RESEARCH ARTICLE

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Efficacy, Safety, and Tolerability of Ferric Carboxymaltose and Iron Sucrose in Iron-Deficiency Anemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Demir Eksikliği Anemisinde Ferrik Karboksimaltoz ve Demir Sükrozun Etkililiği, Güvenirliği ve Tolere Edilebilirliği: Randomize Kontrollü Çalışmaların Sistematik Derlemesi ve Meta-Analizi

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Abstract

Objective: This study comprehensively compares the efficacy, safety, and tolerability of two commonly used intravenous iron preparations, ferric carboxymaltose (FCM) and iron sucrose (IS), in adult patients with iron-deficiency anemia (IDA).

Materials and Methods: A systematic literature search was conducted across the PubMed, Ovid MEDLINE, Web of Science, and Cochrane Library databases up to January 1, 2024, to identify randomized controlled trials directly comparing FCM and IS treatments in adult patients with IDA. The primary outcome of interest was change in hemoglobin (Hb) levels during follow-up. Meta-analyses were conducted with inverse variance random effects models.

Results: Fourteen trials were included in the study, with a total of 4757 patients. FCM resulted in a non-significant increase in Hb levels (mean difference [MD]: 0.45 g/dL, 95% confidence interval [CI]: 0.08 to 0.83, p=0.02) and ferritin levels (MD: 37.32 ng/mL, 95% CI: 18.98 to 55.65, p<0.01) compared to IS. FCM was associated with a higher risk of hypersensitivity reactions compared to IS (relative risk [RR]: 2.97, 95% CI: 1.35 to 6.52, p<0.01) but showed no significant difference in severe adverse events (RR: 1.03, 95% CI: 0.88 to 1.21, p=0.70) and had a non-significant increased risk of hypophosphatemia (RR: 2.84, 95% CI: 0.89 to 9.06, p=0.08).

Conclusion: Ten studies showed some concerns of risk of bias (RoB) and four studies had a high RoB for the change in Hb levels during follow-up. The lack of standardized definitions for hypersensitivity reactions and variability in dosing protocols and follow-up durations across studies may affect the generalizability of our safety findings.

Keywords: Ferric carboxymaltose, Iron sucrose, Iron-deficient anemia, Hypophosphatemia, Hypersensitivity

Öz

Amaç: Bu çalışma, demir eksikliği anemisi (DEA) olan erişkin hastalarda yaygın olarak kullanılan iki intravenöz demir preparatı olan ferrik karboksimaltoz (FCM) ve demir sükrozun (IS) etkililik, güvenirlik ve tolere edilebilirlik açısından kapsamlı bir karşılaştırmasını sunmaktadır.

Gereç ve Yöntemler: DEA tanılı erişkin hastalarda FCM ve IS tedavilerini doğrudan karşılaştıran randomize kontrollü çalışmaları belirlemek amacıyla, 1 Ocak 2024 tarihine kadar PubMed, Ovid MEDLINE, Web of Science ve Cochrane Library veri tabanlarında sistematik bir literatür taraması yapıldı. Birincil çıktı, takip süresince hemoglobin (Hb) düzeyindeki değişiklik olarak belirlendi. Meta-analizler, ters varyanslı random etki modeli kullanılarak gerçekleştirildi.

Bulgular: Çalışmaya toplam 4757 hastayı içeren 14 çalışma dahil edildi. FCM, IS'ye kıyasla Hb düzeylerinde anlamlı olmayan bir artış (ortalama fark [MD]: 0,45 g/dL, %95 güven aralığı [CI] 0,08-0,83, p=0,02) ve ferritin düzeylerinde anlamlı bir artış (MD: 37,32 ng/mL, %95 CI: 18,98–55,65, p<0,01) ile ilişkili bulundu. FCM, IS'ye kıyasla aşırı duyarlılık reaksiyonları açısından daha yüksek bir risk ile ilişkilendirildi (risk oranı [RR]: 2,97, %95 CI: 1,35-6,52, p<0,01); ancak ciddi advers olaylar açısından anlamlı bir fark saptanmadı (RR: 1,03, %95 CI: 0,88 - 1,21, p=0,70). Ayrıca hipofosfatemi açısından FCM ile anlamlı olmayan şekilde artmış bir risk gözlendi (RR: 2,84, %95 CI: 0,89-9,06, p=0,08).

Sonuç: Hb düzeylerindeki değişiklik açısından değerlendirildiğinde yanlılık riskleri 10 çalışmada şüpheli olarak değerlendirilirken 4 çalışmada ise yüksek düzeyde olduğu tespit edildi. Aşırı duyarlılık reaksiyonları için standart tanımların bulunmaması, doz protokollerindeki ve takip sürelerindeki farklılıklar güvenilirlik bulgularımızın genellenebilirliğini sınırlayabilir.

Anahtar Sözcükler: Ferrik karboksimaltoz, Demir sükroz, Demir eksikliği anemisi, Hipofosfatemi, Aşırı duyarlılık reaksiyonları

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Introduction

Iron deficiency anemia (IDA) is a prevalent condition with significant health consequences affecting various patient populations, including individuals with chronic diseases, heavy menstrual bleeding, and gastrointestinal disorders [1,2,3,4]. Intravenous iron therapy is often preferred in cases where rapid iron repletion is necessary or when oral iron formulations are ineffective or poorly tolerated [5,6]. Among intravenous iron therapies, ferric carboxymaltose (FCM) and iron sucrose (IS) are widely used. FCM allows for larger doses in fewer administrations compared to IS, making it more convenient for patients and healthcare providers [7,8,9]. FCM is a colloidal iron(III) hydroxide complexed with carboxymaltose, a carbohydrate polymer that facilitates controlled iron release. This allows for the replenishment of iron stores required for the synthesis of hemoglobin (Hb), myoglobin, and various enzyme systems involved in oxygen transport and cellular metabolism. Unlike dextran-based formulations, FCM enables iron uptake via the reticuloendothelial system without the release of free iron, thereby reducing the risk of oxidative stress. IS is also an iron(III) hydroxide complex with sucrose that undergoes dissociation within the reticuloendothelial system. The released iron contributes to increased serum iron concentrations and is subsequently incorporated into Hb, restoring iron levels in iron-deficient patients [7,8,9].

Previous randomized controlled trials (RCTs) have examined the comparative efficacy and safety of FCM and IS, particularly in the treatment of anemia in various populations [10,11,12,13,14,15,16]. However, the use of FCM and IS in different patient populations and clinical contexts has shown varying efficacy and safety results [6,17,18]. In the REPAIR-IDA trial [15], which included 2584 patients with IDA and chronic kidney disease (CKD), FCM showed a significantly greater increase in Hb levels compared to IS (1.13 g/dL vs. 0.92 g/dL; 95% confidence interval [CI]: 0.13-0.28), with a higher proportion of patients in the FCM group achieving Hb increases of ≥1.0 g/dL (48.6% vs. 41.0%). Importantly, no significant difference was observed between the two treatments regarding cardiovascular safety, including major adverse cardiac events, although FCM was associated with a higher incidence of transient hypertensive episodes.

In a study by Mahey et al. [19] involving 60 women with anemia due to abnormal uterine bleeding, FCM resulted in a more rapid increase in Hb levels at 6 weeks compared to IS (p=0.005), although no significant difference was observed at 12 weeks (p=0.11). Similarly, Lee et al. [20] demonstrated that FCM was as effective as IS in achieving Hb of ≥10 g/dL in women with preoperative anemia due to menorrhagia, with a significantly shorter time to reach this target in the FCM group (7.7 days vs. 10.5 days).

Laso-Morales et al. [21] compared FCM and IS in 104 patients with postoperative anemia following colorectal cancer surgery. Both treatments led to comparable increases in Hb by postoperative day 30 (FCM: 2.5 g/dL vs. IS: 2.4 g/dL), but FCM was associated with a lower infection rate (9.8% vs. 37.2%, p<0.05). In contrast, a study conducted in Japan with patients with IDA due to hypermenorrhea showed the non-inferiority of FCM compared to saccharated ferric oxide, with a mean Hb increase of 3.90 g/dL in the FCM group and 4.05 g/dL in the control group (difference: -0.15 g/dL; 95% CI: -0.35 to 0.04).

A recent trial [22] conducted in China compared the efficacy of FCM and IS in 371 patients with IDA. The primary endpoint of achieving Hb increase of ≥2 g/dL within 8 weeks was met by 99.4% of FCM-treated patients compared to 98.3% of IS-treated patients, confirming non-inferiority (difference: 1.12%; 95% CI: -2.15 to 4.71). Additionally, a higher proportion of FCM-treated patients achieved early Hb response at 2 weeks (85.2% vs. 73.2%; 95% CI: 3.31 to 20.65), and FCM showed a greater increase in transferrin saturation (TSAT) and serum ferritin levels at all time points.

