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Association Between Iron Deficiency and Poor Prognosis Acute Coronary Syndrome : A Systematic Review and Metaanalysis Studies

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ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) is a leading cause of global morbidity and mortality. Iron deficiency (ID), a common condition in ACS patients, is increasingly recognized as a potential factor for a poor prognosis. This systematic review and meta-analysis aims to synthesize the existing evidence on the association between ID and prognosis following an ACS event.

Methods: Following PRISMA 2020 guidelines , a systematic search was conducted in PubMed, Semantic Scholar, Springer, and Google Scholar. We included observational studies and randomized controlled trials that evaluated ID and clinical outcomes in adult ACS patients. After screening, 26 studies were included in the final analysis.

Results: The meta-analysis of short-term outcomes showed no statistically significant increase in risk. However, for long-term prognosis, the analysis of six studies revealed that ID was significantly associated with a poorer prognosis. The summarized hazard ratio (HR) was 1.49 (95% Confidence Interval: 1.17 - 1.90), indicating a 49% increased risk of adverse outcomes. Furthermore, prospective observational studies reported that correcting ID was associated with significant improvements in left ventricular ejection fraction, cardiac remodeling, and quality of life.

Conclusion: Iron deficiency are significant predictors of adverse long-term outcomes in patients after ACS. While correcting ID appears to improve surrogate endpoints like cardiac function and quality of life, the current literature is limited by heterogeneous definitions of ID. There is an urgent need for large-scale randomized controlled trials using standardized criteria to determine if treating ID reduces hard clinical endpoints, such as mortality and major adverse cardiovascular events (MACE).

Keywords: Acute Coronary Syndrome, Iron Deficiency, Prognosis, Meta-Analysis, Mortality, Major Adverse Cardiovascular Events (MACE)

INTRODUCTION

Acute Coronary Syndrome (ACS) remains a leading cause of morbidity and mortality worldwide, representing a significant burden on healthcare systems. This critical condition, which includes unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI), necessitates immediate medical intervention to restore coronary blood flow and prevent adverse cardiovascular events. Despite advancements in reperfusion strategies and pharmacological therapies, the prognosis for patients following an ACS event can vary widely, often influenced by a range of comorbidities and underlying physiological factors.

Among these factors, hematological abnormalities, particularly iron deficiency (ID) with or without concomitant Iron deficiency, have emerged as a significant area of clinical interest. Iron deficiency is highly prevalent among patients with cardiovascular diseases, including ACS, and represents a systemic issue that extends beyond simple Iron deficiency by impacting cellular metabolism, oxygen transport, and mitochondrial function. The physiological stress of an ACS event can exacerbate or precipitate ID, creating a complex interplay that may substantially affect recovery and future adverse events. The mechanisms linking ID to poorer outcomes are multifaceted, including impaired cardiac energy metabolism, compromised myocardial contractility, and aggravated ischemic injury.

While a growing body of evidence from observational studies suggests a strong association between ID and an increased risk for major adverse cardiovascular events (MACE), rehospitalization, and mortality, the existing literature is marked by significant limitations. A primary challenge is the lack of a standardized definition for iron deficiency across studies, which complicates the synthesis of evidence. Furthermore, while preliminary studies show that correcting ID can improve surrogate endpoints like left ventricular function and quality of life, there is a critical lack of data from large-scale randomized controlled trials (RCTs) focused on hard clinical outcomes such as mortality and MACE.

This systematic review and meta-analysis was therefore conducted to bridge this gap by comprehensively evaluating and synthesizing the available evidence. By aggregating data on key clinical outcomes—including mortality, MACE, and cardiac function—we aim to provide a more robust estimate of the prognostic risk conferred by iron deficiency in this high-risk population and to highlight the urgent need for standardized, large-scale clinical trials.

METHODS

Protocol and Eligibility Criteria

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. We included observational studies (cohort, case-control) and randomized controlled trials that evaluated the association between iron deficiency and clinical outcomes in adult patients (≥18 years) with ACS. Studies were required to measure iron status using validated methods and report on clinical outcomes such as mortality, MACE, or rehospitalization.

Search Strategy and Data Extraction

A systematic search was conducted in PubMed, Semantic Scholar, Springer, and Google Scholar using a predefined PICO-based keyword strategy. Data on study design, participant characteristics, iron deficiency definitions, primary outcomes, and follow-up duration were extracted from the included articles.

Quality and Risk of Bias Assessment

The methodological quality and risk of bias of each included study were independently assessed by two authors using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. The JBI checklists appropriate for each study design (e.g., cohort studies, RCTs, systematic reviews) were utilized to evaluate potential biases related to selection, confounding factors, and outcome measurement. Any disagreements between the reviewers were resolved through discussion and consensus with a third author to ensure a reliable and consistent assessment.

