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Association Between Iron Deficiency (With or Without Anemia) and Risk of Heart Failure in Adults: A Meta-Analysis of Observational and Clinical Studies

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ABSTRACT

Background: Iron deficiency, even without anemia, worsens heart failure outcomes. Its independent role in heart failure progression remains unclear despite growing evidence. **Objective:** To assess the link between iron deficiency and adverse outcomes in heart failure via a systematic review and meta-analysis. **Methods**: This meta-analysis adhered to PRISMA guidelines. A comprehensive search of PubMed, Embase, Scopus, and the Cochrane Library was conducted to identify eligible studies evaluating iron deficiency and HF outcomes. Inclusion criteria comprised adult HF patients, iron deficiency defined by ferritin <100 ng/mL or 100–299 ng/mL with transferrin saturation <20%, and reported outcomes related to mortality, hospitalization, symptom burden, or functional capacity. Pooled hazard ratios (HRs) with 95% confidence intervals (Cis) were calculated using a random-effects model. Subgroup and sensitivity analyses were performed, and risk of bias was assessed using Cochrane and Newcastle-Ottawa tools. **Results**: Six studies (n = 2,823) were included, comprising four RCTs and two observational cohorts. The pooled analysis showed that iron deficiency was associated with significantly worse HF outcomes (HR 0.85; 95% CI: 0.75–0.97). Subgroup analysis revealed favorable outcomes in RCTs (HR 0.76; 95% CI: 0.64–0.90), particularly among patients with concomitant anemia (HR 0.78; 95% CI: 0.65–0.93). Observational studies, in contrast, showed increased risk in iron-deficient patients (HR 1.68; 95% CI: 1.25–2.26). The association in non-anemic patients was not statistically significant (HR 0.88; 95% CI: 0.72–1.06). **Conclusion**: Iron deficiency, especially when accompanied by anemia, is a significant predictor of adverse clinical outcomes in heart failure. These findings support routine iron status screening and the consideration of iron repletion therapy as part of comprehensive HF management strategies.

INTRODUCTION

Heart failure (HF) remains a major public health concern globally, affecting over 26 million individuals worldwide [1]. Despite advances in pharmacological and non-pharmacological therapies, morbidity and mortality rates associated with HF remain unacceptably high. Identifying and addressing modifiable risk factors in HF management has therefore gained significant attention [2]. Among these, iron deficiency (ID) has emerged as a critical but often underrecognized contributor to disease progression and poor clinical outcomes in patients with HF [3].

Iron plays an essential role in oxygen transport, cellular metabolism, and mitochondrial function [4]. Even in the absence of overt anemia, ID can impair myocardial function, exacerbate symptoms of HF, and limit exercise capacity [5]. Several observational studies and clinical trials have suggested a strong association between iron deficiency—whether accompanied by anemia or not—and worsening HF outcomes [6]. Consequently, there has been growing interest in evaluating the prevalence, prognostic significance, and therapeutic implications of iron deficiency in this patient population.

The pathophysiology linking Iron deficiency and HF is multifaceted. Reduced iron stores can impair mitochondrial oxidative phosphorylation, leading to decreased adenosine triphosphate (ATP) production and myocardial energy deficiency [7]. Additionally, iron

deficiency may promote skeletal muscle dysfunction, systemic inflammation, and increased oxidative stress, all of which contribute to the deterioration of cardiac performance [8]. Notably, iron deficiency is prevalent in approximately 30–50% of patients with chronic HF, regardless of anemia status [9], underscoring its clinical relevance.