These findings highlight the variability in the efficacy and safety outcomes of FCM and IS across different patient populations and clinical scenarios. To date, there have been no systematic reviews comparing FCM and IS in the management of IDA regardless of etiology. Given the need for more conclusive evidence, we conducted a systematic review and meta-analysis of RCTs to compare the efficacy and safety of FCM and IS in the treatment of IDA.

Materials and Methods

This study was conducted following a predefined protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42022337858).

Eligibility Criteria

We identified RCTs evaluating the efficacy and safety of FCM versus IS in patients with IDA regardless of etiology. We excluded studies that were not RCTs, including observational studies, case reports, case series, narrative reviews, editorials, commentaries, or expert opinions. Studies involving individuals under 18 years of age were also excluded. Additionally, we excluded studies that compared FCM or IS with oral iron, placebos, or other intravenous iron formulations (e.g., ferric derisomaltose or ferric gluconate) without a direct comparison between FCM and IS. Studies that did not report at least one predefined outcome of interest or provided incomplete or unclear data that could not be extracted for meta-analysis and those not published in English were also excluded.

Search Strategy and Study Selection

A systematic search was performed in the Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), Ovid MEDLINE, PubMed, and Web of Science databases up to January 1, 2024. This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. Additionally, the reference lists and citations of included studies from the past 5 years were screened for relevant articles. Only studies published in English were considered. Detailed information about the search strategy is provided in the Supplementary File. References identified through the database searches were imported to EndNote v21.3 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, full-text articles were retrieved if their abstracts were deemed eligible by at least one reviewer. Each full-text article was then independently assessed for final inclusion in this systematic review and meta-analysis, with any disagreements resolved through consensus.

Outcomes

The primary efficacy outcome of interest was the change in Hb level during follow-up, while the primary safety outcome of interest was the risk of serious or severe adverse events (AEs). Secondary outcomes included Hb increase of 2 g/dL during follow-up, achievement of Hb levels of 12 g/dL during follow-up, change in serum ferritin levels from baseline, hypersensitivity reactions, risk of hypophosphatemia, and withdrawals due to AEs.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. The extracted data included:

- Study characteristics: First author, year of publication, study design, etiology, sample size, intervention details (type of iron preparation [FCM or IS] with cumulative dose), primary outcome, and prespecified secondary outcomes in the protocol.

- Participant characteristics: Number of patients, age, gender, race (white, black or African American, Asian, or other), use of erythropoiesis-stimulating agents, previous iron therapy, baseline Hb value (g/dL), baseline ferritin level (ng/mL), baseline TSAT (%), and baseline estimated glomerular filtration rate (mL/min/1.73 m^2) for each arm in the included studies.

Data were double-checked for accuracy and consistency. In the event of incomplete outcome data, we employed available-case analysis, and if a study reported results graphically, we extracted data using a digital analysis tool [24].

Risk of Bias Assessment

Two reviewers (L.H.T. and A.V.H.) independently assessed the risk of bias (RoB) in the included RCTs using the Cochrane RoB2.0 tool [25], with any disagreements resolved through discussion. The RoB2.0 tool evaluates five domains of bias: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. A study was considered to have high RoB if at least one domain was rated as "high risk" or was deemed to have "some concerns" if at least one domain raised concerns without any domains being rated as high RoB.

Statistical Analysis

Meta-analyses were primarily conducted using inverse variance random effects models; for rare outcomes with incidence of <10%, the Mantel-Haenszel method was applied. Between-study variance (τ^2) was calculated using the Paule-Mandel method [26], with CIs adjusted using the Hartung-Knapp method [27]. Dichotomous outcomes were presented as relative risks (RRs) with 95% CIs, and continuous outcomes were presented as mean differences (MDs) with 95% CIs. Between-study heterogeneity was assessed using the Cochran Q test and I^2 statistics, with values of <30% indicating low heterogeneity, 30%-60% moderate heterogeneity, and >75% substantial heterogeneity [28]. Publication bias was visually examined using funnel plots and statistical methods, including Egger tests. Sensitivity analyses were conducted by sequentially excluding each study to assess the impact on pooled RR estimates.

All analyses were performed using R version 4.4.1 (www.r-project.org) with the meta and metafor packages. Statistical tests were two-sided with a significance threshold of $p<0.05$. Values for interaction of $p<0.1$ were considered statistically significant for a given subgroup [29]. Subgroup analyses, based on the etiology of IDA and RoB for primary outcome, were conducted to explore potential sources of heterogeneity.

Results

Study Selection

A total of 688 records were identified through database searches, including Cochrane CENTRAL, PubMed, Ovid MEDLINE, and Web of Science. After the removal of 292 duplicates, 396 records remained for screening. Of these, 331 were excluded based on titles and abstracts. Sixty-three full-text articles were assessed for eligibility and 14 were excluded due to irrelevant interventions, 14 due to unsuitable study designs, 10 due to incorrect publication types, and 2 due to wrong populations. After this screening, 14 RCTs involving a total of 4757 participants [11,12,13,14,15,16,19,20,21,22,30,31,32,33] were included in this meta-analysis (Figure 1).

Study Characteristics

Fourteen RCTs were included in this meta-analysis comparing FCM and IS in various populations with IDA. The included

studies were categorized based on the underlying causes of IDA. Detailed summaries of the study characteristics (Table 1) and patient characteristics (Supplementary Table S1) of each included RCT are provided.

Three studies were identified involving patients with gynecological disorders. Mahey et al. [19] compared FCM and IS in women with IDA due to abnormal uterine bleeding and found that FCM was more effective in raising Hb levels with fewer AEs. Ikuta et al. [11] examined Japanese women with hypermenorrhea-induced IDA, demonstrating the non-inferiority of FCM to IS in both efficacy and safety. Lee et al. [20] investigated patients with preoperative anemia due to menorrhagia, finding that FCM led to a faster and higher increase in Hb levels compared to IS.

For patients with impaired iron absorption, three trials were evaluated. Evstatiev et al. [14] conducted the FERGIcor trial, focusing on IDA due to inflammatory bowel disease, and concluded that FCM was superior to a placebo in improving Hb values. Laso-Morales et al. [21] compared single-dose FCM with multiple doses of IS in postoperative colorectal cancer patients, showing that FCM was more convenient and effective in correcting postoperative anemia. Struppe et al. [33] conducted a pilot study evaluating the impact of intravenous iron on bone

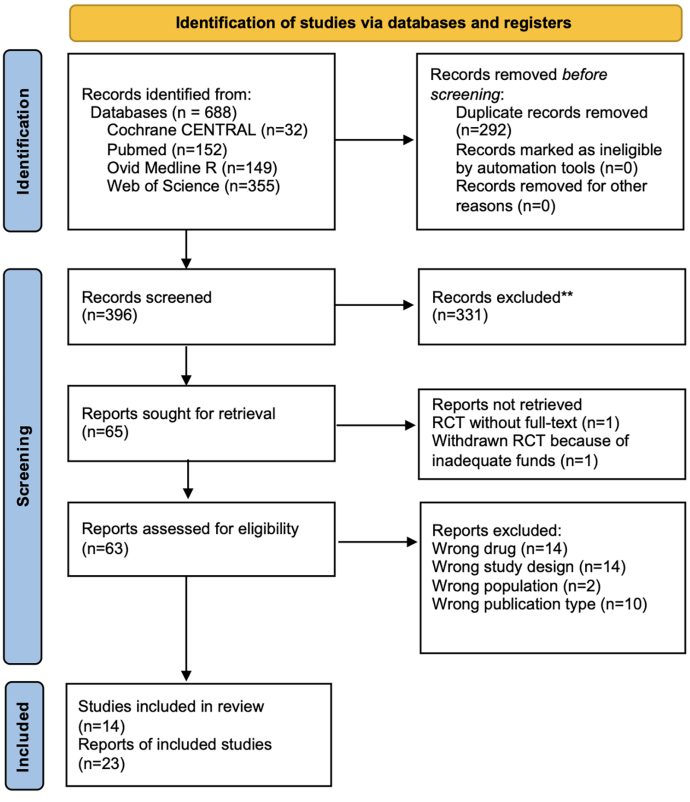

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of eligible studies.

RCT: Randomized controlled trial.

turnover markers and serum phosphate levels, suggesting that FCM had a more favorable safety profile than IS.

Three studies were identified involving patients with impaired renal function. Onken et al. [15] conducted the REPAIR-IDA trial, comparing FCM and IS in patients with IDA and impaired renal function, and found that FCM resulted in a quicker and more sustained increase in Hb levels. Roberts et al. [30] evaluated the effects of intravenous iron on fibroblast growth factor 23 in hemodialysis patients, showing that FCM was associated with better outcomes than IS. Bielesz et al. [12] studied different iron dosing strategies in long-term hemodialysis patients, concluding that FCM was more effective and required fewer doses than IS.

Among the studies involving patients with mixed etiologies, Naqash et al. [13] compared FCM and IS in women with IDA due to various causes, concluding that FCM was more effective and had a better safety profile. Jin et al. [22] conducted a randomized trial with Chinese patients with IDA of mixed etiology and found that FCM was not inferior to IS, with the added benefit of fewer required doses.

