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Ascorbic acid as an adjunct therapy for hyporesponsive anemia in Erythropoietin-treated hemodialysis patients: A systematic review and meta-analysis

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Abstract

Background

Anemia commonly complicates chronic kidney disease (CKD), especially in hemodialysis patients. Erythropoiesis-stimulating agents (ESAs) are standard, but hyporesponsiveness occurs. Ascorbic acid (vitamin C) may improve iron mobilization and ESA response. This study evaluated ascorbic acid in anemic hemodialysis patients on ESAs.

Methods

This systematic review followed PRISMA guidelines and was prospectively registered in PROSPERO (CRD420251054491). Only randomized controlled and Crossover trials in adult hemodialyzed patients with erythropoietin hyporesponsive anemia were included. A systematic search was done in PubMed, Cochrane, Scopus, EMBASE, Web of Science, CINAHL, and Google Scholar through April 2026. Primary outcomes were Hemoglobin, erythropoietin dose, ferritin, serum iron, transferrin saturation, and total iron binding capacity. Random-effects meta-analysis was performed in R, with heterogeneity, sensitivity, and publication bias analyses conducted.

Results

Ten studies (431 patients) were analyzed. Ascorbic acid significantly increased hemoglobin (MD = 1.03 g/dL; 95% CI: 0.63–1.43; $p < 0.01$; $I^2 = 88.0\%$) and TSAT (MD = 9.87%; 95% CI: 4.69–15.06; $p < 0.01$; $I^2 = 93.7\%$). TIBC decreased significantly (MD = − 34.36 µg/dL; 95% CI: −59.08 to − 9.63; $p < 0.01$; $I^2 = 85.7\%$), and ferritin was lower (MD = − 52.90; $p = 0.04$; $I^2 = 39.0\%$). A modest reduction in weight-adjusted erythropoietin dose occurred (MD = − 21.29 IU/kg/week; $p < 0.01$; $I^2 = 0.0\%$). No significant effect on serum iron (MD = − 4.62 µg/dL; $p = 0.81$; $I^2 = 92.0\%$).

Conclusion

Ascorbic acid may offer modest benefits in erythropoietin-hyporesponsive hemodialysis patients, improving hemoglobin and TSAT, lowering ferritin (consistent with enhanced iron mobilization), and reducing ESA dose; however, evidence certainty is low, and safety remains unclear, limiting use.

1. Introduction

The World Health Organization (WHO) defines anemia in adults as hemoglobin (Hb) levels below 12 g/dL for women and below 13 g/dL for men[1]. Among patients with chronic kidney disease (CKD), anemia is exceedingly common, up to 95% of individuals receiving hemodialysis (HD) exhibit some degree of anemia, and its prevalence increases with advancing CKD stage-affecting 50.3% of patients with stage 5 and 53.4% of those with CKD stage 5[2]. This multifactorial condition results from relative erythropoietin deficiency, accumulation of uremic inhibitors of erythropoiesis, shortened erythrocyte lifespan, disordered iron homeostasis, and blood losses related to phlebotomy and the dialysis procedure[3]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines currently recommend erythropoiesis stimulating agents (E-SAs) combined with iron supplementation as the gold standard for CKD related anemia[4]. According to the US Renal Data System 2020 Annual Data Report, more than 85% of HD patients receive ESAs, and 5–10% are hyporesponsive[5]. Erythropoietin (EPO) hyporesponsiveness is defined by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guideline as the failure to achieve an Hb concentration target of 11 g/dl, despite the use of an EPO dosage greater than 450 IU/kg/week for the intravenous (I.V) route or 300 IU/kg/week for the subcutaneous (S.C) route, with iron stores replenished or not deficient[6]. Previous studies have demonstrated that hyporesponsiveness to ESAs is associated with several adverse outcomes that warrant careful consideration[7]. Complications include the need for higher doses of ESAs, which can increase the dose-dependent adverse effects, as well as a greater reliance on blood transfusions that elevate overall mortality risk[8]. Elevated levels of C reactive- protein (CRP), interleukin-6 (IL6), and the -iron regulatory peptide hepcidin have been shown to predict increased ESA requirements in both dialysis and Non dialysis CKD populations. Vitamin C is a key modulator of iron metabolism, it enhances the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron, thereby increasing iron bioavailability for erythropoiesis. In vitro, studies demonstrate that vitamin C supplementation augments the fraction of iron accessible to erythroid cells, but despite evidence that plasma vitamin C levels are often low in dialyzed patients, which is not yet incorporated into standard anemia management protocols[9]. While some abstracts and individual studies have examined the use of vitamin C in this context, updated evidence is needed using more rigorous methodological standards and larger datasets to evaluate its efficacy in enhancing ESA responsiveness and reducing inflammation among anemic HD patients. This systematic review and meta-analysis address this critical gap by synthesizing available evidence to assess the impact of ascorbic acid supplementation as an adjunct to erythropoietin therapy in adult hemodialysis patients with anemia. Our goal is to inform clinical decision-making and guide future research by evaluating outcomes such as hemoglobin (Hb), serum ferritin, serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), erythropoietin dose, and C-reactive protein (CRP).

2. Methodology

The methodology of this systematic review was developed and reported in accordance with the Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA)[10] statement. To enhance transparency and methodological rigor, the review protocol was prospectively registered at the International Prospective Register of Systematic Review (PROSPERO) under registration code CRD420251054491[11].

2.1. Eligibility criteria

2.1.1. Types of Study

This systematic review will consider studies published from the database inception through April 2026. Eligible study designs will be restricted only to randomized controlled trials and crossover studies. Studies will be excluded if they provide insufficient methodological information, report duplicate data, or do not supply the required information after efforts to contact the corresponding authors.

2.1.2. Types of Participants

We included adult patients (> 18 years) with erythropoietin-hyporesponsive anemia receiving hemodialysis (HD) and undergoing treatment with erythropoietin. Studies were excluded if they involved participants under 18 years old, individuals not receiving hemodialysis, patients without anemia, those not treated with erythropoietin, or mixed dialysis patients lacking separate reporting for HD patients.

2.1.3. Types of Interventions/Exposures and Comparators

This review will assess the effects of Ascorbic acid in the study population. Comparators will include patients receiving a placebo or regular treatment. Studies will be excluded if the intervention or exposure is not clearly defined or adequately reported.

