kidney disease, and the use of beta-blockers, mineralocorticoid receptor antagonists, renin-angiotensin-aldosterone system inhibitors, and sodium-glucose cotransporter-2 inhibitors. The rates of Type 1 ID presence and absence were presented using cumulative incidence curves, with a hazard function accounting for one-year all-cause mortality as a competing risk. All statistical analyses were conducted using SPSS version 30.0 (IBM Corp., Armonk, NY, USA).

Table 2. Independent Predictors for One-Year Mortality in the Study Population

	OR	95% CI	P
Age	1.054	1.025–1.084	<0.001
Type 1 ID	1.830	1.044–3.208	0.035

CI, Confidence Interval; ID, Iron Deficiency; OR, Odds Ratio. **The model included age, sex, B-type natriuretic peptide (BNP), heart failure phenotype, hypertension, diabetes mellitus, prior history of myocardial infarction, atrial fibrillation, chronic kidney disease, use of beta-blockers, mineralocorticoid receptor antagonists, renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors, Type 1 iron deficiency, Type 2 or 3 iron deficiency, and guideline-defined iron deficiency.

Results

Among the 570 HF patients with available iron parameters, the median age was 73 years (IQR: 64–79), and 52.6% were female. The cohort had a median LVEF of 50% (IQR: 35–55%). Comorbidities and medication profiles are detailed in Table 1. The median BNP level was 387.21 pg/mL (IQR: 172.76–1006.62), and the median estimated glomerular filtration rate (eGFR) was 64.00 mL/min/1.73 m^2 (IQR: 45.25–84.00) (Table 1).

In the study population, 72.8% met the guideline-defined criteria for ID, 43.9% were classified as having Type 2 or 3 ID, and 30.7% as having Type 1 ID. Anemia was present in 43.3% of HF patients. Iron parameters included a median serum iron level of 42.55 mcg/dL (IQR: 25.47–64.25), TSAT of 14.48% (IQR: 8.80–22.84), and a serum ferritin level of 47.60 ng/mL (IQR: 22.34–110.72). The median Hb concentration in the cohort was 12.20 g/dL (IQR: 10.30–13.50) (Table 1).

Table 3. Comparison of Patient Characteristics Based on the Presence of Type 1 Iron Deficiency

	Type 1 ID Present (n = 175)	Type 1 ID Absent (n = 395)	P
Age (years)	76.00 (70.00–81.00)	71.0 (62.00–78.00)	<0.001
Sex (female/male)	114/61	186/209	<0.001
LVEF (%)	50.00 (35.00–55.00)	50.00 (35.00–55.00)	0.665
Hypertension (n, %)	159 (90.9)	335 (84.8)	0.050
Diabetes mellitus (n, %)	90 (51.4)	185 (46.8)	0.311
Hyperlipidemia (n, %)	69 (39.4)	220 (55.7)	<0.001
Atrial fibrillation (n, %)	94 (53.7)	202 (51.1)	0.570
Previous myocardial infarction (n, %)	34 (19.4)	131 (33.2)	<0.001
CKD (n,%)	96 (54.9)	148 (37.5)	<0.001
History of anemia (n, %)	151 (86.3)	96 (24.3)	<0.001
COPD (n, %)	34 (19.4)	88 (22.3)	0.444
Cerebrovascular event (n, %)	34 (19.4)	52 (13.2)	0.054
Heart failure phenotype			
HFrEF (n, %)	45 (26.8)	123 (73.2)	
HFmrEF (n, %)	42 (36.8)	72 (63.2)	0.198
HFpEF (n, %)	88 (30.6)	200 (69.4)	
Medical therapy			
Beta-blockers (n, %)	135 (77.1)	344 (87.1)	0.003
RASi (n, %)	113 (64.6)	294 (74.4)	0.016
MRA (n, %)	83 (47.4)	226 (57.2)	0.031
SGLT2i (n, %)	27 (15.4)	95 (24.1)	0.021
Furosemide (n, %)	92 (52.6)	233 (59.0)	0.154
Torasemide (n, %)	26 (14.9)	50 (12.7)	0.476
Laboratory variables			
BNP (pg/mL)	553.82 (291.30–1293.20)	296.33 (142.14–828.84)	<0.001
eGFR (mL/min/1.73 m^2)	56.00 (38.00–75.00)	68.00 (49.00–86.00)	<0.001
Hemoglobin (g/dL)	10.10 (9.10–11.00)	12.90 (12.10–14.00)	<0.001
Ferritin (ng/mL)	36.70 (14.40–85.30)	51.10 (26.10–132.20)	<0.001
TSAT (%)	8.00 (5.00–11.00)	19.00 (12.00–26.00)	<0.001
Serum iron (mcg/dL)	24.10 (15.30–33.05)	56.50 (37.29–75.50)	<0.001
TSH (mIU/L)	1.51 (0.70–2.59)	1.53 (0.85–2.72)	0.268