For postpartum anemia, two studies were included. Rathod et al. [16] investigated FCM in Indian women with postpartum anemia, showing significant improvement in Hb levels with a single dose. Similarly, Wajid et al. [32] compared FCM and IS in women with postpartum anemia, concluding that FCM was more effective and safer than IS.

Finally, for pregnancy-related IDA, Jose et al. [31] compared FCM and IS in pregnant women and found that FCM provided superior outcomes in terms of Hb improvement and safety profile.

Risk of Bias and Publication Bias

The Cochrane RoB2.0 tool was used to assess the quality of the included studies. Ten studies were classified as having some concerns of RoB and four studies were deemed to have a high RoB for change in Hb levels during follow-up (Figure 2). All studies had some concerns of RoB in the domain of deviations from the intended interventions, mostly because of their open-label study designs.

To evaluate publication bias, a graphical funnel plot was used. Visual inspection of the plot revealed asymmetry, indicating the presence of publication bias for all studies except two small and negative RCTs (Supplementary Figure 1).

Primary Outcome Results

In the overall analysis of 12 RCTs [11,12,13,15,16,19,21,22, 30,31,32,33] involving 4,734 participants, FCM resulted in a significant increase in Hb levels during follow-up compared to IS (MD: 0.45 g/dL, 95% CI: 0.08 to 0.83, I^2: 97%, p=0.02) (Figure 3). The clinical importance of this finding suggests that FCM

may offer modest benefits over IS in raising Hb levels across a broad population of IDA patients.

Subgroup Analysis Results

When stratified by the etiology of anemia, FCM demonstrated a statistically significant improvement in Hb levels specifically in patients with postpartum anemia [16,32] (MD: 1.04 g/dL, 95% CI: 0.75 to 1.33, p<0.01), but inverse results were obtained for hemodialysis patients [12,30] (MD: -0.24 g/dL, 95% CI: -0.53 to 0.04, p<0.01) compared to IS (Supplementary Figure 2). Upon classifying studies based on impaired iron absorption (MD: 0.17 g/dL, 95% CI: -0.34 to 0.69) [14,21,33], impaired renal function (MD: -0.09 g/dL, 95% CI: -0.46 to 0.28) [12,15,30], gynecological disorders (MD: 0.26 g/dL, 95% CI: -0.62 to 1.14) [11,19,20], postpartum anemia (MD: 1.04 g/dL, 95% CI: 0.75 to 1.33) [16,32], and mixed etiology (MD: 1.10 g/dL, 95% CI: -0.36 to 2.56) [13,22], a significant difference was observed among the subgroups in favor of postpartum anemia for FCM (Supplementary Figure 3).

Table 1. Study characteristics of the included trials.

Reference	Study design	Population	Sample size	Intervention, cumulative dose + SD (mg)	Comparator, cumulative dose + SD (mg)	Primary outcome
Evstatiev et al. [14], 2011	Multicenter open-label RCT	IBD-associated IDA	485	FCM, 1377+381	IS, 1160+316	Hemoglobin response rate at week 12
Onken et al. [15], 2014	Multicenter open-label RCT	NDD-CKD-associated IDA	2584	FCM, 1464+158	IS, 963+138	Non-inferiority in the change from baseline to highest hemoglobin levels at day 56
Mahey et al. [19], 2015	Open-label RCT	Uterine bleeding-associated IDA	60	FCM, N/A	IS, N/A	Rise in hemoglobin levels above baseline
Rathod et al. [16], 2015	Double-blinded RCT	Postpartum-associated IDA	300	FCM, N/A	IS, N/A	Changes in hemoglobin and serum ferritin levels at 2 and 6 weeks after treatment
Roberts et al. [30], 2016	RCT	HD-CKD-associated IDA	42	FCM, 200	IS, 200	Change in fibroblast growth factor 23 levels from pre-infusion to day 2 after infusion
Ikuta et al. [11], 2018	Multicenter open-label RCT	Hypermenorrhea-associated IDA	294	FCM, 1349+N/A	IS, 1357+N/A	Mean change in hemoglobin from baseline to highest observed level
Naqash et al. [13], 2018	RCT	Mixed etiology	200	FCM, N/A	IS, N/A	Achievement of target hemoglobin and ferritin levels
Lee et al. [20], 2019	Multicenter open-label RCT	Hypermenorrhea-associated IDA	101	FCM, 923.1+207.3	IS, 939.6+352.3	Proportion of patients achieving hemoglobin levels of ≥10 g/dL within 2 weeks after the first administration
Jose et al. [31], 2019	Open-label RCT	Pregnancy-associated IDA	100	FCM, 1739.6+105.5	IS, 1730.4+121.9	Improvement in hemoglobin and ferritin levels
Wajid et al. [32], 2021	RCT	Postpartum-associated IDA	160	FCM, N/A	IS, N/A	Recovery of normal hemoglobin levels by day 21
Bielesz et al. [12], 2021	Open-label RCT	HD-CKD-associated IDA	142	FCM, N/A	IS, N/A	Change in hemoglobin at week 40 from baseline
Laso-Morales et al. [21], 2022	Open-label RCT	Colorectal cancer surgery-associated IDA	104	FCM, 1000+N/A	IS, N/A	Change in hemoglobin concentration at postoperative day 30
Struppe et al. [33], 2023	Open-label pilot RCT	IBD-associated IDA	20	FCM, N/A	IS, N/A	Longitudinal evaluation of serum phosphate levels after iron substitution therapy
Jin et al. [22], 2024	Multicenter open-label RCT	Mixed etiology	371	FCM, 1521+231	IS, 1464+325	Achievement of hemoglobin response (increase of ≥2 g/dL from baseline) within 8 weeks

SD: Standard deviation; RCT: randomized controlled trial; IBD: inflammatory bowel disease; IDA: iron-deficiency anemia; NDD-CKD: non-dialysis-dependent chronic kidney disease; HD-CKD: hemodialysis-dependent chronic kidney disease; FCM: ferric carboxymaltose; IS: iron sucrose; N/A: not available.

Secondary Efficacy Outcomes

The proportion of patients achieving an increase of ≥2 g/dL in Hb (3 RCTs, 1078 patients) [14,22,30] was comparable between the FCM group (RR: 1.06, 95% CI: 0.93 to 1.20, p=0.38) and IS (Supplementary Figure 4). FCM also showed non-significant superiority in achieving normal Hb levels during follow-up (RR: 1.77, 95% CI: 0.98 to 3.20, p=0.06) (Supplementary Figure 5) [14,16,21,32].

Ferritin levels during follow-up were significantly improved in the FCM group compared to the IS group (MD: 37.32 ng/mL, 95% CI: 18.98 to 55.65, p<0.01) (Supplementary Figure 6) [13,16,19,22,33].

Figure 2. Risk of bias assessment of the included randomized controlled trials in terms of change in hemoglobin levels during follow-up.

Safety Outcomes

The pooled risk for serious or severe AEs was comparable between the FCM and IS groups (RR: 1.03, 95% CI: 0.88 to 1.21, p=0.70) (Figure 4A) [11,12,13,14,15,16,19,20,22,30,31,32]. This finding suggests that both FCM and IS have acceptable safety profiles with no clinically meaningful differences in serious AEs. FCM was associated with a significantly higher incidence of hypersensitivity reactions compared to IS (RR: 2.97, 95% CI: 1.35 to 6.52, p<0.01) (Figure 4B) [11,12,13,14,15,16,19,21,22,30, 31,32]. The occurrence of hypophosphatemia was more frequent in the FCM group, although the difference did not reach statistical significance (RR: 2.84, 95% CI: 0.89 to 9.06, p=0.08) (Figure 4C) [11,14,15,16,22,31]. Similarly, the results of pooled analysis of all AEs did not differ significantly between FCM and IS (RR: 0.89, 95% CI: 0.63 to 1.27, p=0.53) (Supplementary Figure 7) [11,12,13,14,15,16,19,22,31]. No significant difference in withdrawal rates due to AEs was observed between the two groups (RR: 1.53, 95% CI: 0.60 to 3.89, p=0.37) (Supplementary Figure 8) (Table 2) [11,12,14,19,20,21,22,31].

