Efficacy of oral vs. intravenous iron for the treatment of iron deficiency anemia in different conditions: A systematic review and meta-analysis

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Abstract. The present systematic review and meta-analysis evaluated the efficacy and safety of oral vs. intravenous (IV) iron therapy in managing iron deficiency anemia (IDA) across various clinical conditions. A comprehensive search was conducted in PubMed/MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science, Scopus, and ClinicalTrials.gov, yielding 31 eligible studies. IV iron demonstrated statistically significant superiority over oral iron in increasing hemoglobin levels among patients with chronic kidney disease (CKD), inflammatory bowel disease (IBD), cancer-related anemia and general IDA. Specifically, pooled standardized mean differences (SMD) indicated significant improvements with IV iron for cancer-related anemia (SMD: -0.662, P=0.011), CKD (SMD: -0.492, P=0.035), IBD (SMD: -0.560, P<0.001) and IDA (SMD: -0.397, P<0.001). However, no significant differences were observed for postoperative anemia or restless legs syndrome. IV iron consistently provided faster hemoglobin correction and fewer gastrointestinal side effects compared with oral iron; however, higher costs and logistical requirements may limit its widespread use. Meta-regression analysis revealed that neither treatment duration nor dosage significantly influenced treatment outcomes, highlighting the role of patient-specific factors in determining the efficacy of iron therapy. Despite substantial heterogeneity, sensitivity and publication bias analyses confirmed the robustness of the findings. Overall, IV iron therapy is the preferred choice in conditions with impaired iron absorption or urgent clinical needs, whereas oral iron remains suitable for mild to moderate cases.

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Introduction

Iron deficiency anemia (IDA) is a prevalent nutritional deficiency, globally affecting >1.6 billion people, particularly women of reproductive age, pregnant women, and individuals with chronic diseases such as chronic kidney disease (CKD) and inflammatory bowel disease (IBD) (1). IDA arises when iron levels are inadequate to support hemoglobin synthesis. This condition manifests as fatigue, diminished cognitive performance, and decreased quality of life (2). Timely management of IDA is essential to reduce the risk of complications such as heart failure and mortality, especially among pregnant women and individuals with chronic illnesses.

Oral iron supplementation, usually given as ferrous salts, has been the first-choice treatment for IDA because it is convenient and affordable. However, oral iron often causes gastrointestinal side effects like constipation, nausea and stomach discomfort, which can reduce patient compliance (3). Additionally, oral iron absorption can be greatly affected in patients with gastrointestinal disorders, chronic inflammation, or those using medications that impact gastrointestinal function (4).

The low absorption rate and prolonged treatment duration associated with oral iron have prompted the exploration of intravenous (IV) iron as an alternative. IV iron administration bypasses the gastrointestinal tract, resulting in rapid restoration of iron stores and accelerated improvement of anemia-related symptoms. Evidence indicates that IV iron increases hemoglobin concentrations more efficiently than oral iron, especially in patients with IBD and CKD (5). A meta-analysis comparing IV and oral iron for perioperative anemia management demonstrated that IV iron significantly increased hemoglobin, ferritin, and mean corpuscular volume without a higher risk of adverse effects (5). For pregnant women with IDA, IV iron administration results in higher hemoglobin and ferritin levels at delivery compared with oral iron. This approach also causes fewer gastrointestinal side effects. IV iron is therefore preferable for patients who are unable to tolerate oral iron therapy (6).

IV iron has also shown superiority in treating postpartum anemia. A systematic review reported that women receiving IV iron achieved higher hemoglobin concentrations at six weeks postpartum than those receiving oral iron, with a significantly lower incidence of gastrointestinal side effects such

as constipation and dyspepsia (3). In patients with CKD not undergoing dialysis, IV iron has been shown to improve hemoglobin and ferritin levels more effectively than oral iron, with a comparable safety profile regarding adverse reactions (6).

Despite its benefits, IV iron therapy is associated with higher costs, the need for infusion facilities, and a small risk of hypersensitivity reactions. These factors limit its widespread adoption, particularly in low-resource settings. However, the newer formulations of IV iron, such as ferric carboxy-maltose and iron isomaltose, have demonstrated improved safety profiles and lower risks of serious adverse events compared with older formulations, making them increasingly popular choices for managing IDA (7).

The present systematic review and meta-analysis aimed to provide a comprehensive evaluation of the efficacy and safety of oral vs. IV iron for the treatment of IDA across various clinical conditions. By synthesizing the available evidence, the present study seeks to inform clinical decision-making and guide the selection of the most appropriate iron supplementation strategy based on individual patient profiles and clinical settings.

Materials and methods

Systematic review approach. The present systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). The review question was formulated using a PICOS approach to define the population (patients with IDA), the intervention (oral iron therapy), the comparator (IV iron therapy), the outcomes (changes in hemoglobin), and the study design [randomized controlled trials (RCTs), cohort studies].

Search strategy. A comprehensive literature search was conducted in PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com/), Cochrane CENTRAL (https://www.cochranelibrary.com/), Web of Science (https://clarivate.com/), Scopus (https://www.scopus.com/), and ClinicalTrials.gov (https://clinicaltrials.gov/) from their inception to April 2025. The search strategy included Medical Subject Headings and free-text keywords linked to IDA and iron supplementation, specifically terms such as IDA, oral iron, IV iron, iron supplementation, hemoglobin response, ferritin levels, and postpartum anemia. Boolean operators (AND and OR) were used to refine the search. There were no language restrictions. References from retrieved articles and relevant reviews were also examined to identify additional studies.