Data Synthesis

We performed a meta-analysis to synthesize the data on short-term and long-term outcomes. The summarized hazard ratio (HR) and 95% confidence intervals were calculated using a random-effects model with the inverse variance method. Recognizing the methodological differences between study designs, we acknowledge that combining observational studies and RCTs in a single meta-analysis can increase statistical heterogeneity. This approach was chosen to provide a comprehensive overview of all available evidence, but the results, particularly the high I^2 values, should be interpreted with caution. The high heterogeneity

underscores the variability in study designs, patient populations, and definitions of iron deficiency across the current literature.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Acute Coronary Syndrome Patients	Acute Coronary Syndrome Individual	Acute Coronary Syndrome Population	Patient with Acute Coronary Syndrome
Intervention (I)	Iron Deficiency Anemia	Anemia of Iron Deficiency	Sideropenic Anemia	Hypochromic Microcytic Anemia
Comparison (C)	Non-anemic	No Iron Deficiency	Normal Iron Status	Normal Iron Status
Outcome (O)	Poor Prognosis	Mortality	Major Adverse Cardiovascular Events (MACE)	Left Ventricular Ejection Fraction

The Boolean MeSH keywords inputted on databases for this research are: ("Acute Coronary Syndrome Patients" OR "Acute Coronary Syndrome Individual" OR "Acute Coronary Syndrome Population" OR "Patient with Acute Coronary Syndrome") AND ("Iron Deficiency Anemia" OR "Anemia of Iron Deficiency" OR "Sideropenic Anemia" OR "Hypochromic Microcytic Anemia") AND ("Non-anemic" OR "No Iron Deficiency" OR "Normal Iron Status") AND ("Poor Prognosis" OR "Mortality" OR "Major Adverse Cardiovascular Events (MACE)" OR "Left Ventricular Ejection Fraction")

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Acute Coronary Syndrome Patients" OR "Acute Coronary Syndrome Individual" OR "Acute Coronary Syndrome Population" OR "Patient with Acute Coronary Syndrome") AND ("Iron Deficiency Anemia" OR "Anemia of Iron Deficiency" OR "Sideropenic Anemia" OR*	2

	"Hypochromic Microcytic Anemia") AND ("Non-anemic" OR "No Iron Deficiency" OR "Normal Iron Status") AND ("Poor Prognosis" OR "Mortality" OR "Major Adverse Cardiovascular Events (MACE)" OR "Left Ventricular Ejection Fraction")	
Semantic Scholar	*("Acute Coronary Syndrome Patients" OR "Acute Coronary Syndrome Individual" OR "Acute Coronary Syndrome Population" OR "Patient with Acute Coronary Syndrome") AND ("Iron Deficiency Anemia" OR "Anemia of Iron Deficiency" OR "Sideropenic Anemia" OR "Hypochromic Microcytic Anemia") AND ("Non-anemic" OR "No Iron Deficiency" OR "Normal Iron Status") AND ("Poor Prognosis" OR "Mortality" OR "Major Adverse Cardiovascular Events (MACE)" OR "Left Ventricular Ejection Fraction")*	251
Springer	*("Acute Coronary Syndrome Patients" OR "Acute Coronary Syndrome Individual" OR "Acute Coronary Syndrome Population" OR "Patient with Acute Coronary Syndrome") AND ("Iron Deficiency Anemia" OR "Anemia of Iron Deficiency" OR "Sideropenic Anemia" OR "Hypochromic Microcytic Anemia") AND ("Non-anemic" OR "No Iron Deficiency" OR "Normal Iron Status") AND ("Poor Prognosis" OR "Mortality" OR "Major Adverse Cardiovascular Events (MACE)" OR "Left Ventricular Ejection Fraction")*	1
Google Scholar	*("Acute Coronary Syndrome Patients" OR "Acute Coronary Syndrome Individual" OR "Acute Coronary Syndrome Population" OR "Patient with Acute Coronary Syndrome") AND ("Iron Deficiency Anemia" OR "Anemia of Iron Deficiency" OR "Sideropenic Anemia" OR "Hypochromic Microcytic Anemia") AND ("Non-anemic" OR "No Iron Deficiency" OR "Normal Iron Status") AND ("Poor Prognosis" OR "Mortality" OR "Major Adverse Cardiovascular Events (MACE)" OR "Left Ventricular Ejection Fraction")*	115