BNP, Brain Natriuretic Peptide; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; eGFR, Estimated Glomerular Filtration Rate; HFmrEF, Heart Failure with Mildly Reduced Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; HFrEF, Heart Failure with Reduced Ejection Fraction; ID, Iron Deficiency; LVEF, Left Ventricular Ejection Fraction; MRA, Mineralocorticoid Receptor Antagonists; RASi, Renin-Angiotensin-Aldosterone System Inhibitors; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitors; TSAT, Transferrin Saturation; TSH, Thyroid-Stimulating Hormone.

One-year all-cause mortality was observed in 38.3% of patients with Type 1 ID, 22.7% with Type 2 or 3 ID, and 26.0% among those meeting guideline-defined ID criteria. Binary logistic regression analysis identified increasing age (hazard ratio [HR]: 1.054, 95% confidence interval [CI]: [1.025–1.084]) and the presence of Type 1 ID (HR: 1.830, 95% CI: [1.044–3.208]) as independent predictors of one-year all-cause mortality (Table 2).

Patients with Type 1 ID were observed to be older (76 years [IQR: 70–81] vs. 71 years [IQR: 62–78]) and predominantly female (65% vs. 47%), with a lower prevalence of hyperlipidemia (39.4% vs. 55.7%) and previous myocardial infarction (19.4% vs. 33.2%), but a higher prevalence of chronic kidney disease (CKD) (54.9% vs. 37.5%) and anemia (86.3% vs. 24.3%) compared to those without Type 1 ID. Each component of quadruple therapy for HF was used less frequently in patients with Type 1 ID than in those without (Table 3). Regarding laboratory variables, BNP levels were higher in patients with Type 1 ID (553.82 pg/mL [IQR: 291.30–1293.20] vs. 296.33 pg/mL [IQR: 142.14–828.84]); conversely, eGFR (56.00 mL/min/1.73 m^2 [IQR: 38.00–75.00] vs. 68.00 mL/min/1.73 m^2 [IQR: 49.00–86.00]), ferritin (36.70 ng/mL [IQR: 14.40–85.30] vs. 51.10 ng/mL [IQR: 26.10–132.20]), TSAT (8% [IQR: 5–11] vs. 19% [IQR: 12–26]), serum iron (24.10 mcg/dL [IQR: 15.30–33.05] vs. 56.50 mcg/dL [IQR: 37.29–75.50]), and hemoglobin (10.10 g/