Inclusion and exclusion criteria. Studies were eligible if they enrolled patients diagnosed with IDA of any age or sex, compared oral iron supplementation to IV iron therapy, and measured changes in hemoglobin. Eligible study designs included RCTs, cohort studies, or cross-sectional studies that reported sufficient data for the extraction of relevant outcomes. Reviews, meta-analyses, case reports, conference abstracts, or studies with insufficient outcome data were excluded. Duplicate studies, articles lacking an appropriate comparator, or studies enrolling fewer than 10 participants in each arm were also excluded.

Data extraction and quality assessment. Two reviewers independently screened the titles and abstracts and then examined the full text of articles deemed potentially eligible. Discrepancies during study selection were resolved through discussion or the involvement of a third reviewer. Data were extracted by two independent reviewers using a standardized form, obtaining relevant information on study characteristics, sample sizes, participant demographics, oral and IV iron regimens, and outcome measures. Extracted data were cross-checked for accuracy by a second reviewer. The quality and risk of bias of the included studies were assessed using the Newcastle-Ottawa Scale (NOS) for observational studies. Each domain was rated as low, high, or unclear risk of bias. Disagreements were resolved through discussion or consultation with a third reviewer.

Statistical analysis. Meta-analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 4 (Biostat, https://meta-analysis.com). When reporting changes in continuous variables such as hemoglobin, weighted mean differences or standardized mean differences (SMDs) were calculated, along with 95 percent confidence intervals (CIs). Risk ratios or odds ratios were used to summarize dichotomous outcomes, also with 95% CI. A random-effects model (DerSimonian-Laird) was applied to account for between-study variability. Heterogeneity was evaluated using the I-squared statistic, with values exceeding 50 percent considered indicative of substantial heterogeneity. Publication bias was investigated by examining funnel plots and applying Egger's regression test. If publication bias was suspected, the Duval and Tweedie trim-and-fill method was used to estimate its potential impact. Sensitivity analyses were performed, where appropriate, to test the robustness of the findings, for instance by excluding studies deemed to be at high risk of bias or focusing on specific subpopulations with IDA. Statistically significant difference was set at $P<0.05$ for all analyses.

Results

A total of 2,840 records were initially identified through database searches. Following the removal of 845 duplicates, 1,995 titles and abstracts were screened, of which 1,900 did not meet the inclusion criteria due to reasons such as irrelevant populations, inadequate comparators, or insufficient data on outcomes of interest. The full texts of the remaining 95 articles were examined in detail, and 31 of these fulfilled all eligibility requirements for the meta-analysis. The PRISMA flow diagram that summarizes each stage of the study selection process is illustrated in Fig. 1.

A total of 31 comparative trials (1,7,9-37) of oral vs. IV iron across multiple clinical scenarios are presented in Table SI, including CKD, IBD, postoperative states, postpartum anemia and cancer-related anemia. Although the dosing regimens and target populations varied among studies, a common finding was that IV iron typically resulted in a more rapid or substantial increase in hemoglobin or ferritin than oral iron, particularly in conditions of higher iron requirements or limited oral absorption. Nevertheless, in milder cases or when IV infusions are impractical, oral iron often suffices, albeit with a slower response and possible gastrointestinal side effects that can