2.1.4. Outcomes

The primary outcomes of this review will include Hb, serum ferritin, serum iron, EPO dose, TSAT, and TIBC, all assessed using Laboratory measurements. The Secondary outcomes will be CRP. EPO hyporesponsiveness is defined according to the NKF-K/DOQI Clinical Practice Guideline as failure to achieve an Hb concentration of 11 g/dl, despite the administration of at least 500 U/kg/week of EPO[12]. Studies not reporting at least one of the predefined outcomes will be excluded.

2.1.5. Searching methods

A comprehensive systematic search was performed in April 2026 across PubMed/MEDLINE, Cochrane, Scopus, Web of Science, EMBASE, CINAHL, and Google Scholar. The search strategy combined MeSH terms and free-text keywords, including anemia, hyporesponsive, hemodialysis, chronic kidney disease, erythropoietin, adults, ascorbic acid, and vitamin C. The complete search strategies are detailed in the Supplementary Material (Tables 1–7).

2.1.6. Selection of studies

All references were imported into Rayyan (Rayyan Systems Inc., Cambridge, MA, USA) and duplicate records were removed [13]. Two reviewers (A.C.L. and M.V.S.) independently performed study selection, initially screening titles and abstracts, followed by full-text assessment. Any disagreements were resolved through discussion, with adjudication by a third reviewer (Y.C.C.) when necessary.

2.1.7. Data extraction

Data extraction was independently performed by two reviewers (E.M.C. and Y.C.C.), with discrepancies resolved with consensus. Where multiple overlapping reports originated from the same study population, the most comprehensive report or the earliest publication was retained. Extracted variables included sample size, intervention characteristics, and outcome measures. Standardized data extraction procedures were supplemented with specialized tools, including WebPlotDigitizer (Automeris, Austin, TX, USA) for digitizing graphical data, the Cochrane Calculator for statistical conversions, and StatsToDo for advanced calculations[14–16]. Changes from baseline were calculated as the difference between baseline and post intervention values. These outcomes comprised hemoglobin, serum ferritin, serum iron, erythropoietin dose, TSAT, TIBC, and CRP. Additional extracted data included subgroup characteristics, such as country of study, risk of bias levels, and study design.

2.1.8. Assessment of risk of bias in included studies

Risk of bias assessment was conducted in accordance with Cochrane Guidelines using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for randomized controlled trials (RCTs)[17]. Two reviewers (A.C.L and M.V.S) independently evaluated each study using the predefined domains, with arbitration by a third blinded reviewer (S.A.B.) when necessary.

2.1.9. Assessment of the certainty of the evidence and summary of findings

Two reviewers (A.C.L and Y.C.C.) independently assessed the overall quality of evidence for each outcome using the five domains of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias, large effect, plausible confounding, dose response gradient, via the GRADEpro GDT software[18, 19]. Discrepancies between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer if needed.

2.1.10. Statistical analysis

This meta-analysis was conducted using R software version 3.4.3 (R Core Team) with the meta and metafor packages[20, 21]. Pooled effect estimates were calculated using a random-effects meta-analysis (DerSimonian-Laird approach). When the number of studies available for a given outcome was insufficient for quantitative synthesis, results were summarized narratively. Effect sizes were reported as relative risk (RR), mean difference (MD), or standardized mean difference (SMD), each with a 95% confidence interval. Heterogeneity was assessed using the I^2 statistic and the following cut-off values for interpretation: <25%, 25–50%, and > 50% were considered small, medium, and large heterogeneity, respectively. Sensitivity analyses were performed using a leave-one-out

approach to evaluate the robustness of the pooled estimates. Publication Bias was assessed using Egger's regression test when at least 10 studies were available for a given outcome. Where feasible, subgroup analyses were conducted according to risk of bias and primary outcome measures.

3. Results

3.1. Study selection

In our initial research, we identified 479 potential articles across six databases. After removing 234 duplicate articles, we conducted a screening based on title and abstract, leading to the exclusion of 182 articles. We sought 63 articles for retrieval; however, we could not retrieve 8, leaving 55 articles for eligibility assessment. These 55 articles underwent screening for eligibility, excluding 39 for wrong study design, and 6 more for wrong population. We included 10 studies in this review. We summarized this process in our PRISMA flow diagram (Fig. 1).

3.2. Characteristics of included studies

We analyzed data from 10 studies involving 431 patients: 220 received standard therapy with ascorbic acid, and 211 received standard therapy alone. The studies showed a wide geographic distribution, the largest contributions from Iran (30%), Egypt (20%), Taiwan (20%). While smaller contributions came from United States of America, Türkiye and Korea (10% each). The studies employed RCT design (80%), with a smaller proportion utilizing a cross-over design (20%). Across studies, the frequency of vitamin C administration ranged from 3 to 30 times per month, with doses spanning from 1,500 mg to 7,500 mg.

Regarding Hb, 80% of the studies reported an increase following vitamin C administration, 10% reported no significant effect, and 10% did not assess Hb outcomes. In terms of TSAT, 80% of studies observed improvements, while 20% did not evaluate TSAT. Concerning serum ferritin, 50% of studies reported a decrease, 40% found no significant difference, and 10% did not report on this marker. Improvements or reductions in ESA responsiveness or dosage were observed in 60% of the studies, while 40% did not report EPO-related outcomes. Regarding serum iron, 50% of studies noted an increase, while 20% found no significant changes, and 30% did not report these outcomes. Concerning TIBC, 20% of studies reported a decrease, 40% found no significant difference, and 40% did not report on this marker. CRP was evaluated in 20% of the included studies, all of which reported a reduction in CRP levels following vitamin C supplementation. The remaining 80% did not assess this outcome. We summarized this information in (Table 1)[22–31].