Discussion

Our meta-analysis demonstrated that FCM provides a potential advantage over IS in improving Hb and ferritin levels among patients with IDA. Notably, FCM showed a statistically significant improvement in Hb levels compared to IS, especially in patients with postpartum anemia. This analysis adds to the existing body of evidence by highlighting the differential impacts of FCM and IS across various subpopulations, underscoring FCM's enhanced efficacy in achieving target Hb levels swiftly. Although FCM is associated with

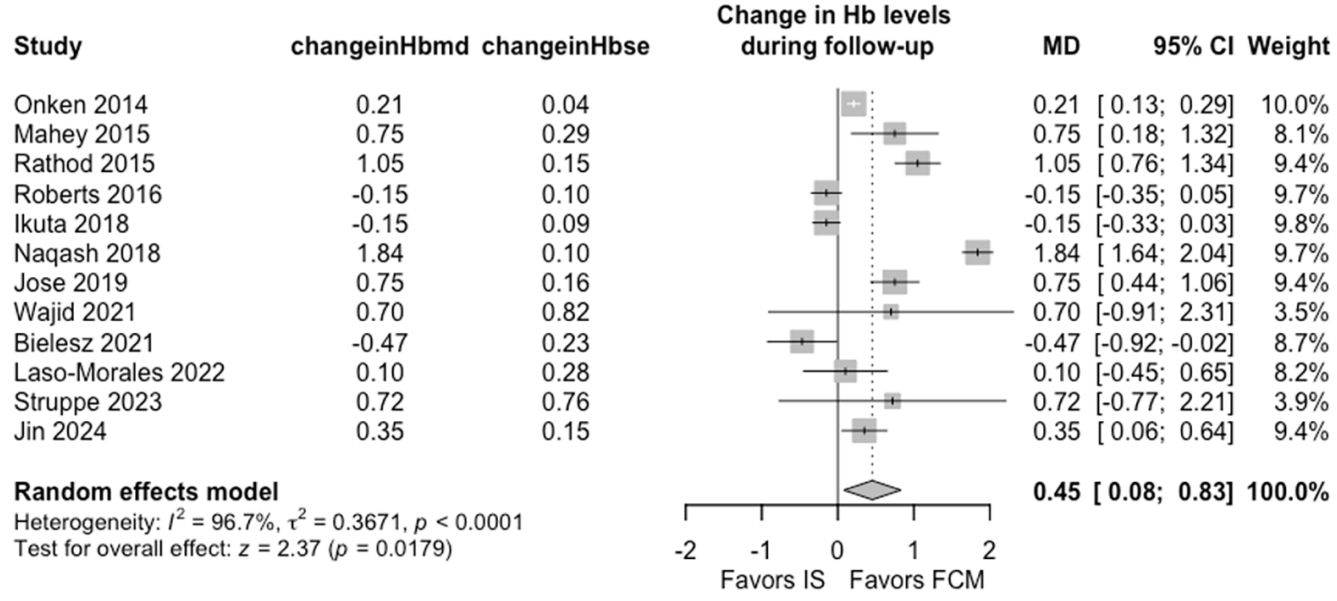

Figure 3. Forest plot of change in hemoglobin levels during follow-up.

Hbmd: Hemoglobin-mean value; Hbse: hemoglobin-standard error; Hb: hemoglobin; MD: mean difference; CI: confidence interval; IS: iron sucrose; FCM: ferric carboxymaltose.

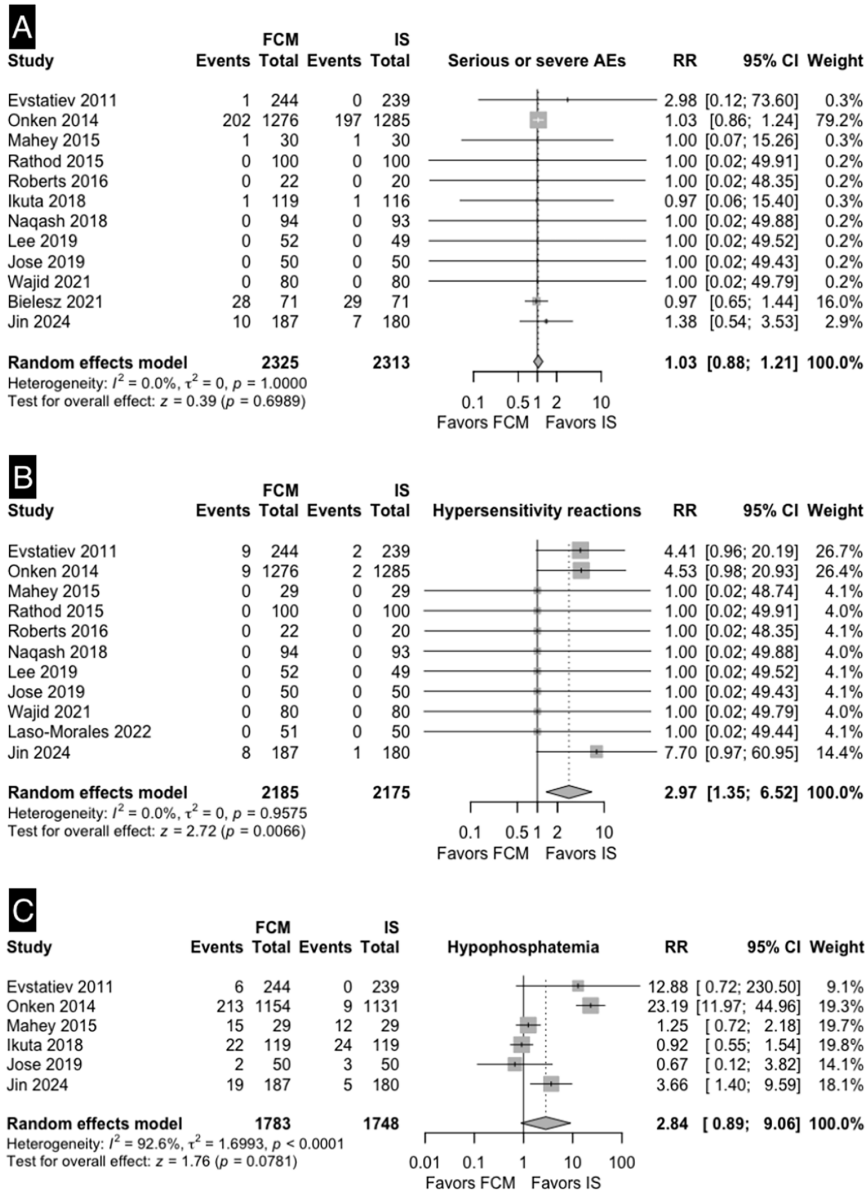

Figure 4. Forest plots of risk of serious or severe adverse events (A), hypersensitivity reactions (B), and hypophosphatemia (C).
FCM: Ferric carboxymaltose; IS: iron sucrose; AE: adverse event; RR: relative risk; CI: confidence interval.

Table 2. Safety of ferric carboxymaltose compared to iron sucrose in anemia patients.

Outcomes	Number of studies	FCM		IS		Pooled effect size RR (95% CI)	p	I^2 (%)
		Number of events	Total number of patients	Number of events	Total number of patients			
Serious or severe AEs	12	243	2325	235	2313	1.03 (0.88 to 1.21)	0.6989	0
Hypersensitivity reactions	11	26	2185	5	2175	2.97 (1.35 to 6.52)	0.0066	0
Hypophosphatemia	6	277	1783	53	1748	2.84 (0.89 to 9.06)	0.0781	92.6
Any AEs	9	470	2169	443	2167	0.89 (0.63 to 1.27)	0.53	47
Withdrawal rate	8	11	804	6	788	1.53 (0.60 to 3.89)	0.37	0

FCM: Ferric carboxymaltose; IS: iron sucrose; RR: relative risk; CI: confidence interval; AE: adverse event.

a significantly increased risk of hypersensitivity reactions and a non-significant increase of hypophosphatemia and serious or severe AEs regardless of the etiology of IDA, our findings suggest the importance of monitoring patients receiving both agents.

IDA represents a significant global health concern due to its widespread prevalence and profound impact on individual health and socioeconomic development. According to the 2021 Global Burden of Disease study [2], the global prevalence of anemia was 24.3%, equating to approximately 1.92 billion cases. Although this marks a decrease from 28.2% in 1990 [34], the absolute number of cases has grown due to population expansion. IDA remains the leading cause of anemia worldwide, constituting 66.2% of total cases, particularly affecting women of reproductive age and children under 5 years of age. The primary etiologies of IDA include dietary iron deficiency, chronic inflammatory diseases, and conditions affecting iron absorption, such as gastrointestinal disorders and CKD [3]. The widespread burden of IDA and its profound effects on quality of life, cognitive function, and physical performance underscore the importance of timely and effective iron repletion, particularly in populations with high physiological demands or significant iron losses [5].

Parenteral iron therapy, such as FCM and IS, is a critical option when oral iron formulations are ineffective, poorly tolerated, or contraindicated, such as in patients with severe IDA, malabsorption syndromes, and CKD or those who cannot adhere to oral regimens due to gastrointestinal side effects [7,35]. FCM offers a practical advantage in delivering higher doses in a single administration, allowing for rapid repletion and improved patient compliance [36]. However, FCM's association with hypersensitivity reactions and hypophosphatemia necessitates careful monitoring [37]. IS, while requiring multiple administrations to achieve adequate iron levels, may be preferable in patients with higher sensitivity to infusion reactions [38]. Thus, the choice of intravenous iron therapy should be tailored to individual patient needs while considering efficacy, safety profiles, and logistical considerations.