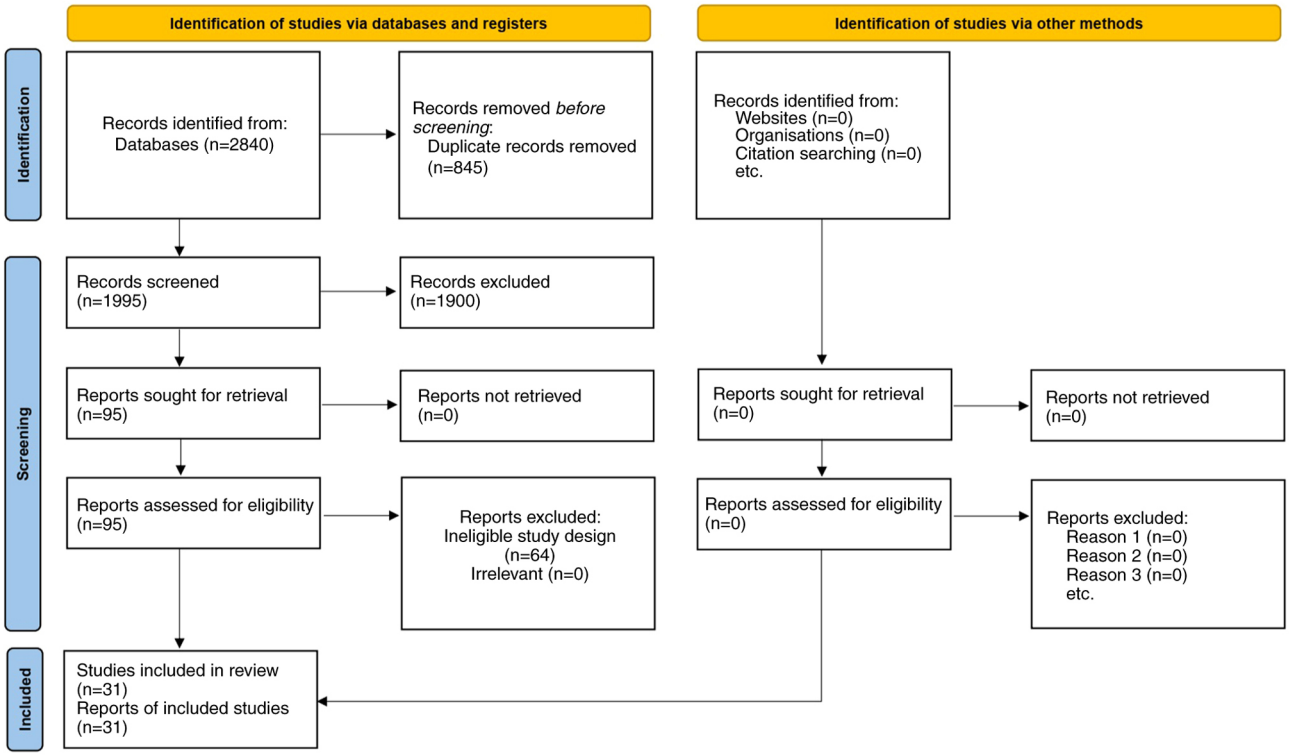

Figure 1. PRISMA flow diagram depicting the systematic review and study selection process. This flowchart details the stages of the systematic review, including initial record identification, screening and final study inclusion, highlighting the reasons for exclusion at each stage.

decrease adherence. Several studies also noted fewer gastrointestinal adverse events with IV iron but highlighted the need to weigh possible infusion reactions or procedural demands against potential benefits in each clinical context.

The meta-analysis (Fig. 2) showed that IV iron was more effective than oral iron in increasing hemoglobin levels in patients with cancer (pooled SMD: -0.662, 95% CI: -1.250 to -0.176, P=0.011), CKD (SMD: -0.492, 95% CI: -0.950 to -0.035, P=0027), IBD (SMD: -0.560, 95% CI: -0.738 to -0.381, P<0.001) and IDA (SMD: -0.397, 95% CI: -0.576 to -0.218, P<0.001). This indicated a statistically significant benefit of IV iron in these subgroups. By contrast, no significant difference was observed between IV and oral iron in post-operative patients (SMD: -0.056, 95% CI: -0.175 to 0.063, P=0.358) and those with restless legs syndrome (RLS) (SMD: 0.316, 95% CI: -0.087 to 0.719, P=0.124). The overall pooled effect size was -0.162 (95% CI: -0.331 to 0.007, P=0.060), suggesting a slight but not statistically significant trend favoring IV iron. The prediction interval for the overall effect was wide (-2.862 to 2.539), indicating substantial heterogeneity and uncertainty in the treatment effect across different populations and settings.

The leave-one-out sensitivity analysis (Fig. 3) showed a stable overall effect size consistently favoring IV iron over oral iron for increasing hemoglobin levels, with a pooled SMD of -0.499 (95% CI: -0.952 to -0.047, P=0.031). The analysis revealed that removing any single study did not substantially alter the overall effect, indicating the robustness of the results. Most individual studies showed a negative SMD, favoring IV iron, with statistically significant results for several, including Adhikary and Acharya, 2011 (37) (SMD: -0.513, 95% CI: -0.978 to -0.048, P=0.031), Birgegård *et al*, 2016 (12) (SMD: -0.512, 95% CI: -0.986 to -0.038, P=0.034), and Khalil *et al*, 2011 (25) (SMD: -0.601, 95% CI: -1.048 to -0.154, P=0.009). No single study disproportionately influenced the overall findings, reinforcing the reliability of the meta-analysis results.

The prediction interval presented in Fig. 4 ranged from -3.24 to 2.24 (P<0.001), suggesting that the true effect size in 95% of all comparable populations could vary widely from favoring oral iron to favoring IV iron. This wide interval highlighted substantial heterogeneity across the included studies. The mean effect size was -0.50 with a 95% CI of -0.95 to -0.05, indicating a statistically significant overall benefit of IV iron over oral iron. However, the broad prediction interval implied that while IV iron was generally more effective, there was considerable variability in the treatment effects, suggesting that in some populations or settings, oral iron might still be effective.

The publication bias analysis showed some evidence of asymmetry in the funnel plot, suggesting potential publication bias, particularly with a greater spread of studies on the left side favoring oral iron (Fig. 5). However, Begg and Mazumdar's test results, with Kendall's tau values of -0.147 (P=0.218) without continuity correction and -0.146 (P=0.224) with continuity correction, indicated no significant publication bias. Similarly, Egger's regression intercept test showed an intercept of -4.145 with a 95% CI of -10.683 to 2.393 and a P-value of 0.205, suggesting the absence of small-study effects. The fail-safe N test found that 1,481 null-effect studies would be required to negate the observed effect, suggesting that the results were robust. Orwin's fail-safe N also indicated that a substantial number of studies with trivial effects would be