Table 1
General outcomes of included studies

Author or and Year	Country	Study design	Cases Age Mean (SD) Females (%) Males (%)	Controls Age Mean (SD) Female (%) Male (%)	Sample Size	Follow Up	Stage of CKD	Vitamin C Admin Route	Vitamin C Admin Frequency (times per month)	Vitamin C Dose	Key Points
El Shinnawy, H. et al, 2021[22]	Egypt	RCT	58.16(8.41) Females: 36% Males:64%	58.84(6.39) Females: 20% Males: 80%	50	6	5	IV	3	1500	IVAA with iron increased levels of Hb and TSAT, while decreased ferritin, TIBC and CRP levels.
Tarng, D. et al, 1998[23]	Taiwan	RCT	54(4) Females:42 Males: 58%	56(5) Females: 33% Males: 67%	24	2	5	IV	12	3600	IVAA showed an increase in TSAT, while decrease EPO doses.
Sedighi, O. et al, 2013[24]	Iran	RCT	57.1(15.1) Females:60% Males:40%	60.1(20.3) Females: 55% Males: 45%	40	3	5	IV	8	2400	IVAA significantly increased Hb, serum iron and TSAT. No significant difference across the rest of the outcomes.
Shahrbanoo, K. et al, 2008[25]	Iran	RCT	54.05(3.2) Females: 60% Males: 40%	54.32(4.1) Famles: 62% Males: 38%	31	3	5	IV	NA	NA	AA improves EPO responsiveness, increases hemoglobin and TSAT, while decreasing ferritin and CRP levels.
Tarng, D. et al, 2004[26]	Taiwan	RCT	55(20) Females: 61.1% Males: 38.9%	59(14) Females: 55.6% Males: 44.4%	36	0,23	5	IV	NA	2000	IVAA showed an increase in TSAT levels.
Attallah, N. et al, 2006[27]	USA	RCT	50.6(4.7) Females: 55% Males: 45%	49(5.9) Females: 55% Males: 45%	42	6	5	IV	3	3600	IVAA improves responsiveness to EPO, increasing Hb, TSAR. While significantly decreased EPO dose, iron binding capacity and CRP.
Jalalzadeh, M. et al, 2012[28]	Iran	Cross-over	51.8(16) Females: 40% Males: 60%	52.4(14) Females: 46% Males: 64%	30	3	5	IV	3	1500	IVAA has an increase Hb and TSAT, while it may decrease ferritin levels.
El-Sharkawy, M. et al, 2013[29]	Egypt	RCT	46.46(12.58) Females: NA Males: NA	43.9(13.98) Females: NA Males: NA	60	2	5	IV	12	3600	IVAA has an increased Hb, serum iron, and TSAT levels, while serum ferritin levels decreased.
Kang, D. et al, 2012[30]	Korea	RCT	54.5(12.1) Females: 55% Males: 45%	56.9(14.6) Females: 52% Males: 48%	58	3	5	IV	12	6000	IVAA has an increase in Hb and TSAT along with a reduction of rhEPO dosage after treatment. While serum ferritin levels were

Author or and Year	Country	Study design	Cases Age Mean (SD) Females (%) Males (%)	Controls Age Mean (SD) Female (%) Male (%)	Sample Size	Follow Up	Stage of CKD	Vitamin C Admin Route	Vitamin C Admin Frequency (times per month)	Vitamin C Dose	Key Points
											significantly decreased.
Keven, K. et al, 2003[31]	Turkey	Cross-over	42.0 (14.3) Females: 57% Males: 43%	40.2(9.5) Females: 53% Males: 47%	60	6	5	IV	12	6000	IVAA resulted in a significant increase in hemoglobin levels.

NA: Not applicable. **RCT**: Randomized clinical trial. **AA**: Ascorbic acid. **CKD**: Chronic kidney disease. **IV**: Intravenous. **IVAA**: Intravenous ascorbic acid. **Hb**: hemoglobin. **TSAT**: Transferrin saturation. **TIBC**: Total iron binding capacity. **CRP**: C-reactive protein. **EPO**: Erythropoietin.

3.3. Risk of Bias

We assessed the risk of bias in eight randomized studies and two crossover studies using the RoB 2.0 tool[17]. We evaluated the risk of bias for each reported outcome across the included studies. A moderate risk of bias was identified in two studies assessing Hb, two evaluating ESA dose, two examining ferritin, two assessing serum iron, and one assessing TIBC. Additionally, one study evaluating TSAT showed a moderate risk of bias. High risk of bias was observed in one study evaluating TIBC and another one evaluating both ESA dose and hemoglobin. All other remaining outcomes were assessed across studies and were deemed low risk of bias.

3.4. Meta Analysis

3.4.1. Hemoglobin levels

We conducted a meta-analysis with 9 studies with a total sample size of 395 subjects, comprising 202 individuals treated with ascorbic acid and 193 in the control group. We estimated the pooled mean difference at 1.03 (95% CI: 0.63 to 1.43, $p < 0.01$, $I^2 = 88.0\%$) using a random effects model (Fig. 2A; See also Table 2 for all outcomes). The prediction interval ranged from − 0.20 to 2.26. The funnel plot revealed asymmetry suggestive of potential publication bias (Fig. 3A). The Egger regression test was not conducted due to a low number of studies. Subgroup analysis showed no significant differences across the examined variables, including risk of bias, route of administration, study design, follow-up duration, ascorbic acid dose, frequency per week, trial center, and year of publication (Supplementary Table 8). Sensitivity analysis identifies Tarng D. et al. 1998[23] (Supplementary Table 9). Omitting this article, the revised MD is 0.86 (CI: 0.62 to 1.09; $I^2 = 0.0\%$). Meta-regression based on dose showed no significant association between Vitamin C dose and treatment effect on hemoglobin levels ($QM(4) = 3.93$, $p = 0.41$). Dose explained some of the between-study heterogeneity ($R^2 = 10.58\%$), and substantial residual heterogeneity remained ($I^2 = 74.33\%$, supplementary Fig. 2A).

3.4.2. TSAT

We conducted a meta-analysis with 9 studies with a total sample size of 420 subjects, comprising 205 individuals treated with ascorbic acid and 215 in the control group. We estimated the pooled MD at 9.87 (95% CI: 4.69 to 15.06, $p < 0.01$, $I^2 = 93.7\%$) using a random effects model (Fig. 2B; See also Table 2 for all outcomes). The prediction interval ranged from − 8.41 to 28.15. The funnel plot revealed asymmetry suggestive of potential publication bias (Fig. 3B). We did not conduct Egger's regression test due to the small number of studies (< 10). Statistically significant differences between subgroups were found for study design ($p = 0.0095$) and year of publication ($p = 0.0048$); however, these results should be interpreted with caution because each comparison involved one subgroup represented by a single study. RCTs (k = 8) showed a pooled MD of 11.10 [6.01; 16.20], whereas the lone cross-over study reported − 1.10 [−8.79; 6.59]. Similarly, the only study published after 2015 showed a higher effect (MD = 18.00 [14.63; 21.37]) compared with studies published before 2015 (k = 8; MD = 8.78 [3.34; 14.23]). Although statistically significant, these subgroup differences rely heavily on single-study comparisons and therefore must be interpreted cautiously (Supplementary Table 10). We observed no significant differences for subgroups defined by risk of bias, route of administration, follow-up time, frequency of administration, or trial center. Sensitivity analysis did not identify any statistically influential studies (Supplementary Table 11). Meta-regression based on dose showed no significant association between Vitamin C dose and treatment effect on TSAT ($QM(4) = 2.78$, $p = 0.59$). Dose explained none of the between-study heterogeneity ($R^2 = 0\%$), and substantial residual heterogeneity remained ($I^2 = 92.32\%$, supplementary Fig. 2B).