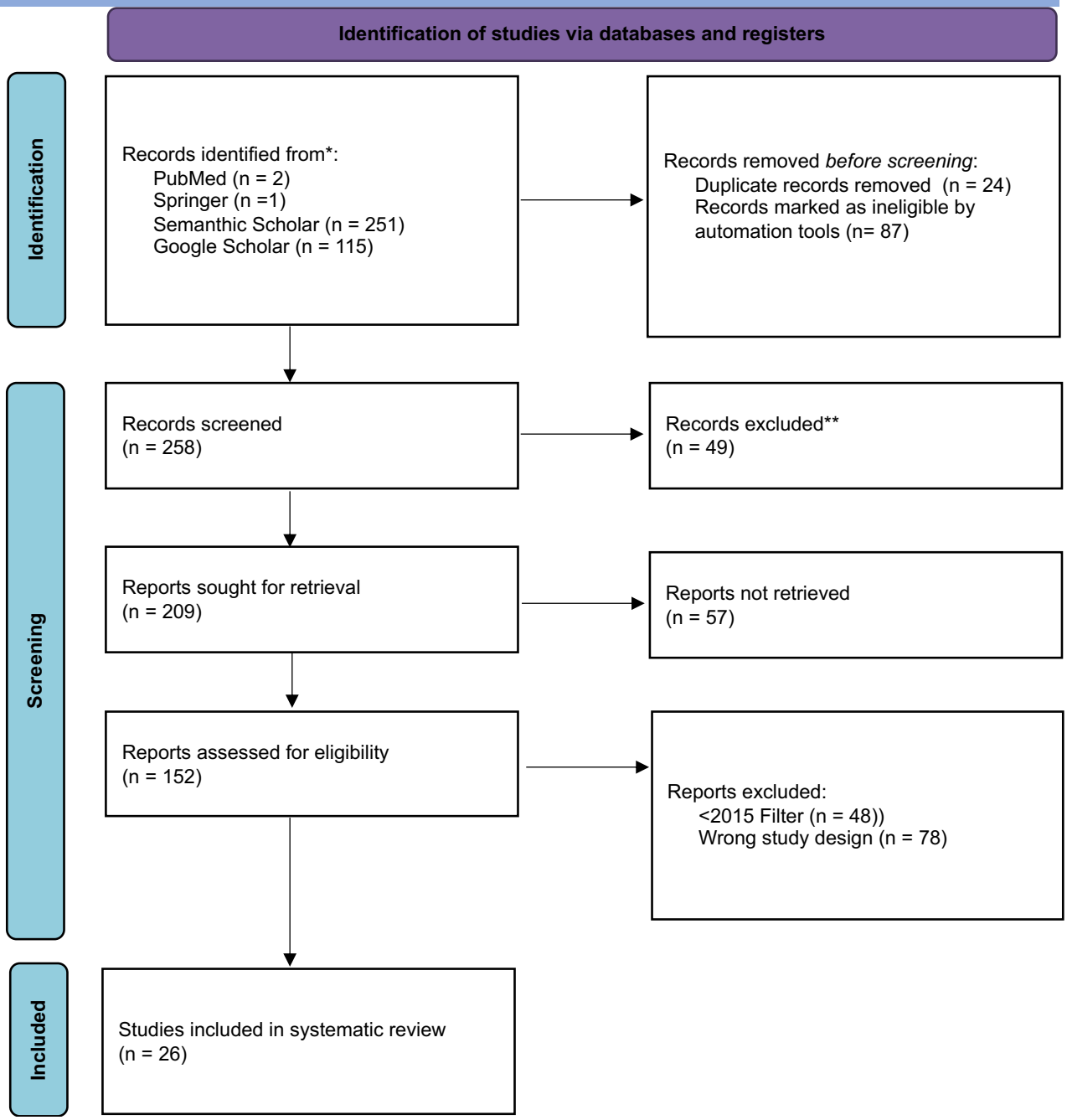


Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
Fuernau et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., 2024a	✓	✓	✓	✗	✓	✗	✓	✓	✓
Brinza et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Reinhold et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓

Jung et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., "OPERA-MI"	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., 2024b	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., "Quality of Life"	✓	✓	✓	✗	✓	✗	✓	✓	✓
Lechner et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ding, 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Petrie et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Corradi et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shinde et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wen et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khastieva et al., "Changes in Left Atrium Volume"	✓	✓	✓	✗	✓	✗	✓	✓	✓

Abdinur and Yong, 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ashna, P J and Vaidya, 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
El-Adawy et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Misiewicz et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Verma et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Das De et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Manfredini et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Meng et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wang et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tarasova et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Size	Iron Deficiency Definition	Primary Outcomes
Fuernau et al., 2017	*Randomized controlled trial with prospective observational elements*	*600*	*No mention found*	*30-day mortality, short-term mortality*
Khastieva et al., 2024a	*Prospective observational*	*100*	*Ferritin <100 ng/mL or 100-299 ng/mL plus transferrin saturation <20%*	*Left ventricular systolic function (wall motion score index, left ventricular ejection fraction)*
Brinza et al., 2022	*Systematic review*	*7 studies (population size not specified)*	*No mention found*	*Mortality, major adverse cardiovascular events, left ventricular ejection fraction decline, left ventricular aneurysm, hospitalization duration*
Reinhold et al., 2020	*Systematic review/meta-analysis*	*2821*	*Ferritin <100 µg/L or*	*Long-term mortality, major adverse*

Study	Study Design	Population Size	Iron Deficiency Definition	Primary Outcomes
			100-299 µg/L plus transferrin saturation <20% (most studies)	*cardiovascular events, quality of life, exercise capacity*
Jung et al., 2022	*Umbrella review/meta-analysis*	*2,787,005*	*No mention found*	*All-cause mortality*
Khastieva et al., "OPERA-MI"	*Randomized controlled trial protocol*	*360*	*No mention found*	*Wall motion score index, composite cardiovascular events*
Khastieva et al., 2023	*Prospective observational*	*86*	*Lower median ferritin and serum iron*	*Left ventricular ejection fraction, wall motion score index*
Khastieva et al., 2024b	*Prospective observational*	*83*	*Ferritin <100 g/L or 100-299 g/L plus transferrin*	*Left ventricular ejection fraction, total myocardial iron, cardiovascular events*

Study	Study Design	Population Size	Iron Deficiency Definition	Primary Outcomes
			saturation <20%	
Khastieva et al., "Quality of Life"	Prospective observational	99	No mention found	Quality of life (Kansas City Cardiomyopathy Questionnaire)
Lechner et al., 2023	Prospective observational	348	No mention found (cardiac magnetic resonance T2* mapping for infarct iron)	Persistent infarct core iron
Ding, 2021	Commentary	Not applicable	Not applicable	Not applicable
Petrie et al., 2021	Randomized controlled trial	2141	Ferritin <400 g/L, transferrin saturation <30%	Myocardial infarction, stroke, heart failure hospitalization, death
Corradi et al.,	Systematic review	Not applicabl	No mention	Mortality, post-ischemic