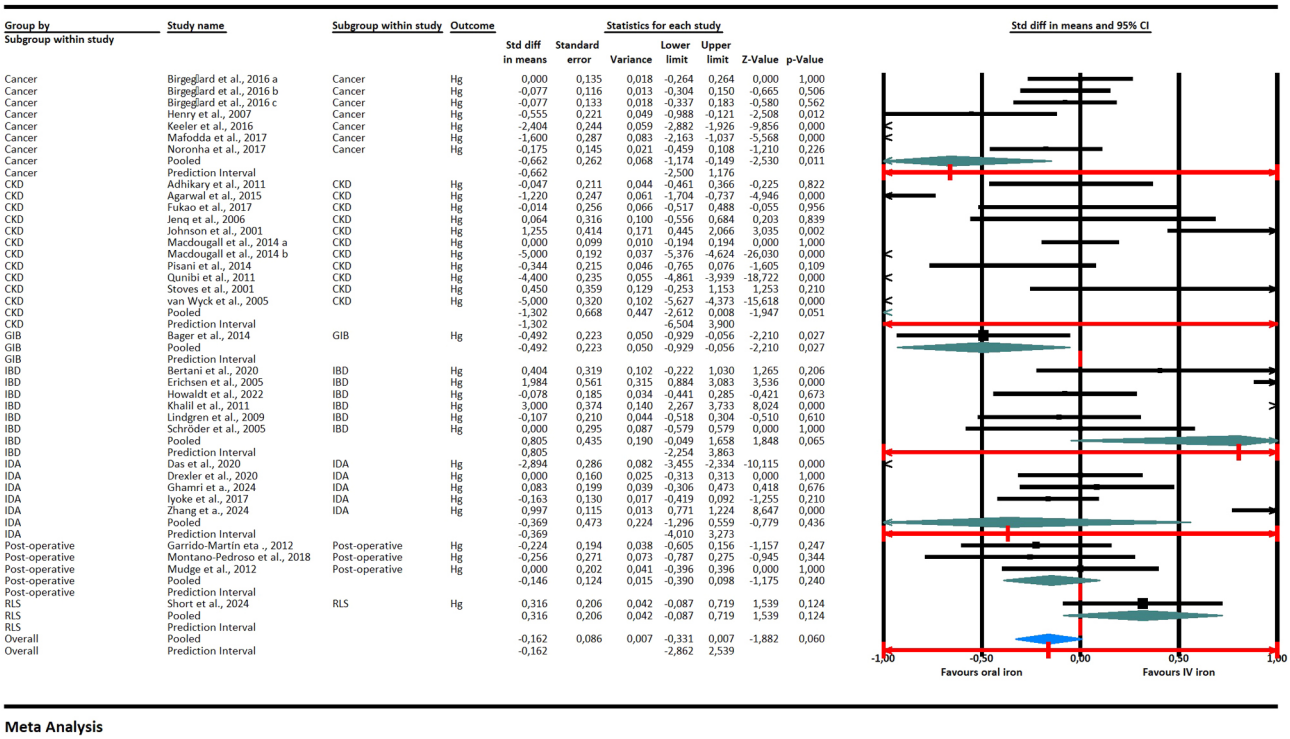

Figure 2. Forest plot illustrating the meta-analysis of hemoglobin response comparing intravenous vs. oral iron therapy across various clinical conditions. The pooled standardized mean differences with 95% confidence intervals demonstrate the comparative effectiveness of intravenous iron over oral iron in subgroups such as cancer-related anemia, CKD, IBD and general IDA. CKD, chronic kidney disease; IBD, inflammatory bowel disease; IDA, iron deficiency anemia.

