REVIEW

# Clinical Outcomes Related to the Gastrointestinal Trophic Effects of Erythropoietin in Preterm Neonates: A Systematic Review and Meta-Analysis

**Anitha Ananthan,[1] Haribalakrishna Balasubramanian,[2] Shripada Rao,[3,4] and Sanjay Patole[4,5]**

*[1] Department of Neonatology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India; [2] Department of Neonatology, Surya Mother and Child Care Hospital, Mumbai, India; [3] Department of Neonatal Pediatrics, Princess Margaret Hospital for Children, Perth, Western Australia, Australia; [4] Center for Neonatal Research and Education, University of Western Australia, Perth, Australia; and [5] Department of Neonatal Pediatrics, King Edward Memorial Hospital for Women, Perth, Western Australia, Australia*

## ABSTRACT

Erythropoietin (EPO) plays an important role in the development and maturation of the gastrointestinal tract. Recombinant EPO (rEPO) has been used to prevent anemia of prematurity. The gastrointestinal trophic effects of EPO may reduce feeding intolerance and necrotizing enterocolitis (NEC) in preterm neonates. The aim of this systematic review of randomized controlled trials (RCTs) was to evaluate the effects of rEPO on clinical outcomes such as feeding intolerance, stage II or higher NEC, any stage NEC, sepsis, retinopathy of prematurity, and bronchopulmonary dysplasia in preterm neonates. Twenty-five RCTs (intravenous: 13; subcutaneous: 10; enteral: 2; $n = 4025$) were eligible for inclusion. Meta-analysis of data from 17 RCTs (rEPO compared with placebo) with the use of a fixed-effects model showed no significant effect of rEPO on stage II or higher NEC (RR: 0.87; 95% CI: 0.64, 1.19; $P = 0.39$). Meta-analysis of data from 25 RCTs (rEPO compared with placebo) showed that rEPO significantly decreased the risk of any stage NEC [cases/total sample: 120/2058 (5.83%) compared with 146/1967 (7.42%); RR: 0.77; 95% CI: 0.61, 0.97; $P = 0.03$]. Only one RCT reported on time to full feedings. Meta-analysis of data from 15 RCTs showed a significant reduction in late-onset sepsis after rEPO administration (RR: 0.81; 95% CI: 0.71, 0.94; $P = 0.004$). Meta-analysis of 13 RCTs showed no significant effect of rEPO on mortality, retinopathy of prematurity, and bronchopulmonary dysplasia. Prophylactic rEPO had no effect on stage II or higher NEC, but it reduced any stage NEC, probably by reducing feeding intolerance, which is often labeled as stage I NEC. Adequately powered RCTs are required to confirm these findings. *Adv Nutr* 2018;9:238–246.

Keywords: infants, erythropoietin, feed intolerance, necrotizing enterocolitis, preterm

## Introduction

The survival of extremely preterm infants has improved significantly following the advances in neonatal intensive care. Optimization of nutrition is a priority in this population, considering its short- as well as long-term benefits on growth and neurodevelopment. Feeding intolerance (e.g., abdominal distension, bile-stained gastric residuals) due to gastrointestinal immaturity is common in the first 2–3 wk of life in extremely preterm neonates born at <28 wk of gestational age (1). This population is also at high risk of necrotizing enterocolitis (NEC)—an illness with significant mortality and morbidity, including long-term neurodevelopmental impairment (1–3). In the absence of a reliable marker, feeding intolerance is often confused with early (stage I) NEC. The frequent stoppage of feeding due to the fear of NEC is associated with suboptimal nutrition in the early postnatal life of extremely preterm infants (3).

Despite implementing strategies such as antenatal glucocorticoids (4, 5), early preferential use of breast milk (6), and standardized feeding regimens (7–9), the burden of definite NEC (stage II or higher) continues to be high, especially in extremely preterm neonates. Probiotics reduce the risk of NEC and improve feeding tolerance, but issues such as the optimal strain or strains, dose, probiotic sepsis, and long-term safety need to be addressed (10–14). The safety and efficacy of lactoferrin in preventing NEC need to be confirmed

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Supplemental Methods, Supplemental Tables 1–3, Supplemental Figures 1–4, and Supplemental References are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Address correspondence to AA (e-mail: ani.gem81@gmail.com).
Abbreviations used: BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FEM, fixed-effects model; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; RCT, randomized controlled trial; REM, random-effects model; rEPO, recombinant erythropoietin; ROB, risk of bias; ROP, retinopathy of prematurity; VLBW, very low birth weight.

in further studies (15, 16). Considering the importance of early optimal nutrition, interventions that will improve the gastrointestinal maturity and function, thereby reducing feed intolerance and NEC, are needed for preterm, especially extremely preterm, infants.