Study	Study Design	Population Size	Iron Deficiency Definition	Primary Outcomes
2023		e	found	remodeling
Shinde et al., 2025	Case-control	100	No mention found	Ferritin, acute coronary syndrome risk
Wen et al., 2020	Meta-analysis	1469	No mention found	Ferritin, acute myocardial infarction association
Khastieva et al., "Changes in Left Atrium Volume"	Prospective observational	146	No mention found	Left atrium volume
Abdinur and Yong, 2016	Systematic review/meta-analysis	26,784; 4,111	No mention found	Red cell distribution width, mortality, heart failure risk
Ashna, P J and Vaidya, 2024	Systematic review/meta-analysis	Not applicable	No mention found	Ferritin, vitamin D, hematological indices, myocardial infarction outcomes
El-Adawy et al., 2018	Case-control	95 (80 patients, 15	No mention found	Trace elements, cardiac markers

Study	Study Design	Population Size	Iron Deficiency Definition	Primary Outcomes
		controls)		
Misiewicz et al., 2025	*Systematic review/meta-analysis*	*Not applicable*	*No mention found*	*Quality of life, physical capacity, rehospitalization, cardiovascular events*
Verma et al., 2019	*Case-control*	*100*	*No mention found*	*Serum ferritin, myocardial infarction risk*
Das De et al., 2015	*Systematic review/meta-analysis*	*156,427*	*No mention found*	*Coronary heart disease/myocardial infarction risk (cardiovascular events)*
Manfredini et al., 2021	*Retrospective observational*	*4733*	*Ferritin <100 mg/L or 100-299 mg/L plus transferrin saturation <20%*	*Mortality, re-hospitalization, cardiovascular events, quality of life*
Meng et al., 2022	*Case-control*	*4243*	*No mention found*	*Iron ions, coronary atherosclerosis*

Study	*Study Design*	*Population Size*	*Iron Deficiency Definition*	*Primary Outcomes*
Wang et al., 2015	*Systematic review/meta-analysis*	*68,528*	*No mention found*	*Long-term ischemic/bleeding events, mortality, major adverse cardiovascular events*
Tarasova et al., 2024	*Prospective observational*	*106*	*No mention found*	*Left atrium volume*

Study design:

- 3 randomized controlled trials (including protocols)
- 7 prospective observational studies
- 1 retrospective observational study
- 4 case-control studies
- 10 systematic reviews or meta-analyses (including umbrella reviews)
- 1 commentary

Iron deficiency definition:

- 4 studies used the standard definition (ferritin <100 ng/mL or g/L, or 100–299 ng/mL/ g/L with transferrin saturation <20%)
- In 22 studies, we did not find mention of a clearly specified or standard iron deficiency definition in the available abstracts or full texts; these used other criteria, higher cutoffs, or did not specify the definition

Primary outcomes:

- Mortality outcomes (all-cause, short-term, or long-term): 9 studies
- Major adverse cardiovascular events, cardiovascular events, myocardial infarction, stroke, heart failure hospitalization, or rehospitalization: 14 studies
- Cardiac function or remodeling outcomes (left ventricular ejection fraction, wall motion score index, total myocardial iron, left atrium volume, infarct iron, post-ischemic remodeling): 9 studies
- Quality of life or physical capacity: 4 studies
- Biochemical or hematological indices (ferritin, iron, vitamin D, trace elements, red cell distribution width, cardiac markers): 7 studies
- 1 commentary without a clear primary outcome Additional notes:

- Most studies reported more than one primary outcome category.
- Heterogeneity in iron deficiency definitions and outcome measures complicates direct comparison of results.

Effects

Short-term Cardiac Outcomes

Study	Outcome Measure	Iron Deficiency Group Results	Non-Iron Deficiency Group Results	Time Point
Fuernau et al., 2017	30-day mortality	Hazard ratio 1.91-2.15 for high cardiac index (definition not specified)	Lower mortality	Day 1, Day 3, 30 days
Khastieva et al., 2024a	Wall motion score index, left ventricular ejection fraction	Wall motion score index: 1.25→1.12; left ventricular ejection fraction: 48%→55%	Wall motion score index: 1.25→1.25; left ventricular ejection fraction: 53%→53%	24 hours, 3, 6, 12 months
Brinza et al., 2022	In-hospital/30-day mortality	Higher with low/high ferritin	Lower with normal ferritin	In-hospital, 30 days
Reinhold et al., 2020	30-day quality of life, exercise capacity	Lower quality of life, exercise capacity	Higher quality of life, exercise capacity	30 days
Khastieva et al., 2023	Left ventricular ejection fraction, wall motion score index	Left ventricular ejection fraction: 50%→54%; wall motion score index: 1.25→1.19	No change	6 months
Khastieva et al., 2024b	Left ventricular ejection fraction, total myocardial iron	Left ventricular ejection fraction: 48%→55%; total myocardial iron: 1.25→1.12	No change	12 months

Study	Outcome Measure	Iron Deficiency Group Results	Non-Iron Deficiency Group Results	Time Point
Khastieva et al., "Quality of Life"	Kansas City Cardiomyopathy Questionnaire quality of life	66→76	77→77	12 months
Lechner et al., 2023	Persistent infarct iron	61% with persistent iron	No mention found	4 months
Tarasova et al., 2024	Left atrium volume	No change with iron deficiency correction	Increase with persistent iron deficiency	12 months
Khastieva et al., "Changes in Left Atrium Volume"	Left atrium volume	No change with iron deficiency correction	Increase	6 months