3.4.3. Ferritin levels

We conducted a meta-analysis with 9 studies with a total sample size of 390 subjects, comprising 190 individuals treated with ascorbic acid and 200 in the control group. We estimated the pooled MD at − 52.90 (95% CI: −105.43 to -0.38, $p = 0.04$, $I^2 = 39.0\%$) using a random effects model (Fig. 2C; See also Table 2 for all outcomes). The prediction interval ranged from − 177.03 to 71.22. The funnel plot appeared symmetrical (Fig. 3C). The Egger's regression test was not conducted due to a low number of studies. Subgroup analyses identified statistically significant differences for risk of bias ($p = 0.03$) and year group ($p = 0.04$). For risk of bias, studies rated as having some concerns showed a larger mean reduction (MD − 131.05; 95% CI − 204.41 to − 57.68) compared with low-risk studies (MD − 19.93; 95% CI − 66.56 to 26.70) and high-risk studies (MD − 193.45; 95% CI − 558.94 to 172.04). Similarly, the year-group analysis indicated that studies conducted before 2015 demonstrated a significant effect (MD − 69.00; 95% CI − 118.00 to − 19.99), whereas the after 2015 subgroup included only one study with a non-significant result (MD 35.55; 95% CI − 54.08 to 125.18). Because the year-group comparison is based on 8 vs. 1 study, these findings should be interpreted with caution due to the substantial imbalance across subgroups, which may limit the reliability of the

observed between-group difference. The rest of the subgroups did not show significant differences (supplementary table 12). Influence analysis identified the study by Tarng D., et al.1998[23], as influential, contributing notably to heterogeneity (Supplementary Table 13). Excluding this study showed a revised MD -32.55086 (95% CI: -77.76 to 12.66; I^2: 20%). Meta-regression based on dose showed a significant association between Vitamin C dose and treatment effect on Ferritin level (QM(4) = 9.13, p = 0.05). Dose explained the between-study heterogeneity (R^2 = 100%), and no residual heterogeneity remained (I^2 = 0.0%, supplementary Fig. 2C).

3.4.4. Iron Levels

We conducted a meta-analysis with 5 studies with a total sample size of 204 subjects, comprising 102 individuals treated with ascorbic acid and 102 in the control group. Changes from baseline were calculated for all included studies. We estimated the pooled MD at − 4.62 (95% CI: -44.37 to 35.13, p = 0.81, I^2 = 92.0%) using a random effects model (Fig. 2D; See also Table 2 for all outcomes). The prediction interval ranged from − 139.01 to 129.77. The funnel plot revealed asymmetry suggestive of potential publication bias (Fig. 3D). We did not conduct Egger's regression test due to the small number of studies. Subgroup analyses identified statistically significant between-group differences for study design (p < 0.0001) and frequency per week (p = 0.037). For study design, RCTs (k = 4) demonstrated a pooled MD of 13.19 (95% CI: −1.83 to 28.21; I^2 = 90.7%), whereas the single cross-over trial (k = 1) showed a markedly different effect of − 102.20 (95% CI: −153.17 to − 51.23). Similarly, frequency-based subgroups showed heterogeneous effects, with the "3 sessions" subgroup (k = 2) yielding an MD of 24.24 (95% CI: 4.10 to 44.37; I^2 = 87.3%), while the "3 sessions in the first week" subgroup (k = 2) showed − 44.47 (95% CI: −151.60 to 62.66; I^2 = 94.2%). However, these significant findings must be interpreted with caution because the comparisons involve highly unbalanced subgroup sizes, including contrasts between groups with as many as 4–8 studies versus subgroups represented by only 1 study, which limits the robustness and generalizability of these differences (Supplementary Table 14). The rest of the subgroups studied were not statistically significant. Sensitivity analysis identified the study by Jalalzadeh M., et al.[28] as influential (Supplementary Table 15). Excluding this study showed an MD of 13.19 (95% CI: -1.83 to 28.21; I^2: 90%). Meta-regression based on dose showed no significant association between Vitamin C dose and treatment effect on Iron level (QM(2) = 1.58, p = 0.45). Dose explained some of the between-study heterogeneity (R^2 = 0.0%), and substantial residual heterogeneity remained (I^2 = 98.11% supplementary Fig. 2D).

3.4.5. TIBC

We conducted a meta-analysis with 6 studies with a total sample size of 280 subjects, comprising 145 individuals treated with ascorbic acid and 135 in the control group. We estimated the pooled MD at − 34.36 (95% CI: −59.08 to − 9.63, p < 0.01, I^2 = 85.7%) using a random effects model (Fig. 2E). The prediction interval ranged from − 110.01 to 41.30. The funnel plot revealed asymmetry suggestive of potential publication bias (Fig. 3E; See also Table 2 for all outcomes). We did not conduct Egger's regression test due to the small number of studies (< 10). Subgroup analyses identified statistically significant differences across several variables. Risk of bias demonstrated a marked contrast (p < 0.01), with studies rated as low risk showing a larger reduction in TIBC (MD = − 61.90; 95% CI, − 75.20 to − 48.60) compared with high-risk studies (MD = − 13.21; 95% CI, − 23.56 to − 2.86). Study design also reached significance (p = 0.0104), where RCTs yielded a stronger effect (MD = − 42.38; 95% CI, − 66.16 to − 18.61) compared with the single cross-over study (MD = 5.00; 95% CI, − 22.37 to 32.37). Significant heterogeneity across follow-up duration (p < 0.01) showed that studies with 6-month follow-up reported the largest reduction (MD = − 61.72; 95% CI, − 75.11 to − 48.33), whereas 3-month (MD = − 16.17; 95% CI, − 47.95 to 15.60) and 2-month (MD = − 13.74; 95% CI, − 25.99 to − 1.49) follow-ups demonstrated smaller effects. Center type produced another significant difference (p = 0.05), with single-center trials showing a greater decrease in TIBC (MD = − 52.88; 95% CI, − 71.98 to − 33.78) than multi-center studies (MD = − 10.23; 95% CI, − 24.70 to 4.24). Finally, the year of publication was significant (p = 0.02), as studies published after 2015 reported stronger effects (MD = − 62.20; 95% CI, − 79.47 to − 44.93) compared with earlier studies (MD = − 27.08; 95% CI, − 53.15 to − 1.01). There were no statistically significant differences between groups across the rest of the studied variables (Supplementary Table 16).