Erythropoietin (EPO) is a glycoprotein hormone that regulates erythropoiesis (17). Halperin et al. (18) first reported the use of recombinant EPO (rEPO) in anemia of prematurity. Subsequently, many clinical studies have shown that rEPO stimulates erythropoiesis and reduces the need for transfusion for anemia of prematurity (19, 20). In addition to its erythropoietic effects, EPO exerts mitogenic, vasodilatory, and angiogenic effects in nonerythropoietic tissues, including the gastrointestinal tract, endothelial cells, neurons, splenic cells, and cardiomyocytes (21–26). EPO receptors are present on the luminal side of villi in human fetal and neonatal intestine, suggesting a physiologic role of EPO in the developing gut (23, 26). EPO treatment promotes cell division, stimulates enterocyte migration, and reduces enterocyte apoptosis (27). Investigators have reported that rEPO exerts a trophic effect on small bowel villi, stimulates the growth of mucosal cells, and increases the villus surface area, length, and density (28). EPO reduces experimental NEC-induced NO production (29) and promotes vasculogenesis, thereby increasing the nutrient supply to the bowel (30). Overall, these data support the hypothesis that the trophic effects of EPO on the gastrointestinal tract may benefit preterm neonates.

A systematic review of randomized controlled trials (RCTs) studying the effects of rEPO in preterm neonates was therefore conducted to report the outcomes reflecting its effects on gastrointestinal maturity and function (eg., feeding intolerence, stage II or higher NEC, sepsis). The minimum effective concentration for the action of EPO is more important than the routes of administration (31, 32). Results of an RCT showed that oral and subcutaneous EPO have similar effects in preterm low-birth-weight infants (33). Hence, it was hypothesized that the effects of EPO will be similar, irrespective of its route of administration.

## Methods

The Cochrane methodology was used for the conduct of this systematic review. RCTs comparing rEPO with placebo or standard treatment without rEPO supplementation were included. Primary outcomes were incidence of stage II or higher NEC (34) and "any stage" NEC. Secondary outcomes were as follows: *1*) feeding intolerance as defined by authors of the RCTs, *2*) time to reach full feedings, *3*) late-onset sepsis