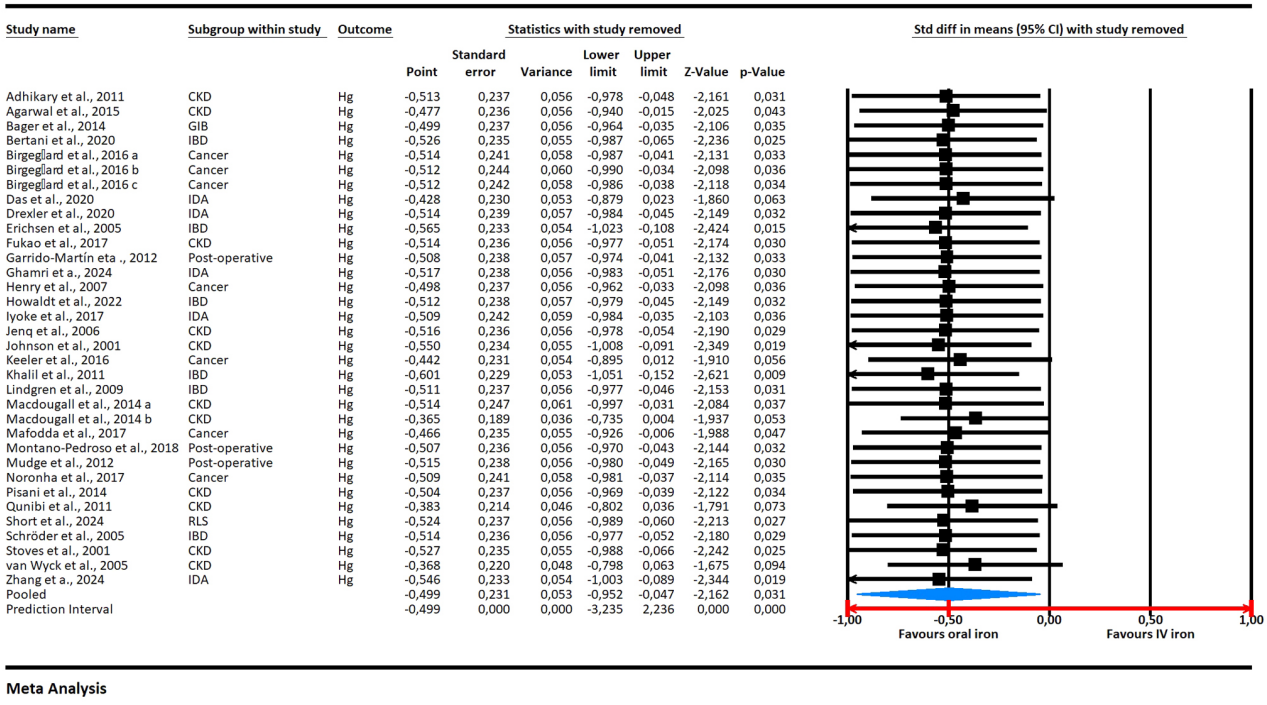

Figure 3. Sensitivity analysis (leave-one-out analysis) assessing the robustness of the meta-analysis findings on hemoglobin response. This plot shows the pooled standardized mean differences after sequential removal of each study, indicating stability and robustness of the overall effect favoring intravenous iron.

needed to change the significance of the results. The trim and fill method identified eight potentially missing studies to the left of the mean, but even after adjustment, the point estimates under both fixed effects (-0.683) and random effects (-0.956) models continued to favor IV iron. These findings suggest that while some publication bias may exist, it is unlikely to substantially alter the overall conclusion that IV iron is more effective than oral iron.

The meta-regression analysis results indicated that none of the covariates, including duration of treatment (coefficient:

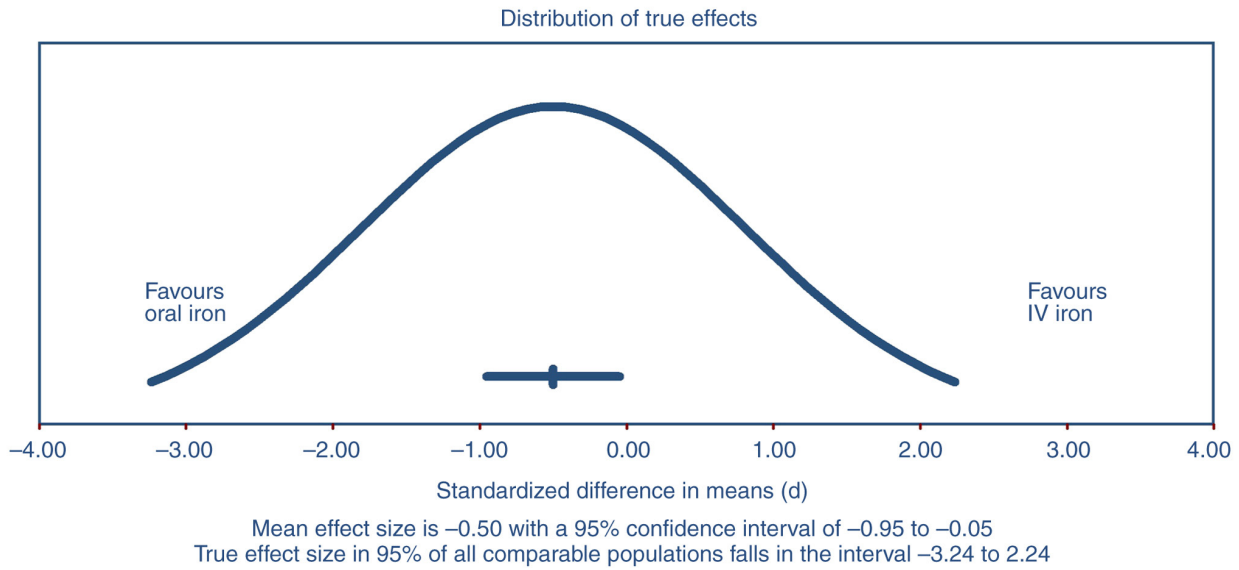

Figure 4. Prediction interval plot illustrating the overall pooled effect size and its variability across different patient populations and settings. The wide prediction interval reflects substantial heterogeneity, indicating that the true effect of intravenous iron vs. oral iron may differ significantly depending on specific clinical contexts.