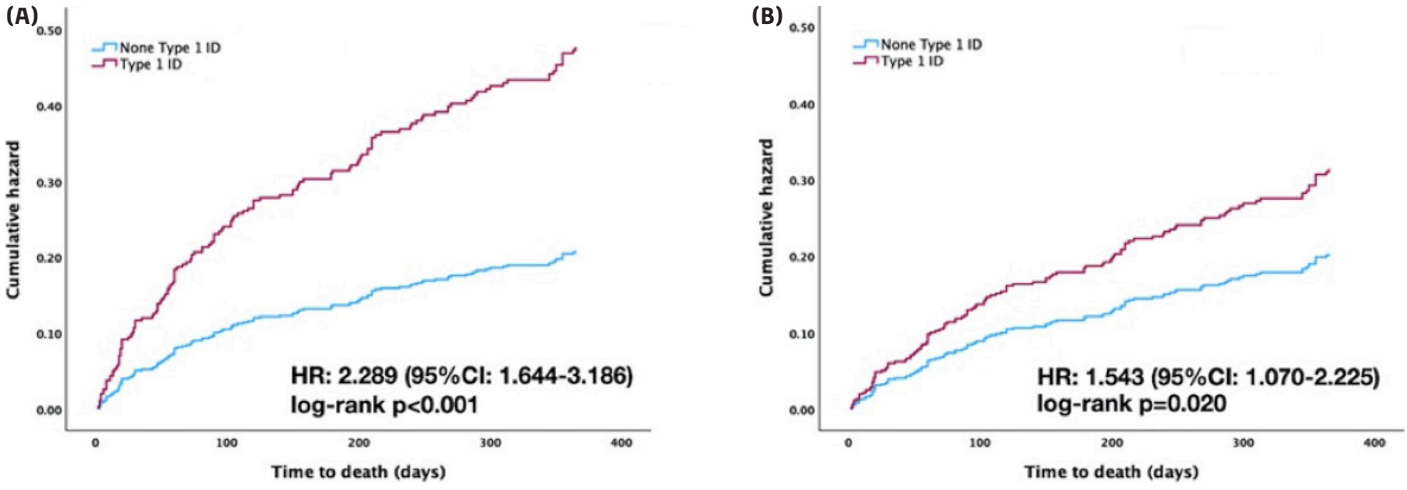

Figure 1. (A) Cox regression analysis curves showing hazard rates for heart failure patients with and without Type 1 iron deficiency in the unadjusted analysis. (B) Cox regression analysis curves showing hazard rates for heart failure patients with and without Type 1 iron deficiency in the adjusted analysis.

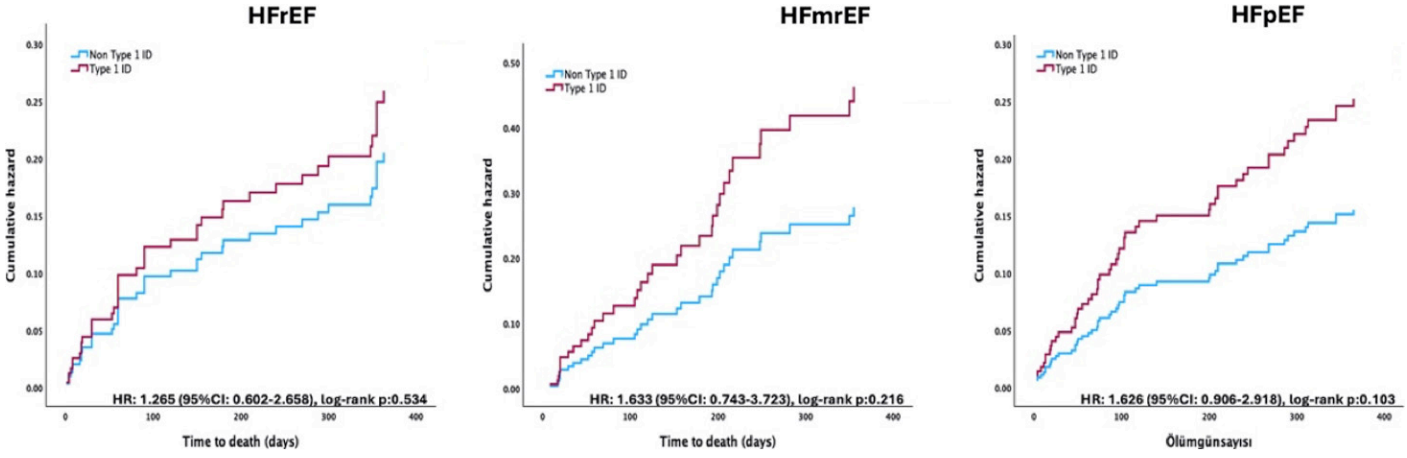

Figure 2. Cox regression analysis showing hazard rates for heart failure patients with and without Type 1 iron deficiency, stratified by heart failure phenotype, in adjusted analyses.

dL [IQR: 9.10–11.00] vs. 12.90 g/dL [IQR: 12.10–14.00]) were all lower compared to patients without Type 1 ID (Table 3). The one-year mortality rate was 38.3% in patients with Type 1 ID, compared to 18.7% in those without Type 1 ID (odds ratio [OR]: 2.691, 95% CI: 1.811–3.998). The overall mean survival time was 305.50 ± 4.92 days. Patients with Type 1 ID had a mean survival time of 274.40 ± 10.17 days, whereas those without Type 1 ID had a mean survival time of 319.27 ± 5.35 days (Chi-Square: 25.531, Log-rank P < 0.001) (Appendix Figure 1). Cox regression analysis showed that patients with Type 1 ID had a 2.289-fold higher one-year all-cause mortality risk (95% CI: 1.644–3.186, P < 0.001) compared to those without Type 1 ID (Figure 1A). The adjusted analysis demonstrated a statistically significant higher cumulative hazard rate for one-year all-cause mortality among HF patients with Type 1 ID compared to those without (HR: 1.543, 95% CI: 1.070–2.225, P = 0.020) (Figure 1B). However, we found that the presence of Type 1 ID was not associated with an increased risk of one-year all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) in adjusted analyses (Figure 2, Appendix Table 2).