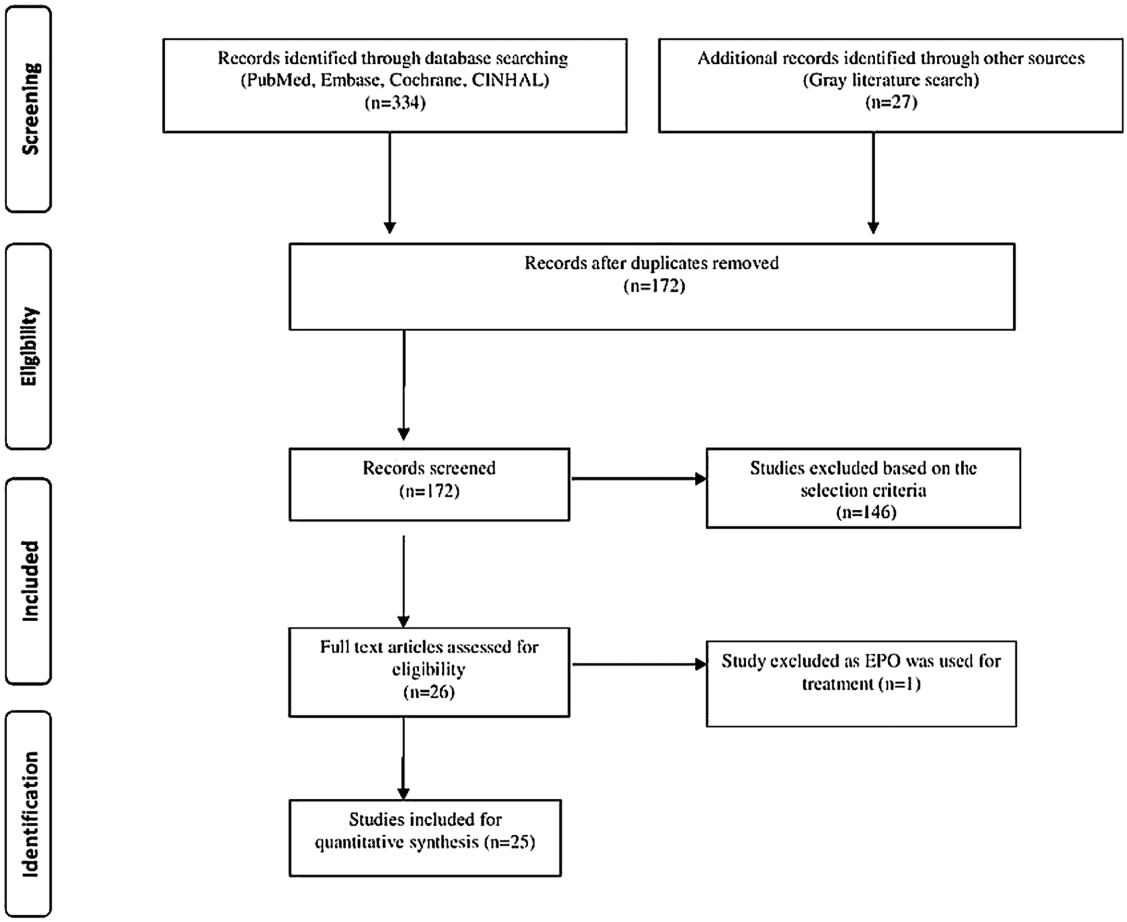


**FIGURE 1** Flowchart showing study selection process. EPO, erythropoietin.

(LOS: blood culture–positive infection 48 h after birth), *4*), bronchopulmonary dysplasia (BPD), and *5*) mortality. LOS was included as a secondary outcome because optimization of feeding is associated with a reduced risk of this outcome in preterm neonates. Given the concern that rEPO may be associated with increased risk of retinopathy of prematurity (ROP), it was included as a safety outcome. The details of the data sources that were searched, study selection process, data extraction, assessment of risk of bias (ROB), data synthesis, assessment of publication bias, and GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) evidence (35) are given in **Supplemental Methods**.

### Subgroup analysis

Subgroup analysis was planned on the basis of the route of rEPO administration.

### Sensitivity analysis

Considering the importance of random-sequence generation and allocation concealment in RCTs, sensitivity analyses were planned by excluding studies with a high ROB in these 2 domains separately (36). A sensitivity analysis was planned by excluding studies in which NEC was not the primary outcome.

### Analysis of data on very-low-birth-weight and extremely low-birth-weight neonates

We aimed to conduct separate analyses of studies by exclusively enrolling *1*) very-low-birth-weight (VLBW; birth weight <1500 g) or *2*) extremely low-birth-weight (ELBW; birth weight <1000 g) neonates considering that they are at high risk of NEC.

## Results

The literature search retrieved 361 potentially relevant citations. After carefully reviewing the abstracts, 189 duplicate studies were excluded. A total of 146 studies were excluded due to nonfulfillment of the inclusion criteria. A total of 26 studies were assessed for eligibility. One study was excluded becaise rEPO was used for treatment rather than for prevention of NEC (37). Finally, 25 RCTs (17, 38–60) were included in the review. The flow diagram of the study selection process is given in **Figure 1**, and the characteristics of the included studies are shown in **Supplemental Table 1**.

### Clinical studies

Among the included 25 RCTs ($n$ = 4025; EPO compared with control: 2058 compared with 1967), 13 studied the effect of intravenous rEPO, 10 studied the effect of subcutaneous rEPO, and 2 studied the effect of enteral rEPO on stage II or higher NEC in preterm infants. The sample size of the included RCTs ranged from 15 to 377. The rEPO dose varied depending on the route of administration (enteral: 88 U/kg; subcutaneous: 100–3000 U/kg; intravenous: 200–3000 U/kg). NEC was the primary outcome in only 2 of 25 RCTs. The detailed characteristics of the included studies,