Sensitivity analysis identified the study by Attallah N., et al.[27] as influential, showing a notable impact on heterogeneity (Supplementary Table 17). Excluding this study showed a revised MD of -26.77 (95% CI: -42.31 to -11.23, I^2 = 51.8%). Meta-regression based on dose showed no significant association between Vitamin C dose and treatment effect on Iron level (QM(4) = 0.84, p = 0.93). Dose explained none of the between-study heterogeneity (R^2 = 0.0%), and substantial residual heterogeneity remained (I^2 = 93.96%, supplementary Fig. 2E).

3.4.6. EPO dosage U/kg/week

We conducted a meta-analysis with 3 studies with a total sample size of 124 subjects, comprising 67 individuals treated with ascorbic acid and 57 in the control group. Using random effects model the estimated the pooled MD at − 21.29 (95% CI: −27.73 to 14.84, p < 0.01, I^2 = 0.0%; Fig. 2F; see also Table 2 for all outcomes). The prediction interval ranged from − 35.43 to − 7.14. The funnel plot revealed a symmetry suggestive of low publication bias (Fig. 3F). Egger's regression test was not conducted due to the small number of studies.

Table 2
Meta-analysis outcomes

Variable studied	Studies	# of participants	Effect size RR (95% CI, I2)	p-value
Hemoglobin	**9**	**395**	1.03 (95% CI: 0.63 to 1.43, 88.0%)	**< 0.01**
Serum Iron	**6**	249	−4.62 (95% CI: −44.37 to 35.13, 92.0%)	0.81
TIBC	**6**	**280**	−34.36 (95% CI: −59.08 to − 9.63, 85.7%)	**< 0.01**
TSAT	**8**	**360**	9.87% (95% CI: 4.69 to 15.06, 93.7%)	**< 0.01**
Ferritin	**9**	**390**	−52.90 (95% CI: −105.43 to -0.38, 39.0%)	**0.04**
EPO dosage	6	269	−21.29 (95% CI: −27.73 to 14.84, 0.0%)	**< 0.01**

TIBC: Total iron binding capacity. **TSAT**: Transferrin saturation. **EPO**: Erythropoietin.

3.4.7. Assessment of the certainty of the evidence and summary of findings

According to the GRADE assessment[19], the certainty of evidence varied across outcomes. Evidence for Hb, serum iron, and TIBC was rated as very low, primarily due to serious inconsistency and imprecision. Evidence for TSAT and EPO dose (units/kg/week) was rated as low, owing to serious inconsistency and risk of bias. The certainty of evidence for ferritin was rated as moderate, although it was also affected by inconsistency (Supplementary Table 20).

4 Discussion

This systematic review and meta-analysis included eight RCTs and two crossover trials with 431 anemic HD patients receiving ESA therapy, addressing ESA hyporesponsiveness in CKD. Ascorbic acid dosages varied widely, from 1,500 mg to 7,500 mg, administered 3 to 30 times per month. The KDIGO 2025 guideline for anemia in CKD prioritizes ESA and iron supplementation; it does not include ascorbic acid in its treatment recommendations[4]. Although the KDIGO 2024 CKD management guideline identifies high-dose ascorbic acid as a potential risk factor for kidney injury via calcium oxalate deposition, it does not specify a dosage and refers only to non-dialysis patients[32]. In our results, ascorbic supplementation was associated with statistically significant increase in Hb and TSAT levels, as well as a reduction in TIBC, ferritin levels, and EPO dosage U/kg/week. However, serum iron did not reach statistical significance. According to GRADE assessment, the certainty of evidence was very low for Hb, iron, and TIBC, and low for TSAT, and EPO dose (Units/kg/week) primarily due to serious inconsistency, imprecision, and suspected publication bias[18, 19].

Our findings align with a previous meta-analysis by Deved et al (2009)[33], which employed similar methods and concentrated on intravenous (IV) ascorbic acid and hematologic outcomes. However, their analysis included studies of acid doses ranging from 500 mg IV once weekly to 500 mg IV 3 times per week, indicating notable heterogeneity in treatment protocols. In our analysis, a statistically significant increase in Hb levels was observed following ascorbic acid administration (MD = 1.03 g/dL; 95% CI: 0.63 to 1.43, $p < 0.01$, $I^2 = 88.0\%$), suggesting a potential benefit, although the certainty of evidence is very low as an adjunct therapy for the management of in ESA-hyporesponsive HD patients. Sensitivity analysis excluding the outlier study yielded a comparable pooled effect size (MD 0.86 g/dL; CI: 0.62 to1.09; $I^2 = 0.0\%$), leading to a complete resolution of heterogeneity, although this finding should be interpreted cautiously given the overall low certainty of evidence. By including both parallel and crossover RCT designs, our study enhanced statistical power and the external validity of the results reported by Deved et al[33]la similar increase in Hb (WMD = 0.9 g/dL; 95% CI: 0.5 to 1.2; $I^2 = 0.0\%$) in HD patients. Additionally, in a previous systematic review and meta-analysis by Deng et al (2023)[34]a moderate statically significant increase in Hb levels following ascorbic acid supplementation in patients diagnosed with iron deficiency anemia (IDA) following ascorbic acid supplementation (MD = 0.14 g/dL; 95% CI: 0.08–0.20; $p \leq 0.01$).

Similarly, our findings demonstrated a statistically significant increase in TSAT percentage (MD = 9.87%; 95% CI: 4.69 to 15.06, $p < 0.01$, $I^2 = 93.7\%$), consistent with Deved et al[33], (WMD = 7.9%; 95% CI: 5.2 to 10.5%; $I^2 = 0.0\%$). This supports the idea of improved iron bioavailability for erythropoiesis, particularly relevant to iron utilization. Heterogeneity from our study may be explained by differences in baseline TSAT levels, routes of ascorbic acid administration, and dialysis efficacy.