Discussion

In this study, we assessed the one-year all-cause mortality risk associated with different definitions of ID, as proposed by Packer et al.[5] and current HF guidelines.[3-5] We found that: (1) the presence of Type 1 ID was an independent predictor of one-year all-cause mortality in patients with HF, (2) HF patients with Type 1 ID were older, predominantly female, and had a higher prevalence of CKD and anemia, but a lower prevalence of myocardial infarction and hyperlipidemia, and (3) compared to those without Type 1 ID, HF patients with Type 1 ID had an increased risk of one-year all-cause mortality in both unadjusted and adjusted analyses. Our findings also suggest that low TSAT values in the presence of anemia may be more reliably associated with hard clinical endpoints in HF patients than the current guideline-defined ID. This challenges the validity of current guideline-defined criteria for identifying ID in this clinical setting.

Patients with HF are at risk of developing ID, even in the presence of adequate total body iron stores, due to a functional deficiency that impairs the release of iron from cellular reservoirs into the circulation.[11] This impaired mobilization is linked to elevated hepcidin levels, often driven by systemic inflammation associated with HF. Increased hepcidin acts to sequester iron within reticuloendothelial cells.[12] Thereby reducing both circulating iron concentrations and its availability to target tissues in patients with HF.[13] Although our study lacked hepcidin level measurements, serum iron levels were found to be significantly lower in HF patients with Type 1 ID compared to those without. Taken together, the available evidence suggests that reduced serum iron levels in this cohort may serve as a significant indicator of developing functional ID. This condition may adversely affect cardiomyocyte function, contributing to HF progression and an increased risk of mortality.

Notably, guideline-defined ID was not associated with mortality in our study. However, Type 1 ID (TSAT ≤ 16%) emerged as an independent predictor of mortality in our study population. Consistently, a validation study assessing guideline-defined ID in patients with HF found that true ID, based on bone marrow iron status, was present in 40% of cases. In the same study, two parameters emerged as optimal diagnostic indicators of bone marrow ID: a TSAT level of ≤ 19.8% (sensitivity: 94.1%, specificity: 84.0%) and a serum iron level of ≤ 13 µmol/L (sensitivity: 94.1%, specificity: 88.0%).[14] Notably, the use of these two criteria for diagnosing ID was associated with increased mortality over a 24-month follow-up period. In contrast, ferritin proved to be a less effective marker for evaluating ID in this cohort.[14-16] Furthermore, intravenous iron therapy has demonstrated beneficial effects on clinical outcomes. Implementing these criteria may improve our ability to identify HF patients with true ID, thereby enhancing prognostic assessment for patients with HF.

Identified risk factors for ID include female sex, older age, advanced stages of HF, and elevated natriuretic peptide levels.[7,17] Kurz et al.[18] reported that TSAT levels were negatively correlated with natriuretic peptide levels and positively correlated with eGFR. Notably, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were elevated in HF patients with the lowest TSAT values.[14,18-20] Consistently, in our study, HF patients with Type 1 ID had significantly higher BNP levels and lower eGFR compared to those without Type 1 ID. This finding suggests that these patients are likely to have more severe HF, as indicated by the combination of elevated BNP and reduced eGFR. Importantly, in advanced HF, when patients were categorized according to three distinct definitions of ID, a consistent pattern emerged: regardless of the definition used, the presence of ID was associated with higher natriuretic peptide levels and lower eGFR values.[15] In this patient population, optimizing quadruple therapy is often not feasible, and certain components may be contraindicated due to severe HF or impaired renal function.[21,22] These findings underscore the relationship between ID and the clinical severity of HF, warranting further investigation into its implications for patient management and prognosis.

Cox regression analysis demonstrated an association between the presence of Type 1 ID and one-year all-cause mortality in patients with HF, irrespective of both iron status and the presence of anemia. While strictly hypothesis-generating, these findings suggest that patients with Type 1 ID may experience significantly worse outcomes in terms of mortality.