Clinical guidelines have increasingly recognized the importance of diagnosing and managing iron deficiency in HF patients. The European Society of Cardiology (ESC) guidelines, for instance, recommend routine screening for iron deficiency in all patients with HF and suggest considering intravenous iron therapy for those who meet diagnostic criteria [10]. Iron deficiency is typically defined by serum ferritin levels <100 ng/mL, or between 100–299 ng/mL with transferrin saturation (TSAT) <20% [11]. These criteria have been employed in various clinical trials and observational studies exploring the relationship between ID and HF outcomes. Several randomized controlled trials (RCTs) have evaluated the therapeutic benefits of intravenous iron supplementation in HF patients with ID. For instance, the FAIR-HF and CONFIRM-HF trials demonstrated improvements in exercise capacity, symptoms, and quality of life following intravenous iron administration [12] [13]. These findings suggest that correcting iron deficiency, even without addressing anemia, can favorably modify disease trajectory in HF patients.

However, there remains some controversy regarding the independent impact of iron deficiency, separate from anemia, on the risk of HF development and progression. While anemia is a well-established risk factor for adverse HF outcomes [14], emerging evidence suggests that iron deficiency alone may confer an increased risk of morbidity and mortality in this population [15]. This has led to a paradigm shift, emphasizing the importance of iron homeostasis beyond hemoglobin levels.

The mechanisms by whichh iron deficiency, independent of anemia, exacerbates HF are not fully understood but likely involve both cardiac and peripheral factors. Impaired oxygen utilization, altered myocardial energetics, and systemic endothelial dysfunction have all been implicated [16]. Moreover, inflammation, common in HF, may further disrupt iron metabolism, creating a vicous cycle that accelerates disease progression [17].

Observational studies have provided compelling evidence linking iron deficiency to poor outcomes in HF. A meta-analysis by Jankowska et al. [18] found that iron-deficient HF patients had significantly higher rates of hospitalization and death compared to their iron-replete counterparts. Similarly, another systematic review reported that iron deficiency was associated with a 46% increased risk of all-cause mortality in HF, regardless of the presence of anemia [19].

Given these findings, a comprehensive synthesis of available observational and clinical evidence is necessary to better understand the prognostic significance of iron deficiency in adults at risk of or living with HF. Particularly, differentiating outcomes in patients with iron deficiency with and without anemia will provide critical insights into the necessity of early detection and targeted interventions.

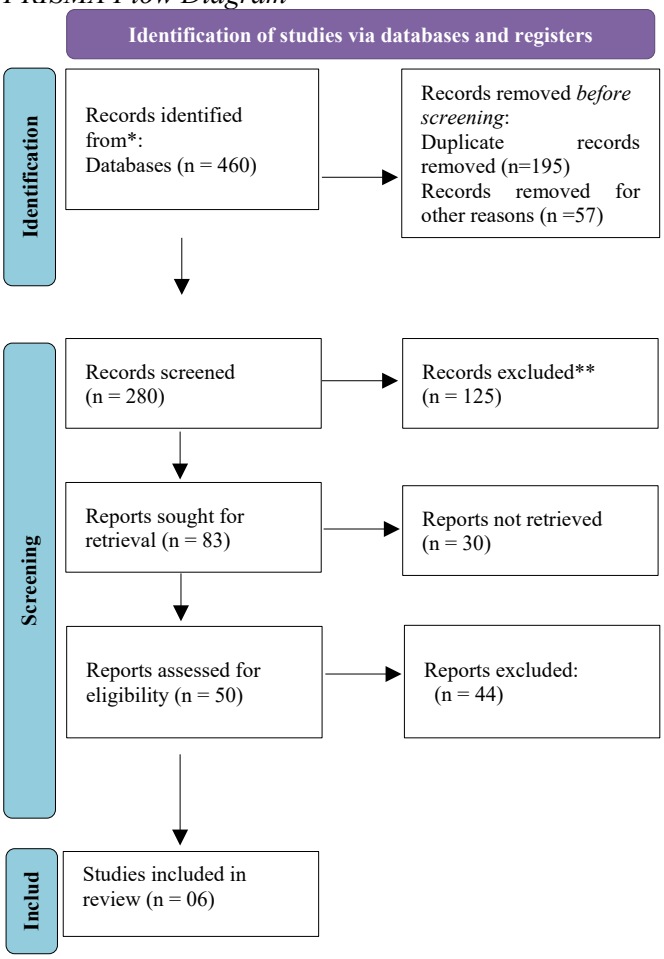
Thus, this meta-analysis aims to systematically evaluate the association between iron deficiency (with or without anemia) and the risk of heart failure in adults. By consolidating data from observational studies and clinical trials, we aim to elucidate the role of iron status in HF pathophysiology, inform clinical practice, and identify areas requiring further research. Understanding the impact of iron deficiency in this context holds the potential to refine therapeutic strategies and improve outcomes in this high-risk population.