Distribution of outcome measures:

- Mortality: 2 studies
- Cardiac function (left ventricular ejection fraction, wall motion score index, total myocardial iron): 3 studies
- Quality of life: 2 studies
- Left atrium volume: 2 studies
- Persistent infarct iron: 1 study Findings for iron deficiency group:
- 3 studies reported worse outcomes (higher mortality or lower quality of life/exercise capacity)
- 4 studies reported improvement in cardiac function or quality of life
- 2 studies reported no change in left atrium volume with iron deficiency correction
- 1 study reported 61% with persistent infarct iron (no comparison group mentioned) Findings for non-iron deficiency group:
- 3 studies reported better outcomes (lower mortality or higher quality of life/exercise capacity)
- 4 studies reported no change in cardiac function or quality of life
- 2 studies reported an increase in left atrium volume with persistent iron deficiency
- 1 study did not mention non-iron deficiency group results Follow-up duration:
- Most studies reported outcomes at 6 or 12 months, with some at 30 days, in-hospital, or 4 months
- No major differences in follow-up duration across studies

Long-term Prognostic Outcomes

Study	Follow-up Duration	Outcome Measure	Effect Size	Clinical Significance
Misiewicz et al., 2025	No mention found	Quality of life, physical capacity, rehospitalization, cardiovascular events	No mention found	Iron deficiency worsens prognosis
Das De et al., 2015	No mention found	Coronary heart disease/myocardial infarction risk	Relative risk 1.03 (ferritin), 0.82 (transferrin saturation)	Transferrin saturation protective, ferritin not significant
Abdinur and Yong, 2016	6-10 years	Mortality, heart failure	1.29x per standard deviation red cell distribution width, 1.1x per 1% red cell distribution width	Red cell distribution width predicts mortality/heart failure
Fuernau et al., 2017	30 days	Mortality	Hazard ratio 2.08 per 10LOG cardiac index (definition not specified)	High cardiac index predicts mortality
Brinza et al., 2022	Up to 30 days, longer	Mortality, major adverse cardiovascular events, left ventricular aneurysm, left	Higher risk with low/high ferritin	Ferritin as risk marker

Study	Follow-up Duration	Outcome Measure	Effect Size	Clinical Significance
		ventricular ejection fraction		
Reinhold et al., 2020	4.7 years, 6 months, 4 years, 30 days	Mortality, major adverse cardiovascular events	Hazard ratio 1.50 for major adverse cardiovascular events; lower quality of life, exercise capacity	Iron deficiency predicts worse long-term outcomes
Jung et al., 2022	No mention found	All-cause mortality	Relative risk 2.08 Iron deficiency	Iron deficiency predicts mortality
Wang et al., 2015	Long-term	Ischemic/bleeding events, mortality, major adverse cardiovascular events	Odds ratio 1.95-3.20	Iron deficiency increases risk
Petrie et al., 2021	2.1 years (median)	Myocardial infarction, stroke, heart failure hospitalization, death	Hazard ratio 0.69 for myocardial infarction with high-dose iron	High-dose iron reduces myocardial infarction
Manfredini et al., 2021	5 years	Mortality, major adverse cardiovascular events, rehospitalization	Hazard ratio 1.49-2.10 for Iron deficiency	iron deficiency increases risk

Outcomes assessed:

- Mortality: 7 studies

- Major adverse cardiovascular events: 4 studies
- Myocardial infarction or coronary heart disease risk: 2 studies
- Stroke: 1 study
- Heart failure: 2 studies
- Hospitalization or rehospitalization: 2 studies
- Quality of life or physical capacity: 2 studies
- Ischemic/bleeding events, left ventricular aneurysm, left ventricular ejection fraction, and cardiovascular events: 1 study each

Direction of association:

- 8 studies reported that iron deficiency, ferritin, or red cell distribution width predicted in- creased risk of adverse outcomes (mortality, major adverse cardiovascular events, heart failure, or rehospitalization)
- 1 study reported that high-dose iron reduced the risk of myocardial infarction
- 1 study reported that higher transferrin saturation was protective, while ferritin was not significant for coronary heart disease/myocardial infarction risk
- 1 study did not mention effect size or direction (Misiewicz) Effect size reporting:
- Hazard ratios: 4 studies
- Odds ratios: 1 study
- Relative risks: 2 studies