Increasing Hb levels in patients with IDA is of paramount importance across diverse subpopulations and etiologies [35,39]. For patients with CKD, there is a consensus that the correction of Hb levels with intravenous iron therapy is linked to improved outcomes in terms of reduced hospitalizations and enhanced quality of life [40]. Additionally, in the obstetric population, correcting Hb in pregnant and postpartum women not only addresses maternal anemia but also reduces the risks associated with postpartum hemorrhage and supports optimal fetal development [41]. Achieving target Hb levels thus has significant implications, serving to mitigate the morbidity associated with anemia and, ultimately, enhance patient-centered outcomes across these varied clinical contexts.

The safety profiles of parenteral iron agents, and particularly those of FCM and IS, are a crucial consideration in clinical practice as they impact adherence, tolerability, and preference in managing IDA. In accordance with our results, FCM has a favorable safety profile with a lower incidence of AEs compared to IS, as also observed in meta-analyses among obstetric and gynecologic populations [10]. FCM's ability to deliver a high dose in a single administration session not only enhances patient adherence by reducing the need for multiple infusions but also aligns well with clinical settings that prioritize efficiency. However, FCM is associated with treatment-emergent hypophosphatemia, especially in cases requiring repeated dosing, which mandates careful monitoring. IS is known to require multiple doses for full iron replenishment in IDA patients and it was shown to carry a higher risk of severe hypersensitivity reactions compared to a carbohydrate-polymer agent [42]. Both agents rarely lead to true anaphylaxis, with most reactions being mild infusion-related responses. The robust safety and tolerability of these agents combined with their low rates of treatment discontinuation due to AEs underscore their suitability and reliability in clinical practice for a range of IDA etiologies.

Shin et al. [10] reported the safety of FCM and IS, which are widely used by obstetric and gynecological IDA patients, in their systematic review. The incidence of AEs was reported to be lower in the FCM group than in the IS group (p=0.003). No serious AEs were reported in either group. In a systematic review and meta-analysis reported by Bharadwaj et al. [43], 26% fewer side effects occurred in the FCM group compared to the IS group (p=0.001). Srimathi et al. [44] reported a meta-analysis of pregnant women aged 15-49 years with IDA who were given FCM or IS. A total of 18 studies were included. Fewer side effects were reported in the FCM group compared to the IS group (p=0.003). In the prospective study conducted by James et al. [45] including 120 pregnant IDA patients, the number of patients given FCM and IS was 60 each. Mild side effects were reported to occur in 7.5% of the patients included in that study.

Hardy and Vandemergel [46] examined the frequency of hypophosphatemia in their retrospective study of the data of patients who received FCM or IS. Fifty-two patients were included in the IS group and 78 patients were included in the FCM group. The phosphate level measured before treatment in the IS group was 1.08±0.23 mmol/L and it was reported not to have changed significantly after IS administration (1.00±0.29 mmol/L; p=0.37). Hypophosphatemia was reported in 22% of the patients after IS infusion, with phosphate levels falling below 0.80 mmol/L, while all had been within the normal range before injection. The mean phosphate level before treatment in the FCM group was 1.08±0.18 mmol/L and it decreased to 0.82±0.29 mmol/L after iron administration (p<0.0001). After FCM administration, 13% of patients had a phosphate level of <0.32 mmol/L and 51% had a phosphate level of <0.80 mmol/L.

It is also important to note that published RCTs lack standardized definitions for hypersensitivity reactions. For instance, Ikuta et al. [11] used MedDRA definitions, which provide a standardized set of terms for hypersensitivity reactions, categorized into five groups and aiding clinicians and researchers in estimating the risk for the general population, whereas Lee et al. [20] used the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) to report AE and safety data. However, both of these studies reported only a few safety outcomes and they did not address hypersensitivity-related AEs. Therefore, our findings on safety parameters, including severe AEs and hypersensitivity reactions, should be interpreted with caution. This uncertainty and heterogeneity in reporting AEs should be considered by guideline developers and policymakers, as this study has provided the most comprehensive data on this subject.

Study Limitations

Our meta-analysis has several strengths, including the large number of patients analyzed across multiple clinical settings and the inclusion of both short-term and long-term efficacy outcomes. However, it is important to acknowledge certain limitations. First, not all trials reported data on key safety outcomes, such as hypophosphatemia or standardized definitions for serious or severe AEs or hypersensitivity, which may limit the generalizability of our findings regarding AEs. Second, while we included a broad range of patient populations, the heterogeneity in dosing protocols, follow-up durations, and etiologies across the included studies may have influenced the observed treatment effects.

Conclusion

This systematic review and meta-analysis has demonstrated the potential advantage of FCM over IS in improving Hb and ferritin levels, particularly among patients with gynecological disorders underlying IDA. While the two iron preparations demonstrated comparable efficacy in the general population, the findings of this review underscore the importance of considering the specific etiology of anemia when choosing between these treatments.

Ethics

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: The article presents a meta-analysis. Therefore, informed consent is not required.

Footnotes

Authorship Contributions

Concept: L.H.T., A.S.; Design: L.H.T., A.S.; Data Collection or Processing: L.H.T., A.S.; Analysis or Interpretation: L.H.T., A.S.; Literature Search: L.H.T., A.S.; Writing: L.H.T., A.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Supplementary File

1. Search algorithms

Web of Science

#1(((((((ALL=(iron deficiency anemia)) OR ALL=(anemia)) OR ALL=(iron deficien*)) OR ALL=(iron deplet*)) OR ALL=(anaemia)) OR ALL=(anemic)) OR ALL=(anaemic))

#2(((ALL=(carboxymaltose)) OR ALL=(ferinject)) OR ALL=(injectafer)) OR ALL=(Dextri-Maltose)

#3((((((((((((((ALL=(sucrose)) OR ALL=(saccharated ferric oxide)) OR ALL=(iron sucrose)) OR ALL=(iron saccharate)) OR ALL=(ferric saccharate)) OR ALL=(ferri saccharate)) OR ALL=(iron (iii) hydroxide sucrose complex)) OR ALL=(venofer)) OR ALL=(hippiron)) OR ALL=(ferrisaccharate)) OR ALL=(ferrivenin)) OR ALL=(sucrofer)) OR ALL=(feojectin)) OR ALL=(ferric oxide saccharate)) OR ALL=(sucroferric oxyhydroxide)

#4#1 AND #2 AND #3

Cochrane Central Register of Controlled Trials (Cochrane CENTRAL)

#1MeSH descriptor: [Anemia, Iron-Deficiency] explode all trees

#2MeSH descriptor: [Anemia] explode all trees

#3#1 OR #2

#4 (carboxymaltose OR ferinject OR injectafer OR dextri-maltose):ti,ab,kw

#5 MeSH descriptor: [Ferric Oxide, Saccharated] explode all trees

#6(sucrose OR 'saccharated ferric oxide' OR 'iron sucrose' OR 'iron saccharate' OR 'ferric saccharate' OR 'ferri saccharate' OR 'iron (iii) hydroxide sucrose complex' OR venofer OR hippiron OR ferrisaccharate OR ferrivenin OR sucrofer OR feojectin OR 'ferric oxide saccharate' OR sucroferric oxyhydroxide)):ti,ab,kw

#7#5 OR #6

#8(#3 AND #4 AND #7) in Trials

Ovid Medline (R) (Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to Jan 1, 2024)

1 (exp *Anemia/ or Anemia.mp.) or (exp *Anemia, Iron-Deficiency/ or Anemia, Iron-Deficiency.mp.) {Including Related Terms}

2 exp *Anemia/ or Anemia.mp.

3 1 or 2

4 exp Ferric Oxide, Saccharated/ or Ferric Oxide, Saccharated.mp.

5 (exp Ferric Oxide, Saccharated/ or Ferric Oxide, Saccharated.mp.) {Including Related Terms}

6 Sucrose/ or sucrose.mp.

7 saccharated ferric oxide.mp.

8 iron sucrose.mp.

9 iron saccharate.mp.

10 ferric saccharate.mp.

11 iron (iii) hydroxide sucrose complex {Including Related Terms}

12 venofer.mp.

13 hippiron.mp.

14 ferrisaccharate.mp.

15 ferrivenin.mp.

16 ferric oxide saccharate.mp.

17 sucroferric oxyhydroxide.mp.

18 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19 Carboxymaltose/ or carboxymaltose.mp.

20 ferinject.mp.

21 injectafer.mp.