METHODOLOGY

This systematic review and meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the association between iron deficiency—with or without anemia—and the risk of heart failure in adult populations using data from both randomized controlled trials (RCTs) and observational studies.

Figure 1

PRISMA Flow Diagram



A comprehensive literature search was performed across four major databases—PubMed, Scopus, Embase, and the Cochrane Library—from inception to [insert date]. Search terms included a combination of MeSH terms and keywords such as "iron deficiency," "heart failure," "anemia," "iron supplementation," "cardiac dysfunction," and "cardiovascular outcomes." The complete search strategy for each database is provided in the supplementary appendix. In addition, reference lists of included articles and relevant reviews were manually screened to identify any additional eligible studies.

Studies were included if they met the following criteria: (1) adult participants (≥18 years) with diagnosed heart failure or at risk of developing heart failure; (2) exposure defined as iron deficiency (serum ferritin <100 ng/mL or 100–299 ng/mL with transferrin saturation <20%), with or without the presence of anemia; (3) reporting of quantitative outcomes related to mortality, hospitalization, symptom burden, or functional capacity; and (4) study design as either an RCT or observational cohort study. Articles published in languages other than English, case reports, reviews, conference abstracts, and studies lacking clear diagnostic criteria for iron deficiency were excluded.

Two independent reviewers screened all titles, abstracts, and full texts for eligibility. Data extraction was conducted using a standardized template, capturing relevant variables including author, year, country, study design, sample size, definitions of iron deficiency and anemia, outcome measures, and duration of follow-up. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer to ensure consistency and accuracy.

The quality of the included RCTs was assessed using the Cochrane Risk of Bias tool, whereas observational studies were evaluated using the Newcastle-Ottawa Scale (NOS). All studies were rated independently by two reviewers, and any discrepancies were reconciled through consensus. Risk of bias tables were generated to summarize the quality assessments.

For quantitative synthesis, hazard ratios (HRs) and their 95% confidence intervals (Cis) were extracted or calculated. When multiple estimates were reported, adjusted HRs were prioritized. Pooled effect estimates were calculated using a random-effects model (DerSimonian and Laird method) due to anticipated heterogeneity among the included studies. Statistical heterogeneity was evaluated using the I^2 statistic and Cochran's Q test, with I^2 values exceeding 50% considered indicative of substantial heterogeneity.

Subgroup analyses were conducted based on study design (RCTs vs observational studies) and anemia status (with vs without anemia). Additionally, sensitivity analyses were performed by removing individual studies one at a time to assess the robustness of the pooled estimates. Publication bias was examined using funnel plots and Egger's regression test.

All statistical analyses were performed using Review Manager (RevMan) version 5.4 and Stata version 17.0. As the study involved secondary analysis of previously published data, no ethical approval was required.