On the other hand, we observed a statistically significant reduction in TIBC (MD = − 34.36 µg/dL; 95% CI: −59.08 to − 9.63, $p < 0.01$, $I^2 = 85.7\%$), although interpretation should be made with caution due to high heterogeneity across studies. Additionally, our meta-analysis demonstrated a significant reduction in EPO dose requirements (MD at − 21.29 U/kg/week; 95% CI: −27.73 to 14.84, $p < 0.01$, $I^2 = 0.0\%$). with Deved et al[33], who reported a significant reduction in EPO dosing (WMD = 17.1 U/kg/week; 95% CI: −26.0 to − 8.2; $I^2 = 1.6\%$). The high heterogeneity in our study may be related to population differences, baseline anemia severity, ESA-hyporesponsive patients, or more comprehensive iron management. In support of this, Koulouridis et al[35], highlighted in a meta-regression that ESA hyporesponsiveness is more common in older, comorbid patients, and those with low GFR-characteristics (WMD = − 34 µg/L; 95% CI: −106 to 37; $I^2 = 0.0\%$). In this context, ascorbic acid may improve TSAT not only by promoting iron absorption but also through its anti-inflammatory properties, which can suppress hepcidin expression, facilitating the mobilization of functional iron, thereby improving iron bioavailability in HD patients and leading to decreased EPO requirements[36].

Ferritin levels showed a significant reduction after ascorbic acid supplementation (MD = − 52.90 ng/mL (95% CI: −105.43 to -0.38, $p = 0.04$, $I^2 = 39.0\%$), aligning with Hajian et al (2022)[37], a triple-blind RCT, reported a significant reduction in ferritin in HD patients with functional IDA ($p \leq 0.05$), suggesting an anti-inflammatory effect. Similarly, Bashardoust et al (2018)[38] an RCT found a reduction in ferritin in HD patients with functional IDA ($p \leq 0.05$), reinforcing the possible therapeutic value of ascorbic acid. These findings reinforce the notion that elevated ferritin in CKD often reflects inflammation.

Serum iron levels remained non-statically significant (MD = − 4.62 µg/dL (95% CI: -44.37 to 35.13, p = 0.81, I^2 = 92.0%). Deved et al[33] did not report on this outcome, limiting direct comparison. The high heterogeneity may reflect differences in baseline iron statuses, measurement techniques, or inconsistent ascorbic acid dosing protocols. Nevertheless, Hajian et al[37] emphasized that IDA is common in HD patients, and ascorbic acid may improve iron absorption from the intestine, facilitates the release of iron from ferritin, and enhances erythropoiesis through its antioxidant properties.

Overall, this meta-analysis suggests a possible role for ascorbic acid as a supportive therapy in managing anemia in CKD patients on HD. Although not currently recommended by KDIGO guidelines, its use may be particularly beneficial in ESA-hyporesponsive cases, which affect an estimated 12.5–30.3% of patients[4], including inflammation, iron dysregulation, and oxidative stress) ascorbic acid's antioxidant and anti-inflammatory effects are particularly relevant for these patients.

Importantly, one limitation to objectively demonstrating the therapeutic impact of ascorbic acid is that most included studies focused exclusively on ESA-hyporesponsive patients with Hb levels below 11 g/dL. These trials did not assess more robust endpoints, such as full correction of anemia (e.g., Hb > 12 g/dL) or an increase in Hb greater than 2 g/dL, thresholds commonly used in hematology and gastroenterology studies[39–41]. This limited approach may have underestimated the potential benefit of ascorbic acid, particularly among broader HD populations, including those with milder or non-refractory anemia.

Therefore, further well-designed clinical trials are warranted to clarify ascorbic acid’s role, particularly in hyporesponsive patients. Considering its low cost, accessibility, and favorable safety profile, ascorbic acid remains a promising adjunct therapy. Therefore, it should be personalized based on inflammation status, iron parameters, and dialysis adequacy to optimize anemia management and improve patient outcomes.

Additionally, future research should explore the potential synergy of ascorbic acid with newer third-generation intravenous iron formulations, even in non-refractory HD patients, to evaluate whether broader application could enhance anemia correction and reduce ESA dependency. However, these findings should be interpreted with caution, as the certainty of evidence was predominantly low to very low across most outcomes according to GRADE.

4.1 Strengths and limitations

This study has several strengths, such as the inclusion of both RCTs and cross-over trials, which enabled a comprehensive synthesis of randomized evidence in a field where trial numbers and sample sizes are limited. This approach maximized statistical power and improved precision of effect estimates for hemoglobin response and EPO requirements, while preserving the benefits of randomization. However, there are some important limitations. Most included studies were published over a decade ago, with only two RCTs conducted within the last five years, potentially limiting applicability to current clinical practice given advances in dialysis and treatment protocols. Inconsistencies in erythropoietin dose reporting hindered standardization and dose-response assessment. Heterogeneity in the study population is driven by differences in dialysis duration, serum iron status, and anemia etiology, which is driven by differences in dialysis duration, serum iron status, and anemia etiology further complicates interpretation. These findings emphasize the need for additional research to define optimal treatment parameters and identify patient subgroups most likely to benefit.

5 Conclusion

This systematic review and meta-analysis indicate that ascorbic acid supplementation may be associated with modest hematologic improvements; however, the certainty of evidence is low to very low in erythropoietin-hyporesponsive hemodialysis patients. Across randomized and crossover trials, vitamin C was associated with significant increases in hemoglobin and transferrin saturation and reductions in total iron-binding capacity, suggesting improved iron mobilization and utilization rather than expansion of circulating iron stores. A modest reduction in weight-adjusted erythropoietin dose was also observed, indicating potential enhancement of ESA responsiveness, whereas serum iron concentrations did not change significantly. Changes in ferritin were heterogeneous across studies, likely reflecting differences in inflammation status and baseline iron stores.

The certainty of evidence ranged from very low to low for most outcomes, with moderate certainty for ferritin, driven primarily by substantial heterogeneity, imprecision, and limited sample sizes, which constrain confidence in the clinical relevance of these findings. Importantly, long-term safety outcomes, including oxalate accumulation, and patient-centered endpoints such as quality of life or transfusion requirements, were not evaluated. Consequently, current evidence is insufficient to support routine use of ascorbic acid in ESA-hyporesponsive anemia. Well-designed, adequately powered trials with standardized dosing, extended follow-up, and robust safety and clinical outcome assessment are needed to clarify its therapeutic role.