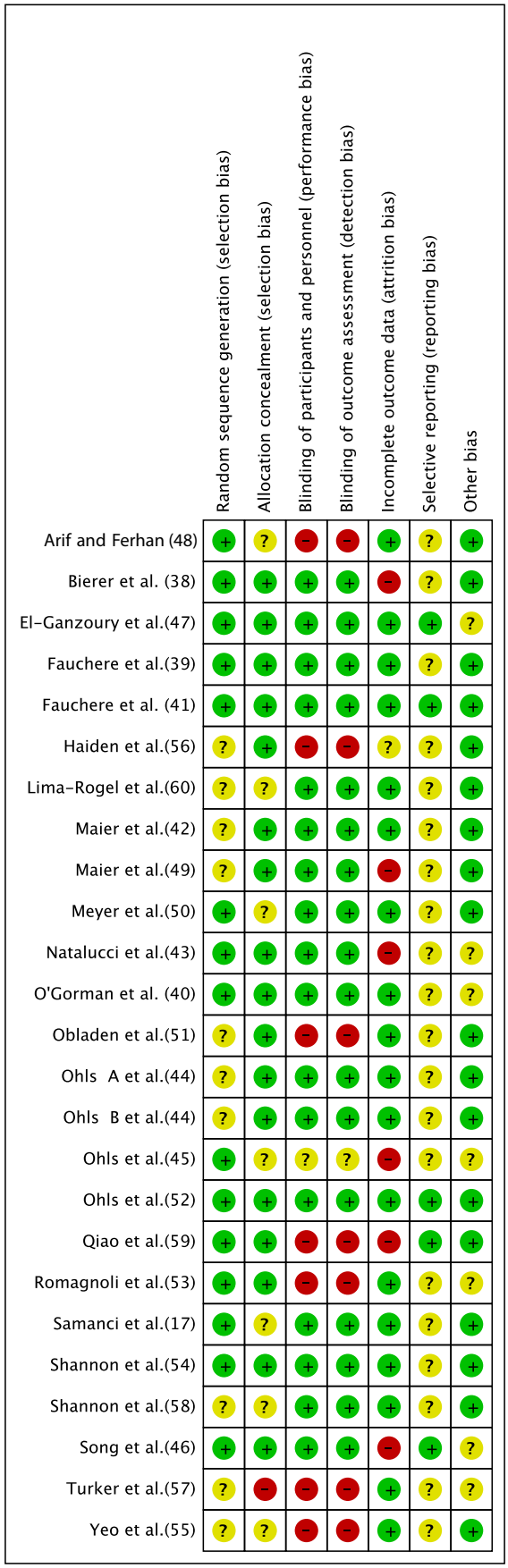


**FIGURE 2** Risk-of-bias summary of the included RCTs. RCT, randomized controlled trial.

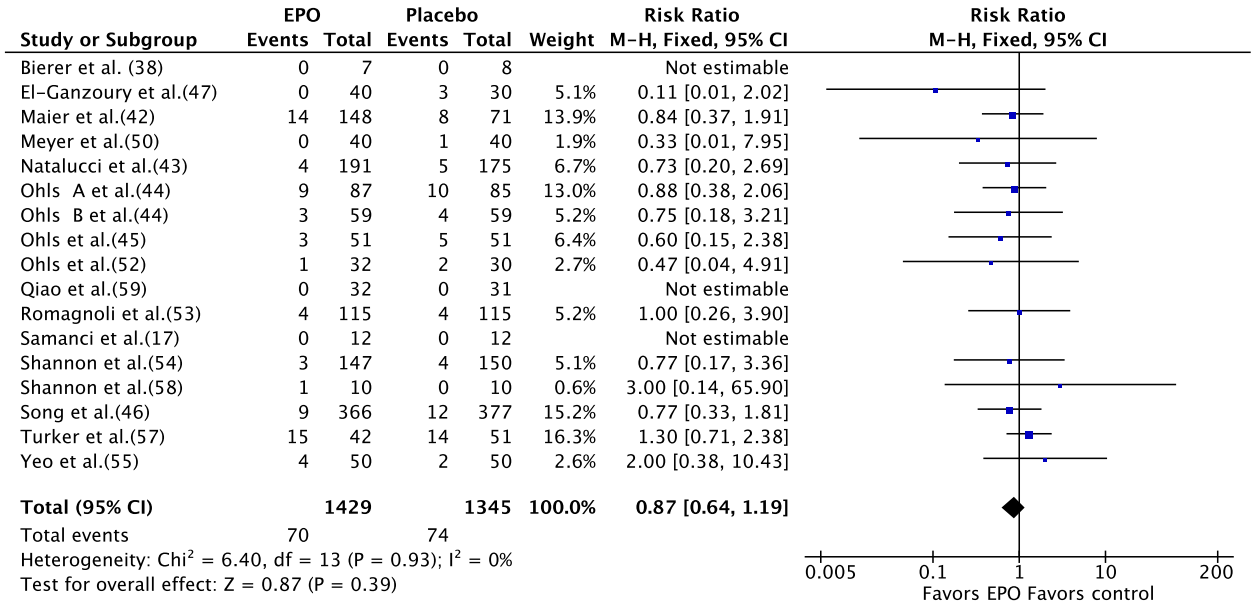


**FIGURE 3** Effect of rEPO on definite necrotizing enterocolitis (stage II or higher) in preterm neonates (fixed-effects model). EPO, erythropoietin; M-H, Mantel-Haenszel method; rEPO, recombinant erythropoietin.

including the route, dose, and duration of EPO supplementation, are given in Supplemental Table 1.