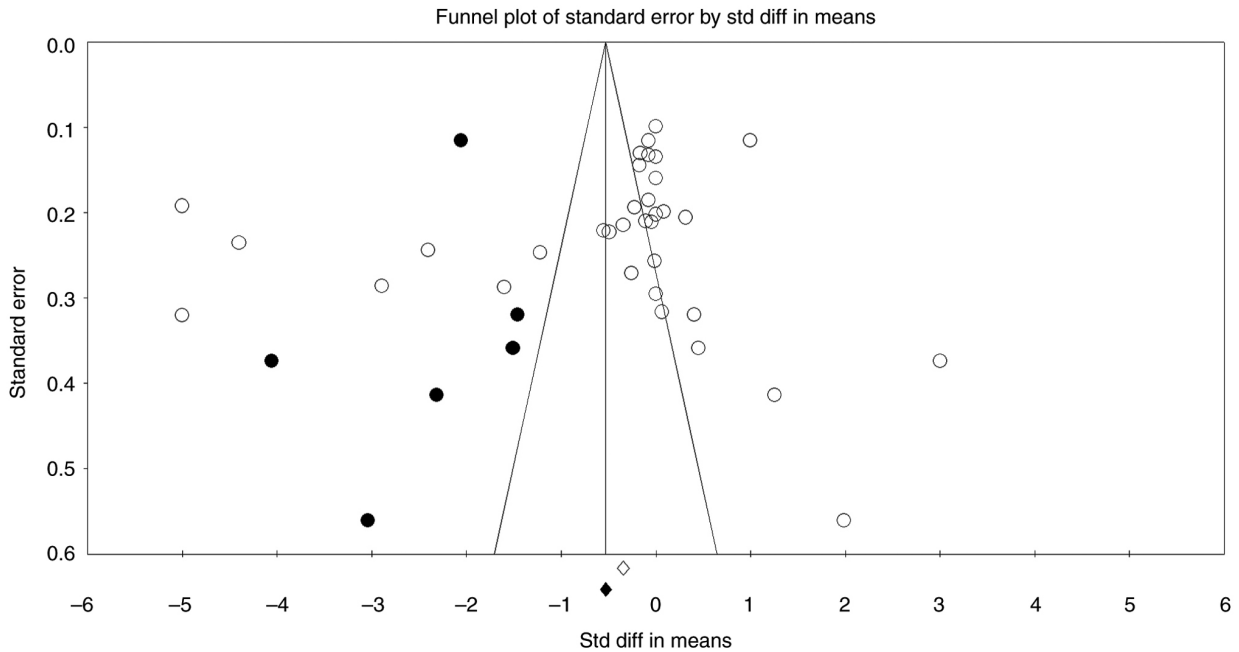

Figure 5. Funnel plot assessing potential publication bias in the meta-analysis of intravenous vs. oral iron therapy for iron deficiency anemia. This plot visually depicts study distribution and symmetry, suggesting some asymmetry indicative of potential publication bias, although statistical tests suggest minimal impact on the overall conclusions.

-0.001, P=0.353), oral iron dose (coefficient: -0.004, P=0.189), and IV iron dose (coefficient: -0.000, P=0.911), had a statistically significant effect on the SMD of hemoglobin levels between oral and IV iron. The intercept was also non-significant (coefficient: 0.244, P=0.674). The test for all coefficients being zero was not significant (Q=3.70, df=3, P=0.296), suggesting that the included covariates did not significantly explain the variation in effect sizes. The I^2 value of 98.13% indicated substantial heterogeneity among studies, which was not accounted for by the covariates in the model. The proportion of between-study variance explained by the model was effectively zero (R^2 analog =0.00), indicating that the model did not reduce the unexplained heterogeneity (Fig. 6A-C). These results suggested that the observed heterogeneity in treatment effects is likely due to factors other than the oral and IV iron doses or treatment duration.

The quality of the 31 included studies was assessed using a modified NOS, which evaluated each study across the domains of selection, comparability and outcome/exposure, with total scores ranging from 4 to 9 stars (Table SII). Overall, the majority of studies received moderate scores, typically 6 stars, reflecting some limitations in blinding and sample