22 Dextri-Maltose.mp.

23 19 or 20 or 21 or 22

24 3 and 18 and 23

Pubmed

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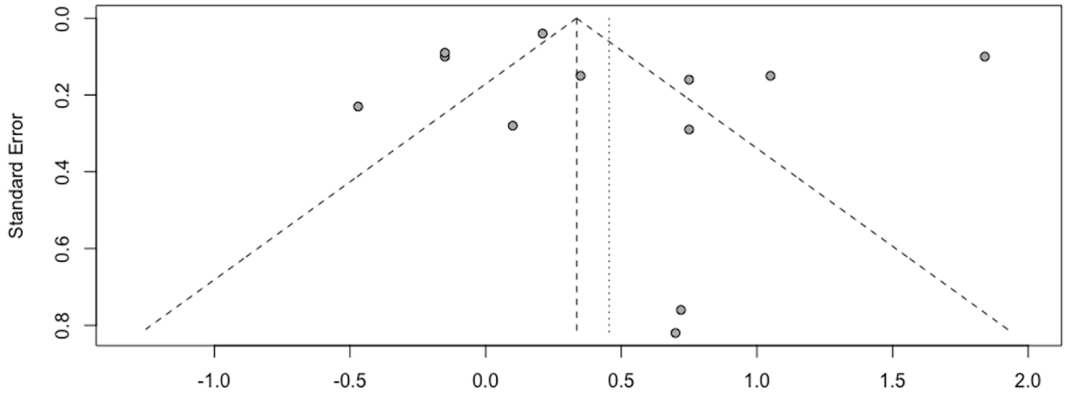
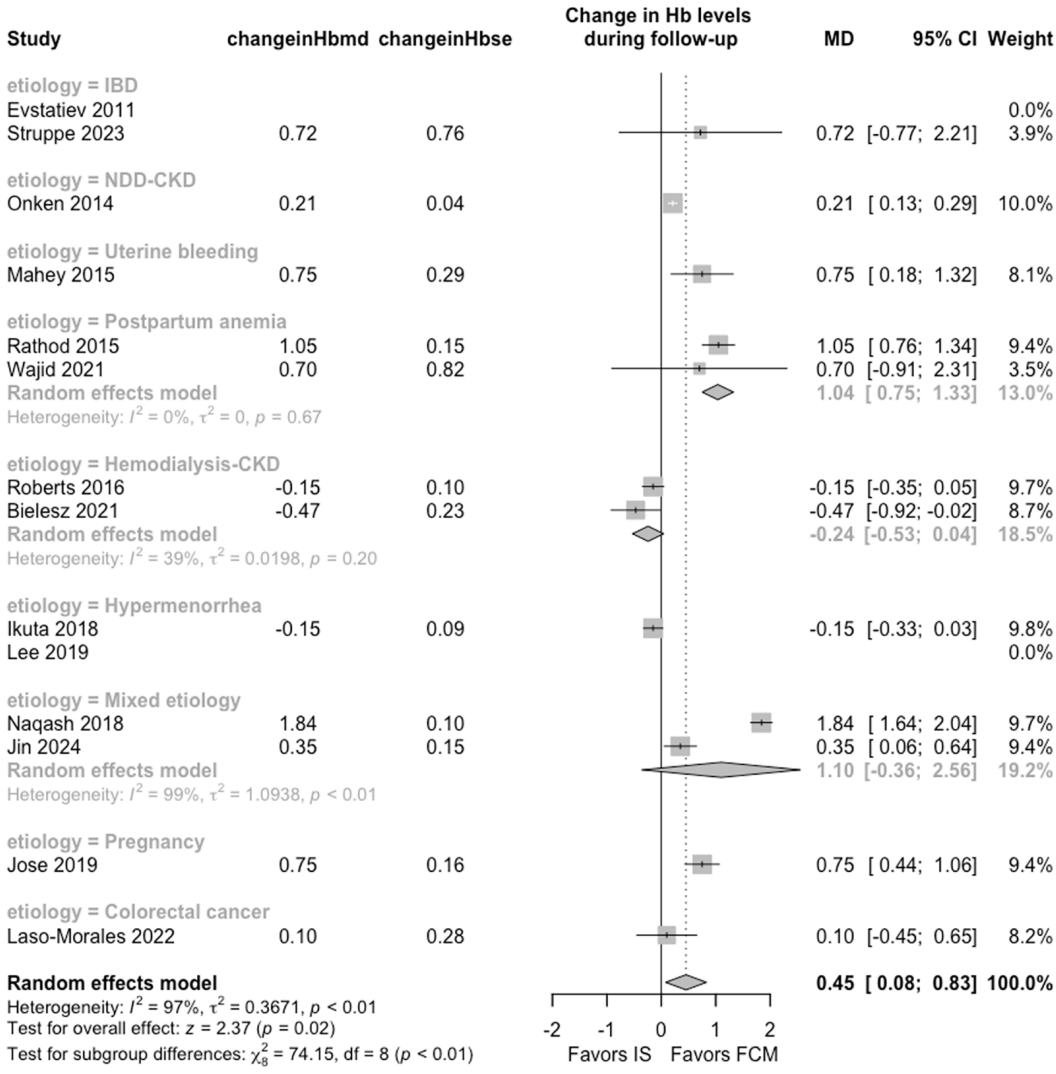
#4#1 AND #2 AND #3

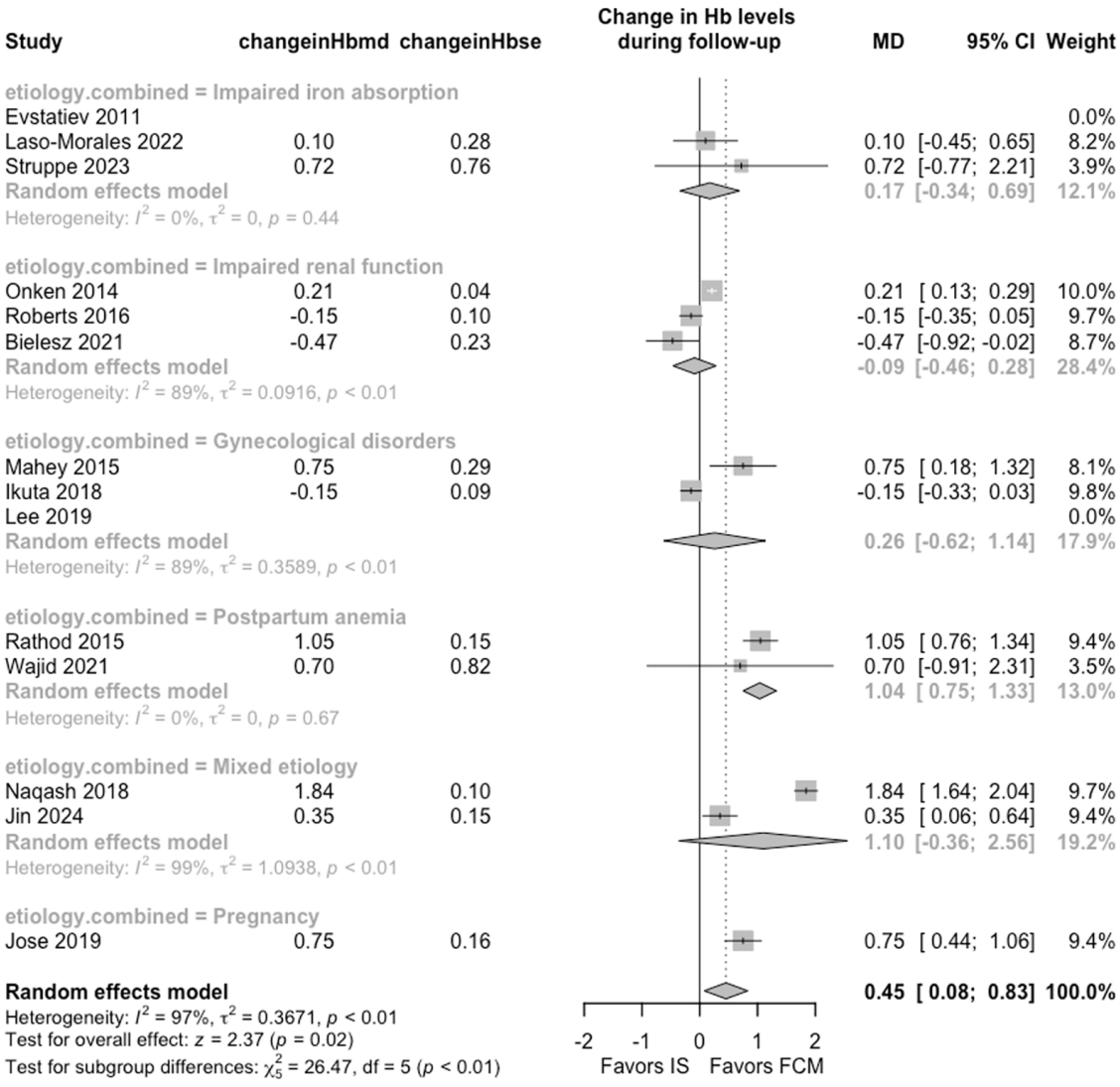


Supplementary Figure 1. Funnel plot with 95% confidence limits of the pooled proportion of change in hemoglobin levels during follow-up.