### ROB of included studies

All of the included RCTs ($n = 25$) had some methodologic weakness. Of the 25 RCTs, 15 (60%) were considered to have low ROB for the domain "random-sequence generation" and 17 (68%) were judged to have low ROB for "allocation concealment." Random-sequence generation was unclear in 10 RCTs (42, 44, 44, 49, 51, 55–58, 60), allocation concealment was unclear in 7 (17, 45, 48, 50, 55, 58, 60), blinding of participants and personnel was unclear in 1 (45), and the risk of performance bias was high in 7 RCTs (48, 51, 53, 55–57, 59). Blinding of outcome assessment and detection bias was high in 7 RCTS (48, 51, 53, 55–57, 59). The risk of attrition bias was high in 6 RCTs (38, 43, 45, 46, 49, 59) and unclear in 1 RCT (56). The information on reporting bias and other bias was unclear in 20 RCTs (17, 38–40, 42–45, 48–51, 53–58, 60) and 7 RCTs (40, 43, 45–47, 53, 57), respectively. The ROB summary of the included RCTs is shown in Figure 2.

### Outcomes

***Primary outcomes.*** Meta-analysis [fixed-effects model (FEM)] of data from the 17 RCTs (rEPO compared with placebo) showed no significant effect of rEPO on stage II or higher NEC (RR: 087; 95% CI: 0.64, 1.19; $P = 0.39$) (Figure 3). Meta-analysis of data from 25 RCTs ($n = 4025$) that compared rEPO with placebo or no rEPO showed that rEPO significantly decreased the incidence of any stage NEC [120/2058 (cases/total sample) (6.14%) compared with 146/1967 (7.42%); RR: 0.77; 95% CI: 0.61, 0.97; $P = 0.03$; $I^2 = 0$; number needed to treat = 59] (Figure 4). The results of meta-analysis that used a random-effects model (REM) were close to those based on FEM (RR: 0.79; 95% CI: 0.62, 1.00; $P = 0.05$; $I^2 = 0$; level of evidence: high] (**Supplemental Figure 1**).Visual inspection of the funnel plot suggested that publication bias was unlikely (Figure 5).

***Subgroup analysis.*** Results of our prestated subgroup (by route of administration) analysis showed that only intravenous rEPO significantly reduced any stage NEC [77/1254 (6.14%) compared with 99/1149 (8.61%); RR: 0.68; 95% CI: 0.51, 0.91; $P = 0.009$ by FEM] (Figure 4). The results remained significant when an REM was used (RR: 0.67; 95% CI: 0.49, 0.90; $P = 0.008$) (Supplemental Figure 1).

***Sensitivity analysis.*** The beneficial effects of rEPO on any stage NEC were observed in studies with low ROB for random sequence generation and for allocation concealment (**Supplemental Table 2**). Only 2 of 20 RCTs reported NEC as the primary outcome, and pooled data did not show beneficial effects.

***ELBW and VLBW infants.*** Preplanned separate analyses in this review showed that rEPO significantly reduced any stage NEC in studies exclusively enrolling VLBW [79/1723 (4.58%) compared with 111/1724 (6.43%); RR: 0.70; 95% CI: 0.53, 0.93; $P = 0.01$] but not ELBW [39/325 (12%) compared with 42/335 (12.53%); RR: 0.98; 95% CI: 0.66, 1.46; $P = 0.94$] infants.