Abbreviations

o **CKD**
Chronic Kidney Disease
o **CRP**
C–reactive protein
o **eGFR**
estimated Glomerular Filtration Rate
o **EPO**
Erythropoietin
o **ESAs**
Erythropoiesis–Stimulating Agents

o **Hb**
Hemoglobin
o **HD**
Hemodialysis
o **IDA**
Iron Deficiency Anemia
o **KDIGO**
The Kidney Disease: Improving Global Outcomes
o **TIBC**
Total Iron Binding Capacity
o **TSAT**
Transferrin Saturation
o **WHO**
World Health Organization

Declarations

Disclosure

• Ethics statement: Given that this meta-analysis utilized previously published data from studies that had already obtained ethics approval and consent to participate, no additional ethics approval or consent was required for this research.

•Availability of data and materials: All the data used to perform this analysis are publicly available in the referenced articles. The rest of the material is at the author's disposal upon reasonable request.

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Author's contributions:

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Figures

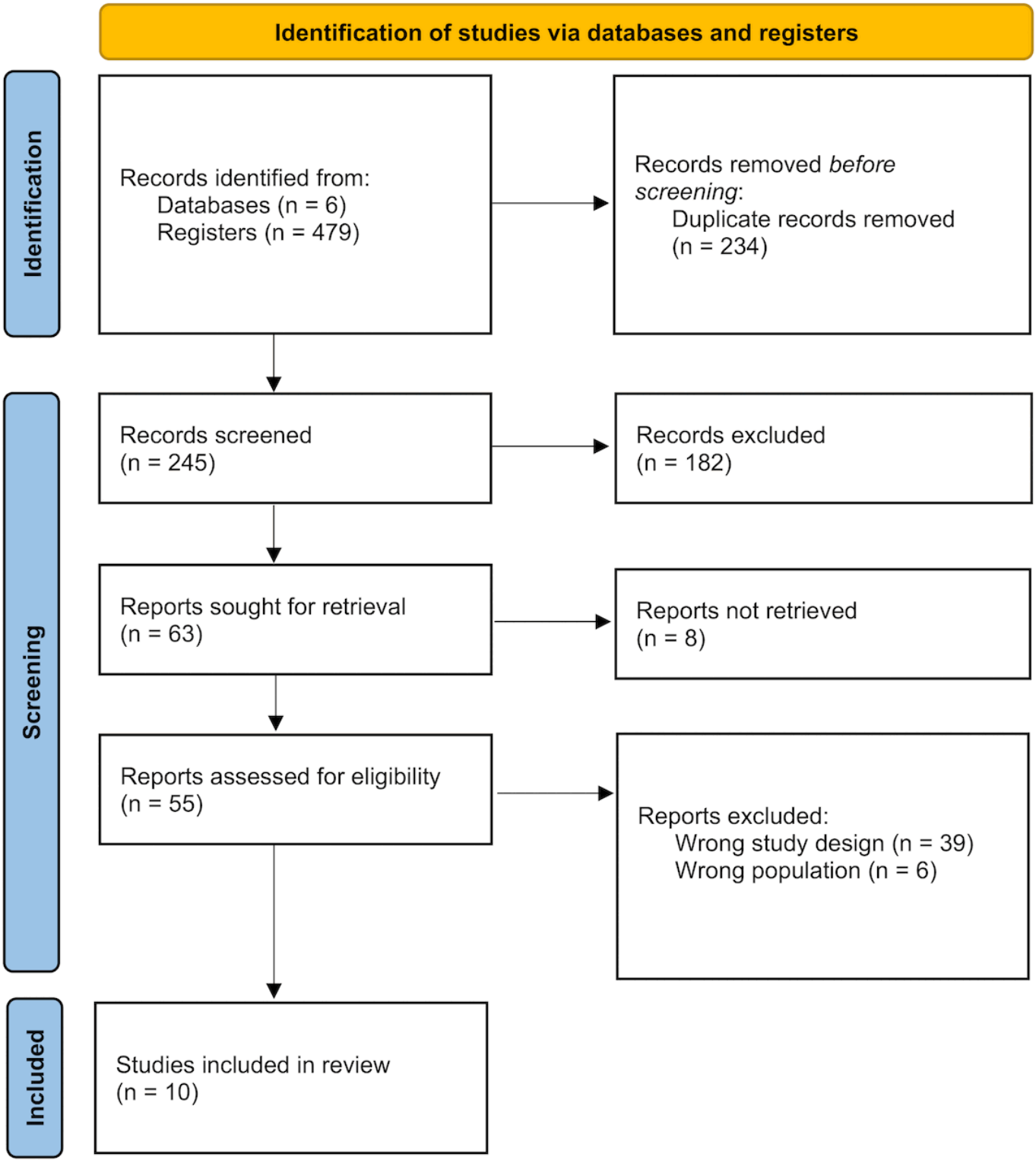


Figure 1

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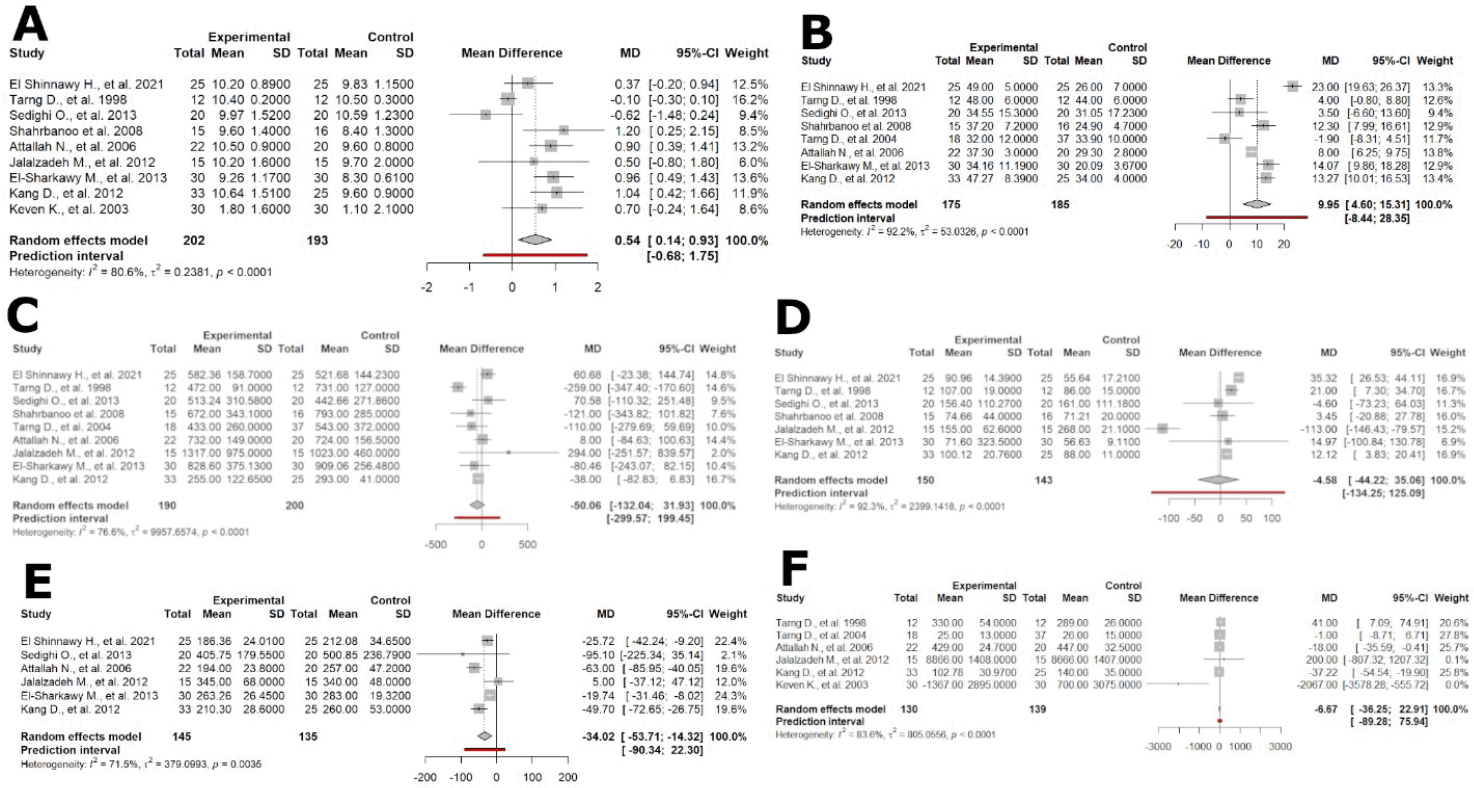


Figure 2

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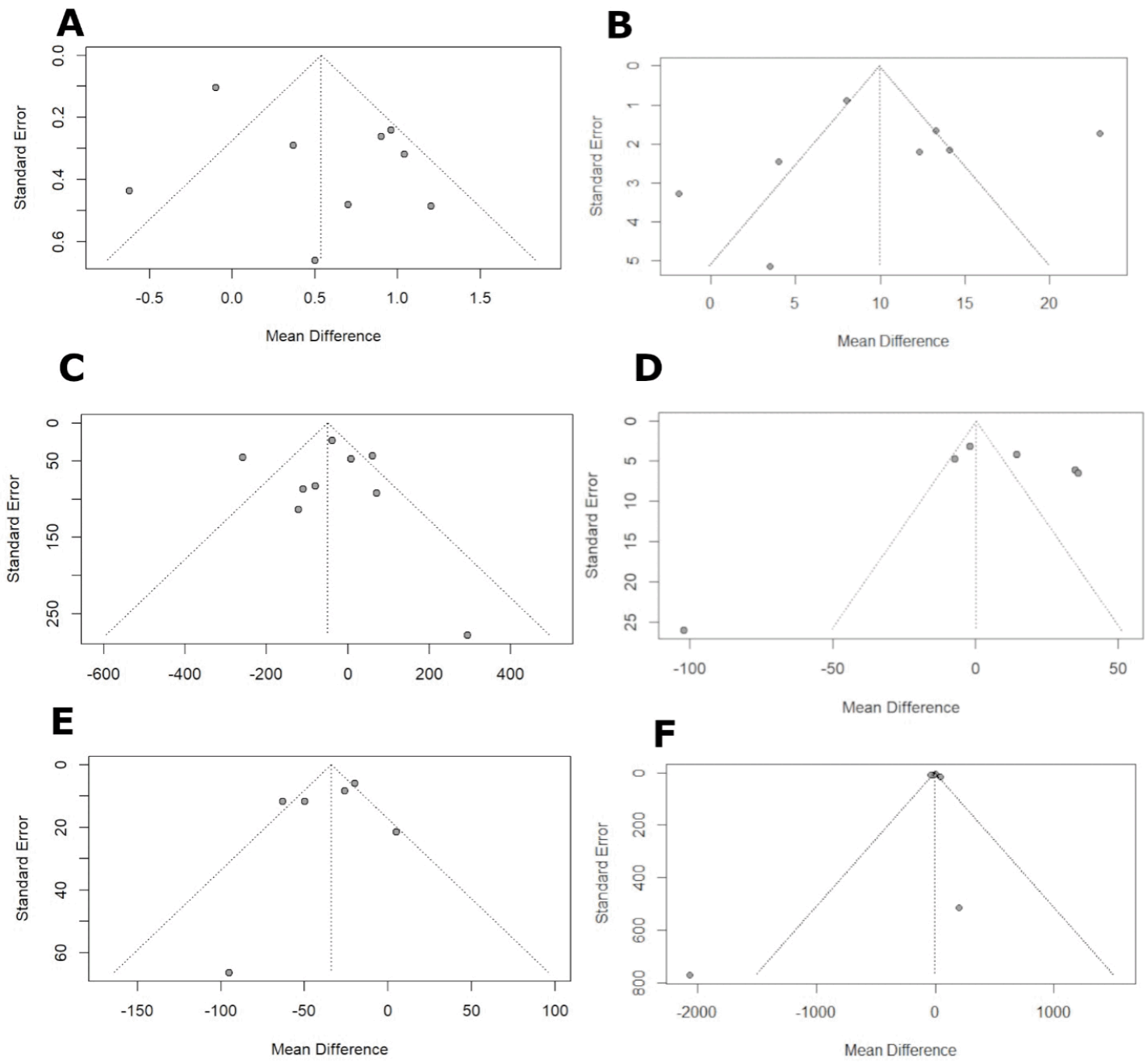


Figure 3

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