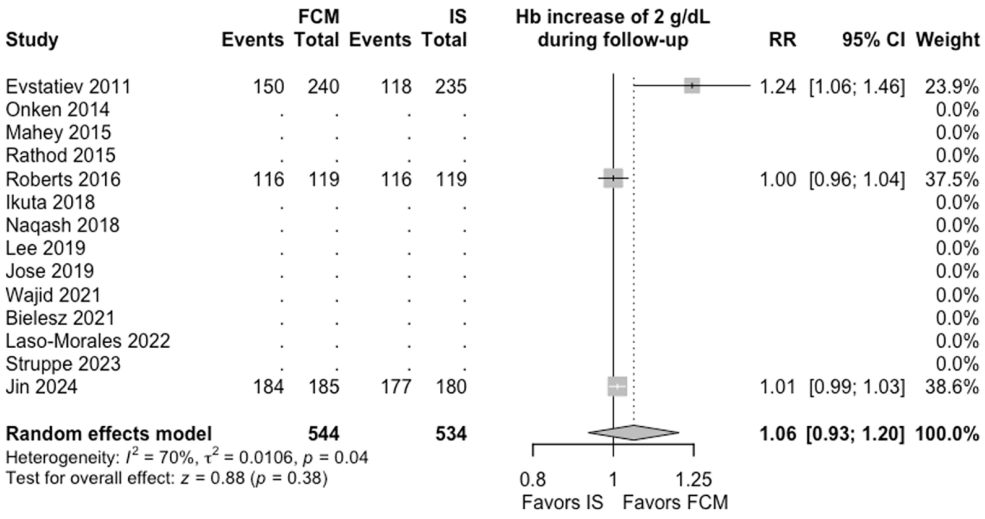
Supplementary Figure 2. Forest plot of subgroups by etiology of change in hemoglobin levels during follow-up.

IBD: Inflammatory bowel disease; NDD-CKD: non-dialysis dependent chronic kidney disease; FCM: ferric carboxymaltose; IS: iron supplementation; Hb: hemoglobin; MD: mean difference; CI: confidence interval.



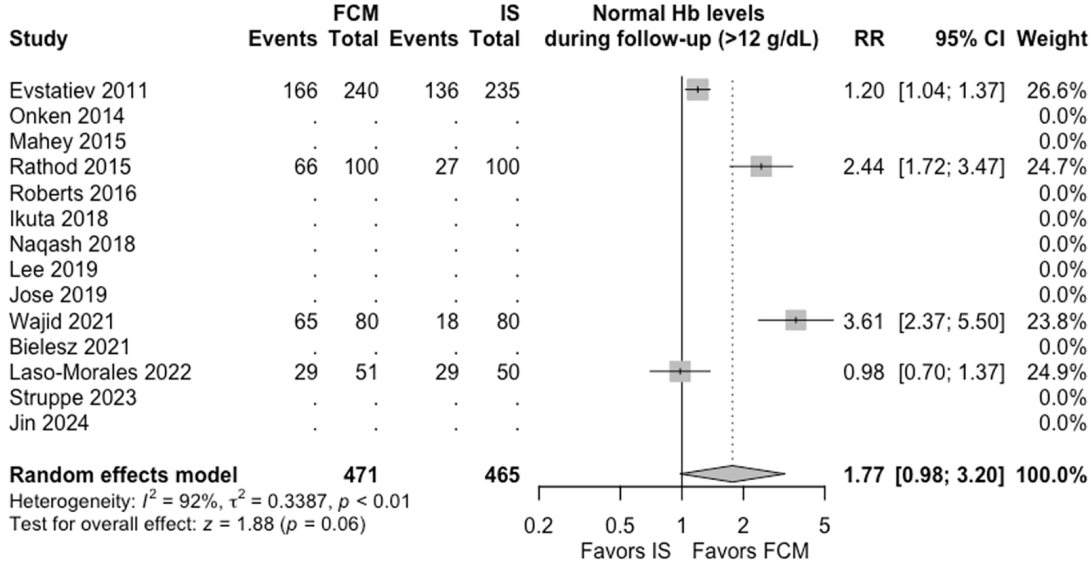
Supplementary Figure 3. Forest plot of subgroups by combined etiology of change in hemoglobin levels during follow-up.

FCM: Ferric carboxymaltose; IS: iron supplementation; Hb: hemoglobin; MD: mean difference; CI: confidence interval.



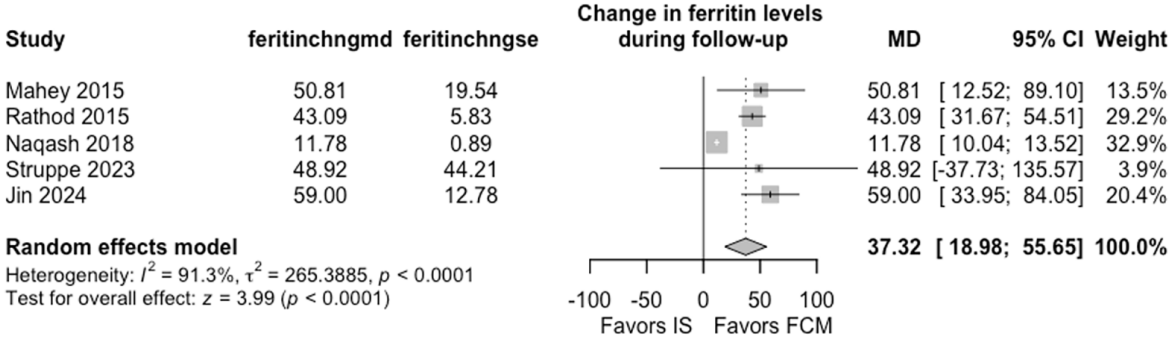
Supplementary Figure 4. Forest plot of hemoglobin increase of 2 g/dL during follow-up.

FCM: Ferric carboxymaltose; IS: iron supplementation; Hb: hemoglobin; RR: relative risk; CI: confidence interval.



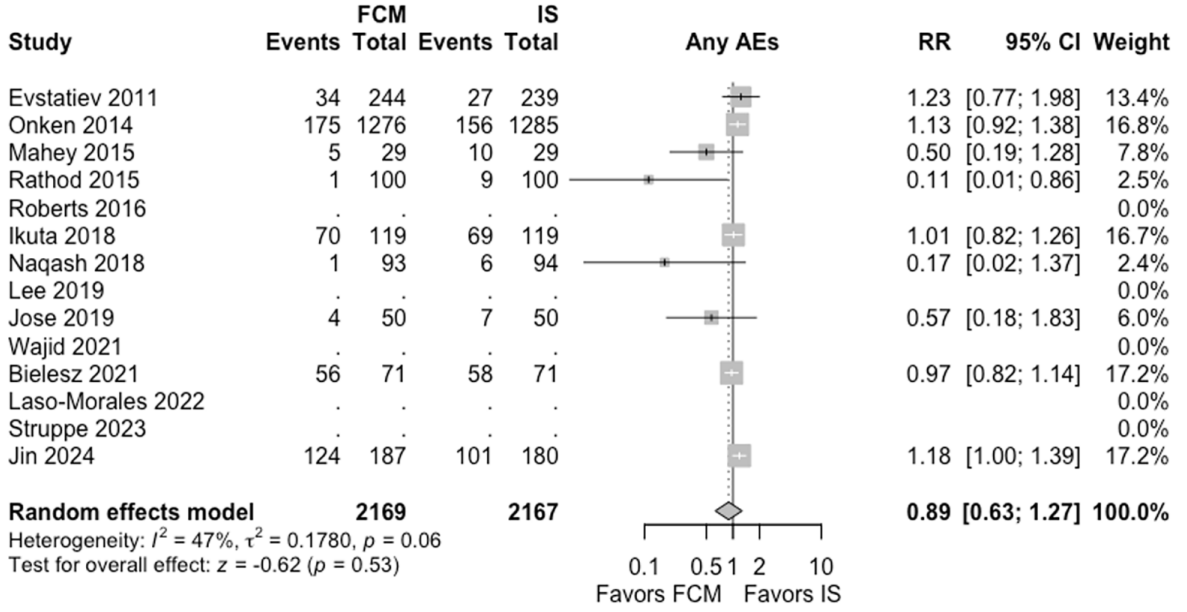
Supplementary Figure 5. Forest plot of risk of achievement at normal hemoglobin levels.

FCM: Ferric carboxymaltose; IS: iron supplementation; Hb: hemoglobin; RR: relative risk; CI: confidence interval.