***Summary of findings.*** The overall evidence as per GRADE guidelines is provided in **Supplemental Table 3**.

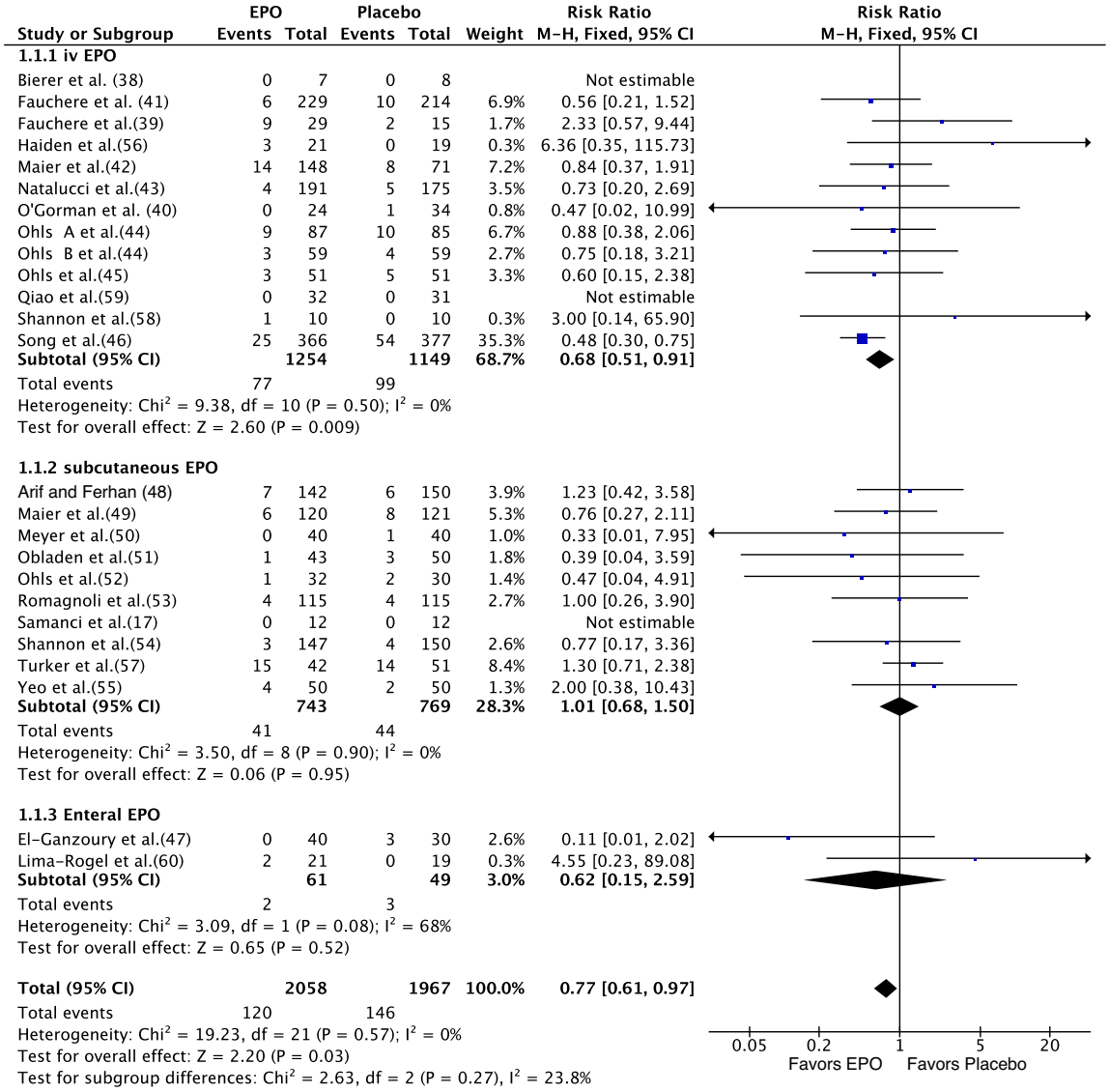


**FIGURE 4** Effect of rEPO on necrotizing enterocolitis in preterm neonates (fixed-effects model). EPO, erythropoietin; M-H, Mantel-Haenszel method; rEPO, recombinant erythropoietin.

***Publication bias.*** The funnel plot showed symmetrical distribution, suggesting that publication bias was less likely (Figure 5).

***Secondary outcomes.*** Time to full feedings and feeding intolerance were secondary outcomes in El-Ganzoury et al. (47) and Shannon et al. (58), respectively. El-Ganzoury et al. (47) reported a significant decrease in the time to full feedings (mean ± SD) in the enteral EPO group infants (EPO compared with placebo: 13.4 ± 4.9 compared with 16.3 ± 5.3 d; $P = 0.032$). Shannon et al. (58) reported feeding intolerance in 7 of the 147 (4.76%) compared with 7 of the 150 (4.66%) EPO infants compared with placebo-group infants; this was not significant. For mortality, in 13 of 25 RCTs that reported the outcome, meta-analysis showed no significant effect of rEPO on mortality [66/995 (6.63%) compared with 81/1010 (8.01%); RR: 0.78; 95% CI: 0.58; 1.04; $P = 0.09$]. Some of the included trials (39–41, 43–46, 48–50, 52–55, 60) reported a significant effect of rEPO on LOS [274/1655 (16.55%) compared with 332/1631 (20.35%); RR: 0.81; 95% CI: 0.71,0.94; $P = 0.004$] (Figure 6, **Supplemental Figure 2**).

***Safety.*** None of the included RCTs reported adverse effects related to the administration of rEPO. The incidence of ROP (38, 40–46, 48, 49, 52–57) and BPD (38–46, 48, 51–53, 55–57) reported in various included RCTs was comparable in rEPO and control-group neonates (**Supplemental Figures 3** and **4**).