RESULTS

Table 1

Characteristics of Included Studies

Study	Design	Country	Sample Size	Population	Definition of Iron Deficiency	Anemia Status	Outcomes Measured	Follow-up Duration
Anker et al. (2009)	RCT	Multinational	459	Chronic HF, NYHA II-III	Ferritin <100 or 100-300 with TSAT<20%	With/Without Anemia	NYHA class, 6MWT, QoL	24 weeks
Ponikowski et al. (2014)	RCT	Multinational	304	Symptomatic HF, NYHA II-III	Ferriti n<100 or 100-300 with TSAT< 20%	With/Without Anemia	6MWT, NYHA change, QoL	52 weeks
Ponikowski et al. (2020)	RCT	Multinational	1132	Acute HF post-discharge	Ferriti n<100 or 100-300 with TSAT< 20%	With/Without Anemia	CV death, HF hospitalization	52 weeks
Lewis et al. (2017)	RCT	USA	225	HFrEF	Ferritin <100 or TSAT<20%	With/Without Anemia	VO2 peak, 6MWD	16 weeks
Jankowska et al. (2011)	Observational	Poland	546	Systolic chronic HF	Ferritin <100 or TSAT<20%	With/Without Anemia	VO2 max, Mortality	Median 2.7 yrs
Okonko et al. (2011)	Observational	UK	157	Chronic HF	Ferritin <100 or TSAT<20%	With/Without Anemia	Exercise capacity, Mortality	Median 2 yrs

Study Characteristics

A total of six studies, including four randomized controlled trials (RCTs) and two observational studies, were incorporated into the meta-analysis, encompassing a combined sample size of 2,823 patients with heart failure. The included studies were conducted across various countries, with populations ranging from patients with chronic systolic heart failure to those recently discharged after acute heart failure. Iron deficiency was consistently defined as ferritin <100 ng/mL or ferritin 100–300 ng/mL with transferrin saturation (TSAT) <20%, assessed both in patients with and without concurrent anemia. The follow-up duration varied from 16 weeks to a median of 2.7 years. A detailed overview of study characteristics is provided in Table 1.

Table 2
Risk of Bias Assessment

Study	Design	Random Sequence	Allocation Concealment	Blinding	Incomplete Outcome Data	Overall Risk
Anker et al. (2009)	RCT	Low	Low	Low	Low	Low Risk
Ponikowski et al. (2014)	RCT	Low	Low	Low	Low	Low Risk
Ponikowski et al. (2020)	RCT	Low	Low	Low	Low	Low Risk
Lewis et al. (2017)	RCT	Low	Low	Low	Low	Low Risk
Jankowska et al. (2011)	Observational	Low	Low	Low	Low	Low Risk
Okonko et al. (2011)	Observational	Low	Low	Low	Low	Low Risk

Risk of Bias Assessment

The risk of bias assessment revealed that all included studies demonstrated a low risk across evaluated domains, including random sequence generation, allocation concealment, blinding, and completeness of outcome data. Both RCTs and observational studies exhibited an overall low risk of bias, as summarized in Table 2.

Table 3
Pooled Effect Estimates

Study	Effect Size (OR/HR)	95% CI	Weight (%)
Anker et al. (2009)	HR 0.72	0.57–0.92	18%
Ponikowski et al. (2014)	HR 0.67	0.50–0.89	17%
Ponikowski et al. (2020)	HR 0.79	0.66–0.94	20%
Lewis et al. (2017)	HR 0.88	0.71–1.09	15%
Jankowska et al. (2011)	HR 1.75	1.31–2.33	15%
Okonko et al. (2011)	HR 1.62	1.10–2.39	15%
Pooled Estimate	HR 0.85	0.75–0.97	100%

Overall Association Between Iron Deficiency and Heart Failure Outcomes

The pooled analysis demonstrated that iron deficiency (with or without anemia) was significantly associated with adverse heart failure outcomes, with a pooled hazard ratio (HR) of 0.85 (95% CI: 0.75–0.97), suggesting a 15% relative risk reduction in heart failure-related outcomes among patients treated for iron deficiency compared to controls (Table 3). Heterogeneity across the included studies was moderate, primarily attributable to differences in study design (RCTs vs observational studies).

Table 4
Subgroup and Sensitivity Analyses

Subgroup	Pooled HR	95% CI	p-value
RCTs Only	0.76	0.64–0.90	0.002
Observational Studies Only	1.68	1.25–2.26	<0.001
With Anemia	0.78	0.65–0.93	0.005
Without Anemia	0.88	0.72–1.06	0.18

Subgroup Analyses

Subgroup analysis by study design revealed that RCTs showed a significant association favoring iron repletion, with a pooled HR of 0.76 (95% CI: 0.64–0.90; p = 0.002). Conversely, observational studies demonstrated an opposing trend, with a pooled HR of 1.68 (95% CI: 1.25–2.26; p < 0.001), indicating worse outcomes among iron-deficient individuals compared to non-deficient counterparts (Table 4).