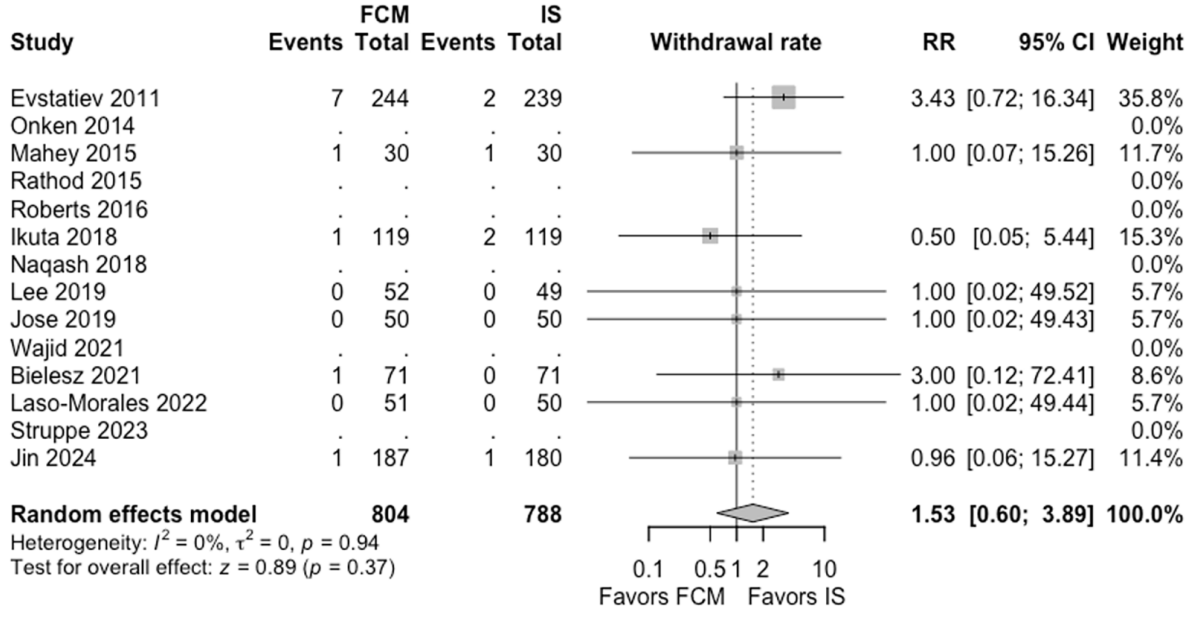
Supplementary Figure 6. Forest plot of change in ferritin levels during follow-up.

MD: Mean difference; CI: confidence interval; FCM: ferric carboxymaltose; IS: iron supplementation.



Supplementary Figure 7. Forest plot of risk of any adverse events.

FCM: Ferric carboxymaltose; IS: iron supplementation; RR: relative risk; CI: confidence interval; AEs: adverse events.



Supplementary Figure 8. Forest plot of risk of withdrawal due to adverse events.

FCM: Ferric carboxymaltose; IS: iron supplementation; RR: relative risk; CI: confidence interval.

Supplementary Table S1. Patient baseline characteristics of the included trials.

Study ID	Arm	Sample size	Age, mean (SD or range), years	Female, n (%)	White, n (%)	Black or African American, n (%)	Asian, n (%)	Other, n (%)	ESA use, n (%)	Previous iron therapy, n (%)	Baseline Hb, g/dL	Baseline ferritin, ng/mL	Baseline TSAT (SD), %	Baseline eGFR, mL/min/1.73 m^2
Evstatiev et al. [14]	FCM	240	39.5 (18-81)	146 (59.8%)	240 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	10.1 (1.5)	14.8 (24.6)	9 (9.1)	-
	IS	235	38 (18-78)	138 (57.7%)	235 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	10.3 (1.5)	17.8 (27.6)	9.6 (9.5)	-
Onken et al. [15]	FCM	1276	67.5 (13)	810 (63.5%)	676 (53%)	334 (26.2%)	20 (1.6%)	12 (0.9%)	230 (18%)	696 (54.5%)	10.31 (0.833)	73.01 (64.6)	19.79 (7.78)	32.5 (14.7)
	IS	1285	67.2 (13)	818 (63.7)	693 (53.9%)	325 (25.3%)	21 (1.6%)	10 (0.8%)	228 (17.7%)	693 (53.9%)	10.32 (0.826)	75.05 (64.1)	19.56 (7.4)	32.27 (14.9)
Mahey et al. [19]	FCM	30	36.3 (9)	30 (100%)	0 (0%)	0 (0%)	0 (0%)	30 (100%)	-	-	7.42 (1.23)	10 (3.9-28)	-	-
	IS	30	35.2 (7.5)	30 (100%)	0 (0%)	0 (0%)	0 (0%)	30 (100%)	-	-	7.73 (1.2)	8.8 (2.3-20)	-	-
Rathod et al. [16]	FCM	100	25.9 (3.57)	100 (100%)	0 (0%)	0 (0%)	0 (0%)	100 (100%)	-	-	7.71 (1.17)	35.52 (20.2)	-	-
	IS	100	26 (3.66)	100 (100%)	0 (0%)	0 (0%)	0 (0%)	100 (100%)	-	-	8.05 (1.07)	38.39 (19.79)	-	-
Roberts et al. [30]	FCM	22	70.9 (66.7-76.8)	6 (27%)	22 (100%)	0 (0%)	0 (0%)	0 (0%)	16 (73%)	-	11.1 (0.9)	21.1 (13.3)	29 (9)	-
	IS	20	75.1 (56.1-79.8)	6 (30%)	20 (100%)	0 (0%)	0 (0%)	0 (0%)	11 (55%)	-	11.5 (1)	18.7 (13)	27 (12)	-
Ikuta et al. [11]	FCM	119	41.3 (6.2)	119 (100%)	0 (0%)	0 (0%)	119 (100%)	0 (0%)	-	-	9.2 (1.15)	-	-	-
	IS	119	41.4 (6.1)	119 (100%)	0 (0%)	0 (0%)	119 (100%)	0 (0%)	-	-	9.25 (1.08)	-	-	-
Naqash et al. [13]	FCM	100	30.41 (7.99)	100 (100%)	0 (0%)	0 (0%)	0 (0%)	100 (100%)	-	-	7.82 (0.75)	18.29 (2.16)	7.67 (1.97)	-
	IS	100	27.32 (4.15)	100 (100%)	0 (0%)	0 (0%)	0 (0%)	100 (100%)	-	-	7.64 (0.72)	18.13 (1.67)	7.02 (1.61)	-
Lee et al. [20]	FCM	52	44 (5.7)	52 (100%)	0 (0%)	0 (0%)	52 (100%)	0 (0%)	-	-	8.4 (1.4)	5.8 (5.7)	6.1 (7.3)	-
	IS	49	43.4 (5)	49 (100%)	0 (0%)	0 (0%)	49 (100%)	0 (0%)	-	-	8.4 (1.1)	5.7 (3.9)	4.8 (5.9)	-
Jose et al. [31]	FCM	50	27.5 (3.9)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	50 (100%)	-	-	8.57 (0.89)	7.9 (0.4-22.3)	8 (0.4-30.5)	-
	IS	50	26.2 (3.6)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	50 (100%)	-	-	8.67 (0.86)	9 (0.94-23)	12.5 (0.03-19.1)	-
Wajid et al. [32]	FCM	80	26.86 (4.32)	80 (100%)	0 (0%)	0 (0%)	0 (0%)	80 (100%)	-	-	-	-	-	-
	IS	80	23.16 (5.17)	80 (100%)	0 (0%)	0 (0%)	0 (0%)	80 (100%)	-	-	-	-	-	-
Bielesz et al. [12]	FCM	71	60 (15)	21 (30%)	69 (97%)	0 (0%)	2 (3%)	0 (0%)	65 (92%)		11.1 (0.9)	210 (109-403)	17 (13-24)	-
	IS	70	57 (14)	20 (28%)	68 (96%)	0 (0%)	3 (4%)	0 (0%)	67 (96%)		11.2 (1.1)	270 (131-414)	21 (13-27)	-
Laso-Morales et al. [21]	FCM	50	73 (10)	31 (62%)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	11.2 (1.6)	102.8 (262.8)	10.6 (5.5)	-
	IS	51	71 (12)	26 (51%)	51 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	11.4 (1.4)	89.6 (194.7)	13.4 (9)	-
Struppe et al. [33]	FCM	10	48 (34-57)	5 (50%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	10.8 (9.2-11.5)	50 (28.25-211.25)	-	-
	IS	10	63 (46-72)	6 (60%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	-	-	9.65 (8.78-11.8)	30 (10.5-141.5)	-	-
Jin et al. [22]	FCM	187	39.9 (9.9)	173 (92.5%)	0 (0%)	0 (0%)	187 (100%)	0 (0%)	-	18 (9.6%)	7.74 (1.49)	4.47 (2.15)	4.82 (1.9)	-
	IS	180	38.9 (8.7)	169 (93.9%)	0 (0%)	0 (0%)	180 (100%)	0 (0%)	-	19 (10.6%)	8.06 (1.45)	4.93 (6.1)	4.92 (2.91)	-

FCM: Ferric carboxymaltose; IS: iron sucrose; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; TSAT: transferrin saturation; eGFR: estimated glomerular filtration rate; SD: standard deviation.