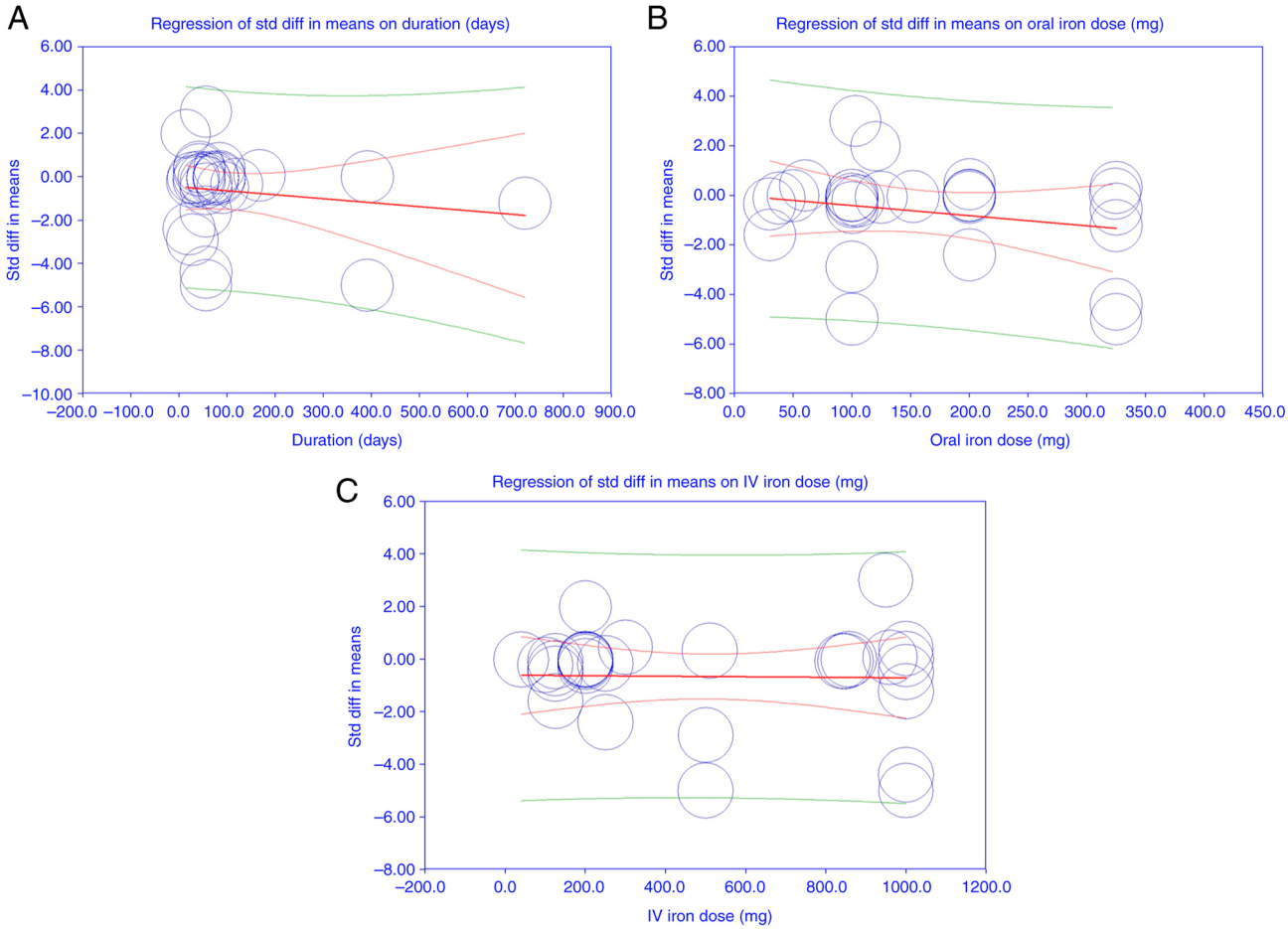

Figure 6. Meta-regression scatter plots showing the relationship between covariates [(A) duration of treatment, (B) oral iron dose and (C) IV iron dose) and the standardized mean differences in hemoglobin levels (a, b, and c). The plots demonstrate no statistically significant relationships, indicating that these factors do not substantially explain the heterogeneity observed in treatment effects. IV, intravenous.

size, particularly among open-label and retrospective designs. By contrast, several studies, such as those by Bager and Dahlerup (10), Garrido-Martín *et al* (17), Lindgren *et al* (26), Macdougall *et al* (27), Short *et al* (33) and Zhang *et al* (38), achieved scores of 9 stars, indicating robust study designs, effective randomization, and strong outcome assessments. These quality ratings were considered in our subsequent analyses, and sensitivity analyses confirmed that the overall conclusions regarding the efficacy and safety of oral vs. IV iron supplementation remained robust despite the observed heterogeneity in study quality.

Discussion

The findings of the present systematic review and meta-analysis emphasize the complexity and variability in choosing between oral and IV iron therapies for managing IDA. The present results demonstrated that IV iron generally provides superior efficacy compared with oral iron in raising hemoglobin and ferritin levels across diverse patient populations, including those with CKD, IBD, cancer-related anemia and postoperative anemia. However, considerable heterogeneity in responses highlights the need for individualized treatment decisions based on clinical context, patient characteristics and practical considerations.

IV iron's superiority in certain populations, such as patients with CKD and IBD, aligns with previous literature (1,27). Patients with these conditions typically experience reduced gastrointestinal absorption of oral iron due to chronic inflammation or disrupted intestinal mucosa, making IV administration more effective (3). Similarly, patients with cancer often have chronic inflammation and concurrent treatments, which impair oral iron absorption (39). The present findings that IV iron significantly improves hemoglobin levels in these patients reinforce previous clinical recommendations favoring IV iron for populations with chronic inflammation or malabsorption issues (40).

By contrast, the lack of significant difference observed in postoperative anemia and RLS populations indicates a nuanced clinical decision-making process. In postoperative contexts, anemia may resolve spontaneously or through other supportive measures, reducing the apparent advantage of IV iron (2). Similarly, patients with RLS may represent a distinct subgroup where iron deficiency is less severe or absorption is less compromised, reducing the necessity of IV iron over oral administration (37).

Despite IV iron's advantages, the current meta-analysis acknowledges substantial heterogeneity, reflected in wide prediction intervals. This means that, although IV iron generally leads to improved outcomes, considerable variation exists

across different patient groups and clinical settings. This heterogeneity is multifactorial, potentially driven by differences in iron formulations, dosages, treatment durations, patient compliance and underlying patient pathology (7,41). For instance, newer IV iron formulations such as ferric carboxy-maltose and iron isomaltose offer improved safety profiles and efficacy over older formulations. This positively influences clinical outcomes and potentially contributes to variability across studies (42,43).

Safety profile is another critical aspect influencing the choice of iron supplementation method. Although IV iron showed fewer gastrointestinal adverse effects, the necessity for infusion facilities, higher upfront costs and risk of hypersensitivity reactions limit its application, especially in resource-constrained environments (4,26). Nonetheless, advances have significantly decreased these safety concerns, increasing clinician confidence in IV iron therapy for broader patient populations, including pregnant women and postpartum patients (4,6).