Limitations

The study design presents several limitations. As a retrospective, single-center observational study focused exclusively on HF patients admitted to the cardiology outpatient clinic, the findings may not be generalizable to the broader HF population. The limited sample size also restricted the statistical power of subgroup analyses, preventing them from reaching significance. Therefore, the conclusions drawn from this study should be interpreted with caution. Iron deficiency was assessed using serum iron, TSAT, and ferritin levels; however, other circulating iron biomarkers were not evaluated. Additionally, iron deficiency was not confirmed using a gold standard method. We also lacked data on systemic inflammatory biomarkers, such as C-reactive protein. Moreover, we did not collect data on New York Heart Association (NYHA) class, which limited our ability to select patients with advanced HF. Finally, given the observational nature of the analysis, the potential for residual confounding cannot be excluded.

Conclusion

Type 1 ID is characterized by reduced TSAT and hemoglobin levels. Unlike Type 2 or 3 ID and guideline-defined ID, Type 1 ID may offer critical insights into the true iron requirements of cardiomyocytes and help identify HF patients at particularly high risk of poor outcomes. Addressing this form of iron deficiency with intravenous iron supplementation may be a promising therapeutic strategy, targeting disrupted iron metabolism and potentially reducing the elevated mortality rate in patients with HF.

Ethics Committee Approval: Ethics committee approval was obtained from Karabük University Rectorate Non-Interventional Clinical Research Ethics Committee (Approval Number: 2024/1862, Date: 10.09.2024).

Informed Consent: Written informed consent was obtained from all patients.

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References

1. Wahid M, Islam S, Sepehrvand N, et al. Iron Deficiency, Anemia, and Iron Supplementation in Patients With Heart Failure: A Population-Level Study. *Circ Heart Fail*. 2024;17(4):e011351. [CrossRef]
2. Cohen-Solal A, Leclercq C, Deray G, et al. Iron deficiency: an emerging therapeutic target in heart failure. *Heart*. 2014;100(18):1414-1420. [CrossRef]

3. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639. Erratum in: *Eur Heart J*. 2024;45(1):53. [CrossRef]
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e876-e894. [CrossRef]
5. Packer M, Anker SD, Butler J, et al. Identification of three mechanistic pathways for iron-deficient heart failure. *Eur Heart J*. 2024;45(26):2281-2293. [CrossRef]
6. Vasques-Nóvoa F, Pimentel MJ, Marques P, et al. Ferritin, inflammation, and iron deficiency in acute heart failure: evidence from the EDIFICA cohort. *Clin Res Cardiol*. Sep 19, 2024. doi: 10.1007/s00392-024-02535-x. [Epub ahead of print]. [CrossRef]
7. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron Deficiency in Heart Failure: An Overview. *JACC Heart Fail*. 2019;7(1):36-46. [CrossRef]
8. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *Eur J Heart Fail*. 2023;25(4):528-537. [CrossRef]
9. Masini G, Graham FJ, Pellicori P, et al. Criteria for Iron Deficiency in Patients With Heart Failure. *J Am Coll Cardiol*. 2022;79(4):341-351. [CrossRef]
10. World Health Organization. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. Accessed April 4, 2025. https://www.who.int/publications/i/item/9789240088542
11. Galy B, Conrad M, Muckenthaler M. Mechanisms controlling cellular and systemic iron homeostasis. *Nat Rev Mol Cell Biol*. 2024;25(2):133-155. [CrossRef]
12. Sow FB, Alvarez GR, Gross RP, et al. Role of STAT1, NF-kappaB, and C/EBPbeta in the macrophage transcriptional regulation of hepcidin by mycobacterial infection and IFN-gamma. *J Leukoc Biol*. 2009;86(5):1247-1258. [CrossRef]
13. Jankowska EA, Malyszko J, Ardehali H, et al. Iron status in patients with chronic heart failure. *Eur Heart J*. 2013;34(11):827-834. [CrossRef]
14. Grote Beverborg N, Klip IT, Meijers WC, et al. Definition of Iron Deficiency Based on the Gold Standard of Bone Marrow Iron Staining in Heart Failure Patients. *Circ Heart Fail*. 2018;11(2):e004519. [CrossRef]
15. Papadopoulou C, Reinhold J, Grüner-Hegge N, et al. Prognostic value of three iron deficiency definitions in patients with advanced heart failure. *Eur J Heart Fail*. 2023;25(11):2067-2074. [CrossRef]
16. Cleland JG, Zhang J, Pellicori P, et al. Prevalence and Outcomes of Anemia and Hematinic Deficiencies in Patients With Chronic Heart Failure. *JAMA Cardiol*. 2016;1(5):539-547. [CrossRef]
17. Jankowska EA, Kasztura M, Sokolski M, et al. Iron deficiency defined as depleted iron stores accompanied by unmet cellular iron requirements identifies patients at the highest risk of death after an episode of acute heart failure. *Eur Heart J*. 2014;35(36):2468-2476. [CrossRef]
18. Kurz K, Lanser L, Seifert M, Kocher F, Pölzl G, Weiss G. Anaemia, iron status, and gender predict the outcome in patients with chronic heart failure. *ESC Heart Fail*. 2020;7(4):1880-1890. [CrossRef]
19. Campodonico J, Nicoli F, Motta I, et al. Prognostic role of transferrin saturation in heart failure patients. *Eur J Prev Cardiol*. 2021;28(15):1639-1646. [CrossRef]
20. De Biase N, Del Punta L, L'Hoyes W, et al. Associations of iron deficiency with cardiac function, congestion, exercise capacity and prognosis in heart failure. *Eur J Heart Fail*. Nov 28, 2024. doi: 10.1002/ejhf.3534. [Epub ahead of print]. [CrossRef]
21. 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. [CrossRef]
22. Quiroga B, Ortiz A, Núñez S, et al.; Cardiorenal Medicine Group (CaReSEN) of the Spanish Society of Nephrology. Treatment of Chronic Heart Failure in Advanced Chronic Kidney Disease: The HAKA Multicenter Retrospective Real-World Study. *Cardiorenal Med*. 2024;14(1):202-214. [CrossRef]