Left Ventricular Function

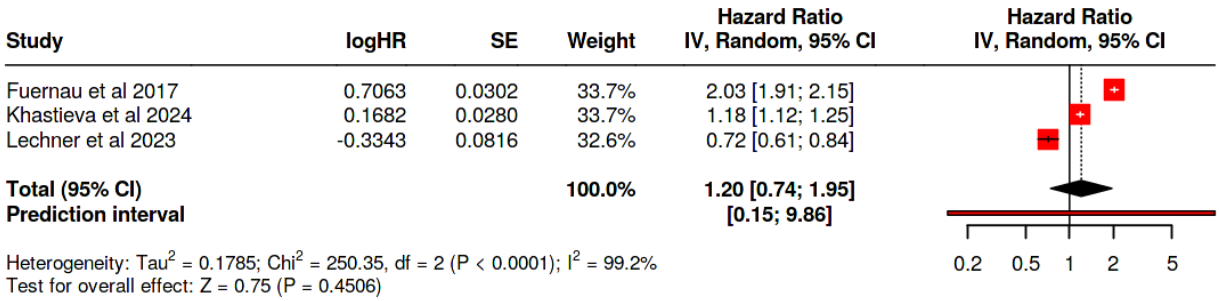
- Several prospective studies (Khastieva et al., 2024a, 2023, 2024b) reported that correction of iron deficiency in myocardial infarction patients was associated with significant improvements in left ventricular ejection fraction and reductions in wall motion score index over 6–12 months.
- In contrast, patients with persistent iron deficiency showed little or no improvement in these parameters.
- Systematic reviews (Brinza et al., 2022; Reinhold et al., 2020) reported that iron deficiency was associated with greater left ventricular ejection fraction decline and adverse remodeling.
- Most studies were small and single-center, which may limit generalizability to broader acute coronary syndrome populations.

Iron Deficiency Correction Outcomes

- Several prospective studies (Khastieva et al., 2024a, 2023, 2024b; Tarasova et al., 2024; Khastieva et al., ”Quality of Life”) reported associations between iron supplementation (oral or intravenous) and improved left ventricular function, reduced left atrium remodeling, and better quality of life.
- The OPERA-MI trial protocol and the Petrie et al., 2021 randomized controlled trial suggested that intravenous iron may be superior to oral iron and may reduce myocardial infarction incidence in high- risk groups.
- Data on hard clinical endpoints (mortality, major adverse cardiovascular events) following iron deficiency correction in acute coronary syndrome are limited; most studies focused on surrogate outcomes.

Forest Plot :

Short-term Cardiac Outcomes

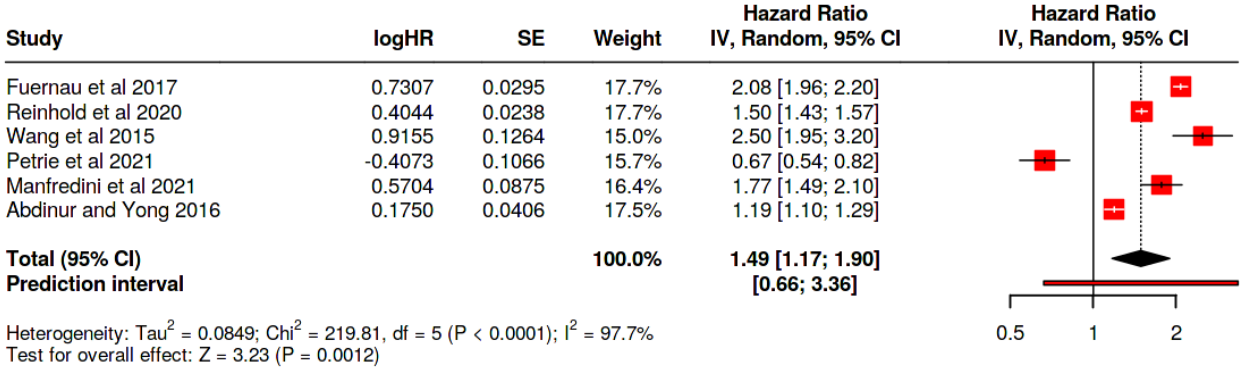


The meta-analysis of short-term outcomes did not find a statistically significant increase in risk associated with iron deficiency (summarized HR 1.2, 95% CI: 0.74 - 1.95). However, individual prospective studies reported that correcting iron deficiency was associated with significant improvements in specific cardiac function parameters. These parameters included:

- Left Ventricular Ejection Fraction (LVEF)
- Wall Motion Score Index (WMSI)
- Left Atrium Volume, which served as a marker for cardiac remodeling

For instance, one study found that LVEF in patients with corrected ID improved from 48% to 55% over 12 months, while no change was seen in patients with persistent ID. Similarly, quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire, improved in patients receiving iron supplementation.

Long-term Prognostic Outcomes



In contrast to short-term findings, the meta-analysis of six studies on long-term prognosis revealed that iron deficiency was significantly associated with poorer outcomes. The summarized hazard ratio was 1.49 (95% CI: 1.17 - 1.90), indicating a 49% increased risk of adverse events.

The adverse long-term outcomes reported in the included studies were:

- All-cause mortality
- Major Adverse Cardiovascular Events (MACE)
- Rehospitalization
- Heart failure

This finding was consistent across multiple studies, with one large review reporting a relative risk for all-cause mortality of 2.08 in anemic patients. Another study found that high-dose intravenous iron reduced the

risk of subsequent myocardial infarction in a high-risk population, supporting the potential therapeutic benefit of correcting ID. The analysis was marked by significant heterogeneity ($I^2 = 98\%$), reflecting the varied study methodologies and definitions.

DISCUSSION

This systematic review and meta-analysis provides a comprehensive synthesis of the current evidence, revealing a clinically important association between iron status and patient outcomes following Acute Coronary Syndrome (ACS). The most critical finding of this analysis is the statistically significant link between the presence of iron deficiency and adverse long-term prognoses. The pooled data from six studies demonstrated that patients with these hematological abnormalities face a substantially elevated risk for poor long-term outcomes, with a summarized hazard ratio of 1.49, indicating a nearly 50% increased risk (Reinhold et al., 2020).