## Discussion

This systematic review of 25 RCTs showed that rEPO had no effect on stage II or higher NEC, but it significantly decreased the incidence of any stage NEC in preterm neonates. The prestated subgroup analysis indicated that intravenous

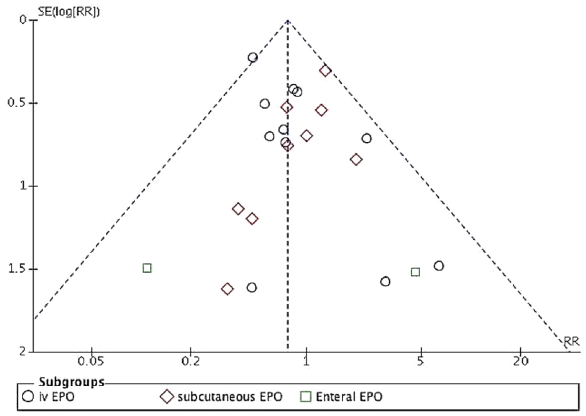


**FIGURE 5** Funnel plot of the included RCTs for assessing publication bias. EPO, erythropoietin; RCT, randomized controlled trial.

rEPO reduced the risk of any stage NEC. Improvement only in stage II or higher (i.e., definite) NEC is usually considered as a significant outcome in such studies. However, improvement in any stage NEC (stage I or higher) is important in the context of the gastrointestinal trophic effects of rEPO that are expected to reduce "feeding intolerance"—an entity that is often confused or reported as stage I NEC. The findings that LOS was reduced significantly and the risk of BPD, ROP, and mortality was not higher after EPO administration support the safety of rEPO in preterm neonates. To our knowledge, this is the first systematic review and meta-analysis of RCTs of rEPO in preterm neonates that reported outcomes (e.g., NEC and feeding intolerance) related to improvement in gastrointestinal maturity and function after the intervention.

The results of this review are in contrast to previous meta-analyses that focused on rEPO for reducing the need for transfusion for anemia of prematurity (19, 20). They did not report significant benefits of early (11 RCTs; $n = 1347$) (19) or late (6 RCTs; $n = 656$) (20) administration of rEPO on NEC (any stage or stage II or higher NEC) in preterm neonates. The likely reason for this difference is the inclusion of the large RCT ($n = 743$) by Song et al. (46) in this systematic review, which had 2465 more preterm neonates than the 2 previous reviews, increasing its power to detect a significant effect of EPO on NEC (19, 20).

RCTs with high ROB are known to overestimate the effect size, leading to spuriously optimistic results (36). It was reassuring to note that the results of the sensitivity analyses were significant after excluding studies with high ROB on random-sequence generation and allocation concealment separately. Subgroup analysis of 18 studies ($n = 3447$) including more mature preterm (born at <33 wk) VLBW neonates showed that rEPO reduced the incidence of any stage NEC (RR: 0.70; 95% CI: 0.53, 0·93; $P = 0.01$).The lack of benefits in ELBW neonates may relate to the small sample size of this subgroup ($n = 660$).

The effect of rEPO is based on the duration for which its critical blood concentration is maintained and this is unrelated to the route of administration (31). Subgroup analysis in this review showed a significant benefit of rEPO on any stage NEC only with the intravenous route. The lack of beneficial effect of subcutaneous EPO on NEC is difficult to explain, knowing that subcutaneous EPO has been shown to be beneficial in stimulating erythropoiesis in preterm infants (48, 61–64).

The strength of this review includes its comprehensive nature and robust methodology. Furthermore, the value of $I^2$, a marker of statistical heterogeneity, was zero, and REM results were close to FEM results, increasing their validity. The benefits of intravenous rEPO in reducing any stage NEC are valid considering the total sample size, consistency of results, narrow CIs, and very small $P$ values. The limitations include