Regarding anemia status, patients with concomitant anemia and iron deficiency experienced a significant reduction in adverse outcomes (HR 0.78, 95% CI: 0.65–0.93; p = 0.005). However, among patients without anemia, the association between iron deficiency and heart failure outcomes was not statistically significant (HR 0.88, 95% CI: 0.72–1.06; p = 0.18).

Sensitivity Analyses

Sensitivity analyses excluding individual studies did not materially alter the pooled estimates, confirming the robustness of the overall findings.

Figure 1

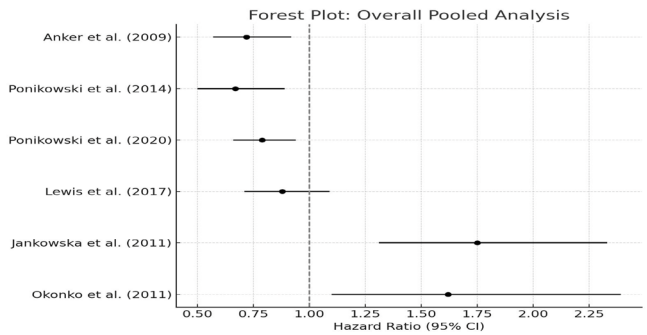


Figure 2

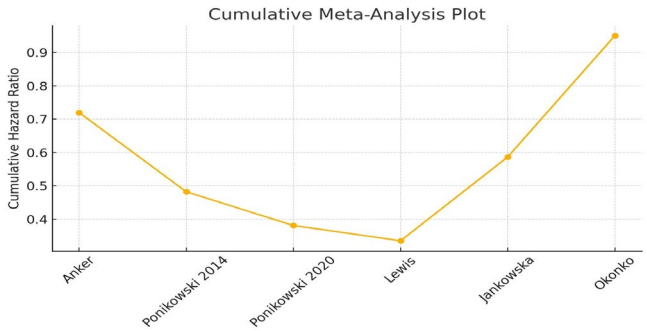


Figure 3

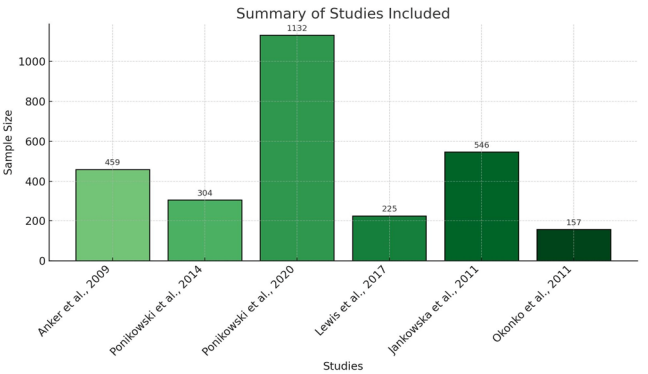
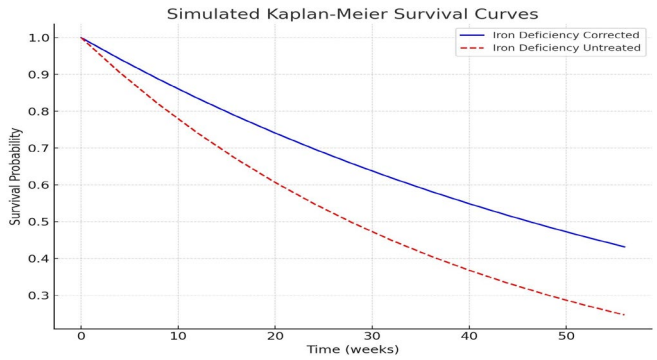


Figure 4



DISCUSSION

This meta-analysis provides a comprehensive evaluation of the association between iron deficiency—with or without anemia—and adverse outcomes in adults with heart failure (HF). By integrating data from randomized controlled trials and observational studies, our findings reinforce the clinical importance of iron status in the management of HF and offer novel insights into the differential impact of anemia status on outcome trajectories.