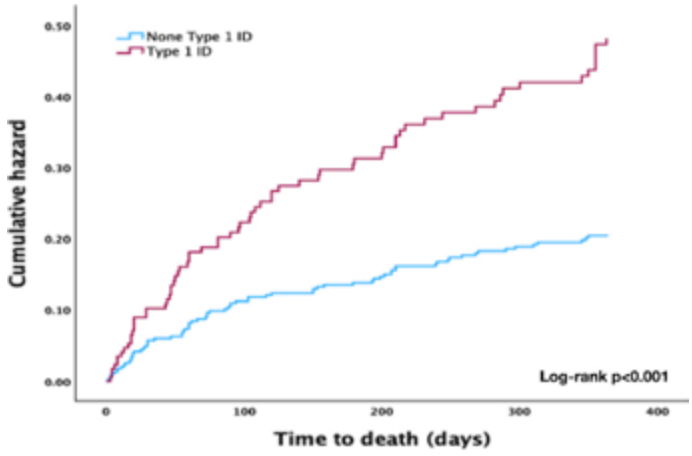
Appendix Table 1. ICD-10 codes used in diagnosis and determination of comorbidities

Diagnosis	ICD-10 code
Heart failure	I50.0, I50.1, I50.9, I11.0, I13.0, I13.2, I42.0
Comorbidities	
Hypertension n, (%)	I10
Dyslipidemia n, (%)	E78
Diabetes mellitus n, (%)	E10, E11, E13, E14
Chronic obstructive pulmonary disease n, (%)	J44
Anaemia n, (%)	D63, D64,
Atrial fibrillation n, (%)	I48
Iron deficiency anaemia n, (%)	D50
Acute myocardial infarction n, (%)	I21
Chronic kidney disease n, (%)	N18
Cerebrovascular event n, (%)	G45, I63

Appendix Table 2. Different iron deficiency types regarding mechanistic pathway in each heart failure phenotype

	HFrEF (n=168)	HFmrEF (n=114)	HFpEF (n=288)	P
Type 1 ID (n, %)	45 (26.7)	42 (36.8)	88 (30.6)	0.198
Type 2 or 3 ID (n, %)	78 (46.4)	43 (37.7)	129 (44.8)	0.317

HFrEF, Heart Failure With Reduced Ejection Fraction; HFmrEF, Heart Failure With Mildly Reduced Ejection Fraction; HFpEF, Heart Failure With Preserved Ejection Fraction; ID, Iron Deficiency.



Appendix Figure 1. Kaplan-Meier analysis curves for patients with and without Type 1 iron deficiency.