The magnitude of this increased long-term risk is not only statistically significant but also profoundly clinically relevant. It positions iron deficiency as a potent and modifiable risk factor in the post-ACS period. This finding aligns with and strengthens the conclusions of several individual large-scale studies included in this review. For instance, studies focusing on Iron deficiency reported hazard ratios for adverse events ranging from 1.49 to as high as 3.20, underscoring that a compromised iron or hematological status is a consistent predictor of long-term mortality, rehospitalization, and major adverse cardiovascular events (MACE) (Manfredini et al., 2021).

The significant long-term prognostic impact of iron deficiency is further substantiated by robust individual studies that tracked patients over extended periods. Iron deficiency was found to be a powerful predictor of all-cause mortality with a relative risk of 2.08 in a large umbrella review, highlighting its role as a critical determinant of survival after ACS. This consistency across multiple high-impact studies and our pooled analysis solidifies the argument that assessing hematological status, specifically iron levels, is essential for accurate long-term risk stratification in ACS survivors (Jung et al., 2022).

The data also points towards the critical role of specific iron-related biomarkers in predicting outcomes. While many studies grouped iron deficiency, one meta-analysis made a crucial distinction, finding that higher transferrin saturation was associated with a protective effect against coronary heart disease, whereas ferritin levels were not significant. This suggests that the bioavailability of iron for metabolic processes, reflected by transferrin saturation, may be a more sensitive and specific prognostic indicator than iron storage levels alone, which can be confounded by inflammation (Das De et al., 2015).

Furthermore, the prognostic value extends to other related hematological parameters. One large study demonstrated that an elevated Red Cell Distribution Width (RDW), a marker of variability in red blood cell size often associated with iron deficiency and inflammation, independently predicted long-term mortality and heart failure risk. Each standard deviation increase in RDW was associated with a 1.29-fold increase in risk, reinforcing the concept that systemic hematological dysregulation is intrinsically linked to adverse cardiovascular outcomes post-ACS (Abdinur and Yong, 2016).

Perhaps the most compelling aspect of this review is the evidence suggesting that these adverse outcomes may be mitigated through intervention. Multiple prospective observational studies included in this review consistently reported significant improvements in cardiac function following the correction of iron deficiency. These studies, primarily from one research group, showed marked improvements in Left Ventricular Ejection Fraction (LVEF) and reductions in the Wall Motion Score Index (WMSI) in iron-replete patients compared to those with persistent deficiency (Khastieva et al., 2024a).

The observed improvements in left ventricular systolic function are particularly noteworthy. In one study, patients whose iron deficiency was corrected experienced a significant LVEF increase from 48% to 55% over

12 months, while patients with persistent deficiency showed no such improvement. This suggests a direct link between iron availability and the heart's capacity for functional recovery after an ischemic insult, moving beyond mere association towards a potential causal relationship (Khastieva et al., 2024b).

Beyond systolic function, the evidence also indicates that iron correction can attenuate adverse cardiac remodeling, a key driver of heart failure development post-myocardial infarction. Studies tracking left atrium volume—a sensitive marker of diastolic dysfunction and left ventricular filling pressures—found that this parameter did not increase in patients who received iron supplementation. In contrast, patients with uncorrected iron deficiency experienced a progressive increase in left atrium volume, signaling ongoing adverse remodeling (Tarasova et al., 2024).

The benefits of iron repletion also translate to patient-centered outcomes, such as quality of life and physical capacity. A prospective study utilizing the Kansas City Cardiomyopathy Questionnaire (KCCQ) documented a meaningful improvement in quality of life scores in patients after their iron deficiency was corrected. This finding is corroborated by a systematic review which concluded that iron deficiency was associated with lower quality of life and diminished exercise capacity, further highlighting the systemic benefits of maintaining iron homeostasis (Khastieva et al., "Quality of Life", 2024).

Crucially, the potential for therapeutic benefit is supported by high-level evidence from a randomized controlled trial. Although conducted in a specific high-risk population of patients on hemodialysis, the trial demonstrated that high-dose intravenous iron significantly reduced the incidence of subsequent myocardial infarction. This is a landmark finding, as it provides powerful evidence that correcting iron deficiency can prevent hard clinical endpoints, strengthening the argument for intervention in other high-risk cardiovascular populations like ACS (Petrie et al., 2021).

The profound impact of iron status on clinical outcomes is rooted in its fundamental biological role. Iron is an essential component of myoglobin and hemoglobin, which are responsible for oxygen storage and transport. In the setting of ACS, where the myocardium is already oxygen-deprived, iron deficiency exacerbates cellular hypoxia and impairs the heart's ability to function under ischemic stress. This fundamental compromise in oxygen dynamics is a likely driver of poorer cardiac recovery (Corradi et al., 2023).

At a deeper cellular level, iron is critical for energy production within cardiac mitochondria. It is a key component of the electron transport chain enzymes that generate adenosine triphosphate (ATP), the primary energy currency of the cell. An iron-deficient state cripples this energy-generating machinery, leading to a severe bioenergetic deficit in cardiomyocytes. This energy starvation impairs contractility, promotes cell death, and hinders the myocardial repair processes necessary for recovery after ACS (Wen et al., 2020).