The sensitivity analyses of the present study confirmed robustness, suggesting that observed benefits favoring IV iron are unlikely due to isolated influential studies. This consistency strengthens confidence in the current findings, indicating that IV iron's effectiveness in raising hemoglobin and ferritin is robust across varied study conditions. However, the presence of considerable unexplained heterogeneity necessitates cautious interpretation. Future research should explore additional variables, including patient adherence, specific iron formulations and detailed patient subgroups, to further elucidate contributors to this heterogeneity.

Potential publication bias detected in funnel plots highlights a common limitation in meta-analyses, particularly in favor of IV iron. However, extensive bias analyses (Begg and Mazumdar's, Egger's regression, and trim-and-fill tests) suggest that such biases minimally affect the overall conclusion. Even after adjustments for possible missing studies, the superiority of IV iron persisted, confirming the strength of the present findings. Nonetheless, the presence of such biases emphasizes the importance of rigorous peer review, transparency in reporting, and cautious clinical application of these results.

The present meta-regression analysis failed to identify significant associations between treatment effects and commonly examined covariates such as iron dosage and duration of treatment. This suggests that patient-specific factors rather than treatment protocol variations drive the observed differences in efficacy. These findings highlight a critical gap in understanding which clinical and biological variables most strongly predict responses to oral vs. IV iron, warranting further targeted research to personalize IDA management strategies (33).

Quality assessments using validated tools indicated moderate to high methodological rigor across included studies, enhancing the reliability of our conclusions. High-quality studies uniformly demonstrated clear superiority of IV iron in specific clinical contexts, particularly in managing severe anemia or conditions with impaired iron absorption (27,43). Conversely, moderate-quality studies tended to present less definitive results, highlighting the importance of methodological rigor in future research efforts.

Clinically, the present results emphasize that IV iron is preferable in conditions with compromised oral absorption, urgent correction needs, or intolerance to oral supplements. Conversely, oral iron remains practical and cost-effective for mild-to-moderate cases without significant gastrointestinal barriers or in low-resource settings where IV therapy is impractical or unaffordable (2,3). Thus, personalized treatment strategies based on patient preference, tolerability, clinical urgency, and local resource availability should guide therapy selection.

The present meta-analytic systematic review has several limitations that must be acknowledged. Considerable between-study heterogeneity was present across populations, dosing regimens, follow-up intervals and outcome definitions; despite random-effects synthesis and planned subgroup/meta-regression analyses, substantial residual heterogeneity remained, limiting generalizability and suggesting unmeasured modifiers (for example, adherence, comorbidity burden, concomitant medications and disease severity). Study quality was moderate overall, with frequent open-label designs and small sample sizes; thus, residual confounding and risk of bias cannot be excluded even after sensitivity analyses. Heterogeneity statistics (I^2, τ^2) and 95% prediction intervals were reported to reflect expected dispersion of true effects across settings. Publication-bias assessment (funnel plots, Egger's test) suggested mild small-study effects; trim-and-fill did not materially change the pooled estimate. Use of standardized mean differences for hemoglobin, necessitated by varying measurement time-points and assays, may reduce clinical interpretability relative to raw mean differences. Individual-patient data were unavailable, precluding harmonized outcome definitions and more granular subgroup analyses. The protocol was not prospectively registered (for example, PROSPERO). Safety outcomes and economic/practical considerations (for example, infusion logistics, costs and access in low-resource settings) were inconsistently reported across studies and were not meta-analyzed; these factors should inform shared decision-making alongside our efficacy estimates.

Future research should include comprehensive cost-effectiveness analyses to facilitate informed decision-making, especially in resource-limited settings. Finally, patient-reported outcomes, including quality-of-life metrics, were inconsistently reported or absent from most included studies, preventing a thorough comparison of the patient-centered impacts of oral vs. IV iron therapies. Future studies should incorporate standardized assessments of patient-reported outcomes to facilitate comprehensive evaluations of treatment strategies.

In conclusion, the present systematic review and meta-analysis demonstrated that IV iron therapy was generally more effective than oral iron supplementation in increasing hemoglobin levels among patients with IDA, particularly those with CKD, IBD, cancer-related anemia and general IDA. Specifically, IV iron showed statistically significant superiority over oral iron in improving hemoglobin levels in these patient subgroups. However, in postoperative patients and those with RLS, IV iron did not demonstrate a significant advantage compared with oral iron, suggesting that clinical context plays a critical role in determining the optimal iron supplementation strategy.

Despite the overall benefit favoring IV iron, considerable heterogeneity across included studies indicates that individual patient characteristics and specific clinical scenarios must be carefully considered when choosing between oral and IV iron

treatments. The observed variability emphasizes the necessity for clinicians to balance the faster and more robust hemoglobin response associated with IV iron against its higher costs, logistical constraints and potential risks of adverse reactions. In scenarios where gastrointestinal tolerance, compliance, or absorption is significantly compromised, IV iron emerges as a superior therapeutic choice.

Overall, the current findings support the targeted use of IV iron supplementation as an effective approach for managing IDA, particularly in patient populations where oral iron is less effective or poorly tolerated. Further research addressing long-term outcomes, patient-centered measures and cost-effectiveness is needed to fully clarify treatment decision-making across diverse clinical settings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CZ conceived and designed the study, performed the literature search, participated in data extraction, and drafted the manuscript. WH performed data extraction, contributed to data analysis and interpretation, and revised the manuscript. Both authors contributed equally to the present study. Both authors confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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