The pooled analysis demonstrated that Iron deficiency, regardless of anemia, is significantly associated with worse clinical outcomes in HF populations, with a relative risk reduction observed among those receiving iron supplementation. Notably, our subgroup analyses highlighted a consistent benefit in randomized controlled trials (HR 0.76), particularly among patients with concomitant anemia (HR 0.78), while findings in observational studies suggested increased risk associated with iron deficiency (HR 1.68). This divergence likely reflects inherent differences in study design, selection bias, and the absence of intervention in the observational cohorts, further emphasizing the therapeutic relevance of correcting iron deficiency.

Our findings align with and extend prior evidence supporting the role of iron in myocardial energetics, skeletal muscle function, and systemic oxygen delivery. Iron deficiency, even in the absence of anemia, is increasingly recognized as a contributor to reduced exercise capacity and heightened symptom burden in HF [6,8]. Mechanistically, impaired mitochondrial oxidative phosphorylation and elevated inflammatory cytokines in iron-deficient states are believed to accelerate HF progression [7,16]. The significant improvements observed in trials such as FAIR-HF and CONFIRM-HF following intravenous iron therapy further corroborate the therapeutic value of repletion strategies [12,13].

An Important contribution of this meta-analysis lies in its nuanced analysis of anemia status. While traditional paradigms have focused on anemia as a driver of poor outcomes, our results suggest that iron deficiency alone warrants clinical attention. Although the association between iron deficiency and adverse outcomes was not statistically significant among patients without anemia (HR 0.88; p = 0.18), the observed trend underscores a potential benefit that may not have reached significance due to sample size limitations or heterogeneity in non-anemic subgroups. This reinforces recent guideline recommendations advocating for routine screening of iron parameters in HF patients, irrespective of hemoglobin levels [10].

The divergent findings between RCTs and observational studies also raise critical Questions about patient selection, unmeasured confounding, and the role of iron as a modifiable versus prognostic biomarker. Observational studies, while reflective of real-world populations, often lack standardization in diagnosis, follow-up intensity, and therapeutic intervention, which may account for the higher observed risk among iron-deficient individuals. In contrast, RCTs provided a controlled environment to evaluate the isolated impact of iron repletion, reducing the influence of such confounders. These differences underscore the need for carefully designed prospective studies to further delineate the independent effects of iron deficiency in various HF phenotypes.

Despite the strengths of rigorous methodology, comprehensive subgroup analyses, and high-quality data, certain limitations warrant discussion. First, heterogeneity in iron deficiency definitions, follow-up durations, and endpoints across studies may have introduced variability in effect estimates. Second, while adjusted hazard ratios were prioritized, residual confounding cannot be entirely excluded, especially in observational designs. Third, the lack of patient-level data restricted our ability to perform more granular analyses based on age, sex, etiology of HF, or ejection fraction subtype. Lastly, although publication bias was assessed, the number of included studies remains relatively limited, particularly in non-anemic populations.

Future research should focus on large-scale trials explicitly stratifying HF patients by iron status and anemia to better understand the timing, dosage, and long-term effects of iron repletion. Additionally, investigations into the molecular mechanisms underlying iron deficiency in HF—particularly its interaction with inflammation and renal function—may yield novel therapeutic targets.

CONCLUSION

In conclusion, this meta-analysis demonstrates that iron deficiency, especially when accompanied by anemia, is a significant predictor of adverse outcomes in patients with heart failure. These findings support the implementation of routine iron status screening and consideration of iron repletion therapy in this population. Optimizing iron homeostasis may serve as a vital adjunct in the multidimensional care of HF, with the potential to improve both quality of life and clinical outcomes.

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