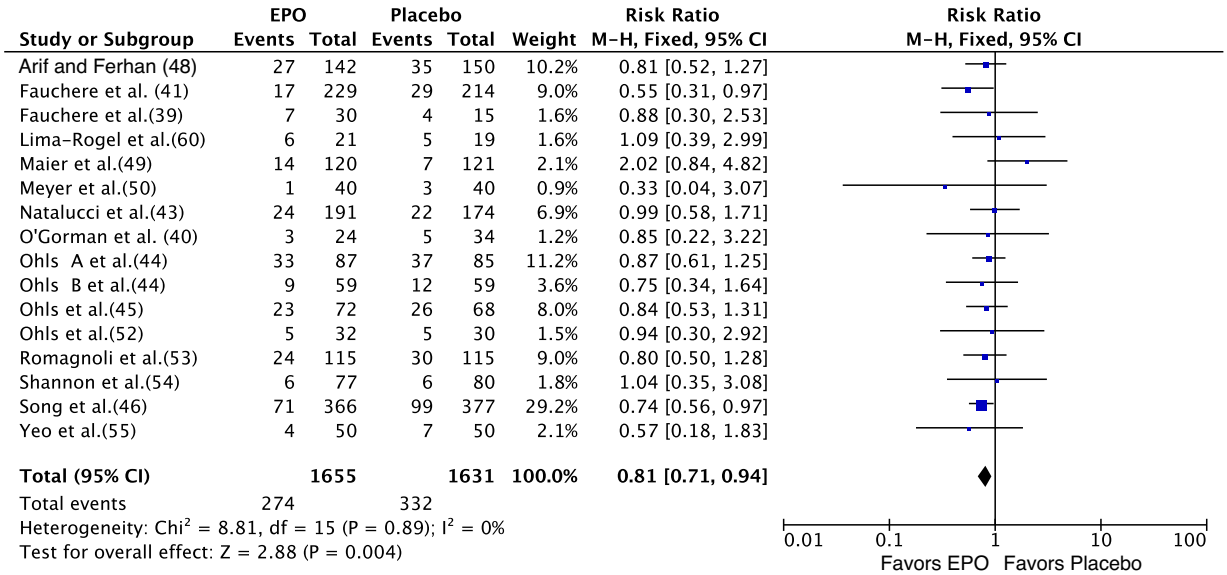


**FIGURE 6** Effect of rEPO on sepsis in preterm neonates (fixed-effects model). EPO, erythropoietin; M-H, Mantel-Haenszel method; rEPO, recombinant erythropoietin.

variations in the rEPO protocol in the included trials, the fact that NEC was not the primary outcome in majority of the trials, and data on NEC were not available from 40 of 57 RCTs of EPO for anemia of prematurity (19, 20).The use of Bell staging for classifying NEC is a limitation, but a universally agreed-on alternative classification is not yet available (65). Due to the lack of relevant data and small sample size, the effect of dose or AUC relation could not be explored in this review.

The neuroprotective effects of EPO are important in the context of our results (66, 67). Fischer et al. (68) reported a systematic review and meta-analysis of data from RCTs ($n = 4$; 1133 participants) (43, 45, 46, 52), assessing if prophylactic rEPO improves neurodevelopmental outcomes in very preterm infants (68, 65). Prophylactic rhEPO significantly reduced the incidence of children with a Mental Developmental Index <70 on the Bayley Scales of Infant Development assessment (primary outcome) at 18–24 mo of corrected age (OR: 0.51; 95% CI: 0.31, 0.81; $P < 0.005$; number needed to treat: 14). EPO had no effect on the secondary outcomes of Psychomotor Development Index <70, cerebral palsy, visual impairment, and hearing impairment (68). Lowe et al. (69) assessed the effect of erythropoiesis-stimulating agent (ESAs) exposure during the early postnatal period and family demographic factors on early childhood behavior. Preterm infants (birth weight: 500–1250 g) who had participated in an RCT of ESAs ($n = 35$) compared with placebo ($n = 14$) and term healthy infants (controls: $n = 22$) were followed at 3.5–4 y of age. The Socioeconomic Composite scores on behavioral symptoms ($P = 0.04$) and externalizing scales ($P = 0.04$) were significantly better in the ESA group than in the placebo group. An interaction was observed between study group and Socioeconomic Composite score ($P = 0.001$) (66, 69).

In summary, the results in this review indicate that rEPO, particularly intravenous rEPO, has the potential to prevent NEC in preterm infants. A definitive RCT is required to confirm our findings. Because the definition of stage II or higher NEC is more precise than "any stage NEC," the primary outcome interest for such an RCT could be "stage II or higher NEC." Another reason for choosing "stage II or higher NEC" as the primary outcome is the enormous burden associated with this condition in preterm infants (1, 2). The sample size for such a trial would be ~3000 (1500/arm) to detect a significant reduction of 30% in the risk of stage II or higher NEC (baseline incidence: 10%) in ELBW infants with 80% power and a significance of $P < 0.05$. Providing separate data for different stages of NEC and assessment of other enteral nutrition–related outcomes and long-term neurodevelopmental follow-up will be important aspects of such a trial.

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The authors' responsibilities were as follows—SP: was responsible for the concept and design, rechecked the data and analysis, and gave input for revision of the initial and final versions of the manuscript; AA and HB: performed the independent literature search, study selection, data extraction, and analysis, and wrote the first and final draft of the manuscript with guidance from SR and SP; SR: rechecked the methodology and interpretation; and all authors: read and approved the final manuscript.

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