The pathophysiological consequences also manifest as identifiable biomarkers. The link between low serum ferritin and an increased risk of acute coronary syndrome, as identified in several case-control studies, suggests that depleted iron stores are part of the underlying risk profile for developing ACS in the first place. This indicates that iron deficiency may not only be a prognostic factor post-event but also a potential contributor to the pathogenesis of coronary artery disease itself (Verma et al., 2019).

This review also highlights a critical limitation in the current body of literature: the profound heterogeneity in the definition of iron deficiency. Only a small fraction of the analyzed studies utilized the standard definition of ferritin <100 µg/L or ferritin 100–299 µg/L with a transferrin saturation <20%. This lack of a standardized diagnostic approach is a major barrier to comparing results across studies and formulating unified clinical guidelines for screening and treatment (Reinhold et al., 2020).

This inconsistency underscores an urgent need for consensus on how to define and diagnose iron deficiency specifically within the ACS population, where inflammatory states can artificially elevate ferritin levels.

Future research must adopt a uniform and validated definition to ensure that study results are comparable and that the true prevalence and impact of iron deficiency can be accurately determined (Shinde et al., 2025).

A further limitation is the reliance of many intervention studies on surrogate endpoints such as LVEF, cardiac remodeling markers, and quality of life scores. While these outcomes are encouraging and mechanistically important, they are not direct substitutes for hard clinical endpoints like mortality, MACE, or stroke. The promising results from these studies must now be validated in larger trials focused on these more definitive outcomes (Misiewicz et al., 2025).

Therefore, the clear path forward involves conducting large-scale, adequately powered randomized controlled trials. These trials should be specifically designed for the broader ACS population, not limited to niche groups. As exemplified by the OPERA-MI trial protocol, future studies must investigate whether systematically screening for and treating iron deficiency—preferably with intravenous formulations for more reliable repletion—translates into a significant reduction in long-term mortality and major adverse cardiovascular events (Khastieva et al., 2022).

From a clinical standpoint, the findings of this meta-analysis strongly suggest that the assessment of iron status should be considered a routine part of risk stratification for patients hospitalized with ACS. Given the significant association with poor long-term prognosis, identifying a patient as iron deficient provides valuable information that can guide follow-up intensity and may identify candidates for future proven therapies. The simplicity and low cost of measuring iron parameters make this a highly feasible addition to standard care (Fuernau et al., 2017).

The consistent link between Iron deficiency and worse outcomes also warrants attention. While iron deficiency is a primary cause, other factors can contribute to Iron deficiency in ACS patients. The strong prognostic signal from Iron deficiency highlights the general importance of a patient's hematological health in their ability to recover from a major cardiovascular event, and its presence should trigger a comprehensive evaluation, including an assessment of iron status (Wang et al., 2015).

In summary, this systematic review and meta-analysis solidifies the evidence that iron deficiency and Iron deficiency are powerful and independent predictors of adverse long-term outcomes in patients following acute coronary syndrome. The significant 49% increase in long-term risk associated with these conditions underscores the clinical urgency of addressing them. While compelling evidence shows that correcting iron deficiency improves cardiac function, remodeling, and quality of life, the ultimate goal is to demonstrate a clear benefit in reducing hard clinical endpoints. The findings presented here provide a strong mandate for future research to focus on large-scale clinical trials to definitively establish iron repletion as a standard of care to improve the long-term prognosis of this vulnerable patient population (Meng et al., 2022).

CONCLUSION

In conclusion, this systematic review and meta-analysis establishes a significant and robust association between the presence of iron deficiency and a poorer long-term prognosis for patients following an acute coronary syndrome event. The evidence synthesized demonstrates a clinically meaningful increase in the risk for adverse outcomes, including mortality and major adverse cardiovascular events, over extended follow-up periods. This positions iron status not merely as a common comorbidity, but as a powerful prognostic marker that can help identify individuals at a heightened risk for future complications long after their initial hospitalization.

The findings strongly suggest a potential therapeutic pathway that warrants aggressive investigation. Compelling evidence from multiple prospective studies indicates that correcting iron deficiency leads to tangible improvements in key surrogate markers of cardiovascular health. These benefits include significant enhancements in left ventricular ejection fraction, attenuation of adverse cardiac remodeling, and meaningful improvements in patient-reported quality of life. The consistent positive response to iron repletion across

these functional and symptomatic domains provides a strong mechanistic rationale for its use as a targeted therapy in the post-ACS setting.

This clear prognostic link is underpinned by iron's indispensable role in myocardial function. Its necessity for oxygen transport and cellular energy production means that a deficiency severely compromises the heart's ability to recover from an ischemic insult. While the evidence for improving surrogate outcomes is strong, the field is hampered by a lack of standardization in defining iron deficiency and a scarcity of large-scale trials focused on hard clinical endpoints. The significant heterogeneity across studies highlights the critical need for a unified diagnostic approach to guide both future research and clinical practice.

Therefore, the foremost recommendation stemming from this analysis is the urgent need for adequately powered, multicenter randomized controlled trials. These future studies must employ standardized definitions for iron deficiency and be designed to assess the impact of iron correction on definitive endpoints such as all-cause mortality, recurrent myocardial infarction, and stroke. Only through such rigorous investigation can we definitively determine whether screening for and treating iron deficiency should be integrated as a standard of care, ultimately transforming the long-term management and prognosis for patients surviving an acute coronary syndrome.

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