

Efficacy and Safety of Erythropoietin to Prevent Acute Kidney Injury in Patients With Critical Illness or Perioperative Care: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Chen Zhao, MD, PhD, Zhenchuan Lin, MM, Qimei Luo, MD, Xi Xia, MD, Xueqing Yu, MD, and Fengxian Huang, MD

INTRODUCTION

Acute kidney injury (AKI), defined as an abrupt drop of renal function within a short period, is a frequent and serious complication in the intensive care unit (ICU) or after surgery, with an incidence of 7.7%–42% in patients with previous normal renal function.^{1,2} AKI or even a minor increase in serum creatinine level from baseline was independently associated with increased length of hospitalization, health care costs, cardiovascular events, and mortality.^{3,4} Although there have been many clinical studies on the protection of kidney function in patients with critical illness or perioperative care, such as the administration of N-acetylcysteine, atrial natriuretic peptide, and fenoldopam, the results of such interventions are somewhat contradictory or unproven.⁵ Consequently, it is paramount that more attention should be paid to explore effective preventative and therapeutic strategies for the management of AKI.

Erythropoietin (EPO), a 30-kDa glycoprotein hormone, is produced by the kidney to regulate the hematopoiesis in bone marrow, and recombinant human EPO has been widely used in the treatment of anemia, especially in end-stage renal disease and certain hematologic diseases.⁶ Interestingly, there is considerable evidence indicating that EPO acts as a novel renoprotective agent against ischemic, toxic, and septic AKI in animal experiments by reducing apoptosis, stimulating cell proliferation and eliciting its antioxidative and anti-inflammatory functions.^{7,8} Recently, a few randomized controlled trials (RCTs) analyzed the role of EPO to prevent AKI in patients within the ICU or after surgery who were at high risk of AKI.^{9–18} However, the results from these trials were inconsistent, partly because they involved single-site studies with small-scale samples.

Therefore, we conducted a systematic review and meta-analysis of RCTs to determine whether the use of EPO in patients with critical illness or perioperative care could ameliorate the incidence of AKI and assess its adverse event.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for

Objective: The aim was to investigate the efficacy and safety of erythropoietin (EPO) to prevent acute kidney injury (AKI) in patients with critical illness or perioperative care.

Methods: Randomized controlled trials comparing EPO with placebo for AKI prevention in adult patients with critical illness or perioperative care were searched in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Web of Science, and Clinical Trials.gov until October 2014. The outcomes of interest included the incidence of AKI, dialysis requirement, mortality, and adverse event. Fixed effect model was used to calculate the pooled risk ratio (RR) and 95% confidence interval (CI) for eligible studies.

Results: Ten randomized controlled trials involving 2759 participants were identified and included in the analysis. Compared with placebo, EPO administration did not reduce the incidence of AKI (RR, 0.97; 95% CI, 0.79–1.19; $P = 0.782$), dialysis requirement (RR, 0.72; 95% CI, 0.31–1.70; $P = 0.457$), or mortality (RR, 0.96; 95% CI, 0.78–1.18; $P = 0.705$). Moreover, EPO had no effect on the risk of adverse events, but estimations of RR were difficult due to their relatively infrequent occurrence.

Conclusions: This meta-analysis suggests that prophylactic administration of EPO in patients with critical illness or perioperative care does not prevent AKI, dialysis requirement, or mortality.

Key Words: critical illness, perioperative care, erythropoietin, acute kidney injury, meta-analysis

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From the Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health, Guangzhou, China.

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C. Zhao and Z. Lin have contributed equally to this study.

Reprints: Fengxian Huang, MD, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, 58th Zhongshan Rd II, Guangzhou 510080, China (e-mail: hfxyl@163.net).

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Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations.¹⁹

Search Strategy

A comprehensive search was conducted in MEDLINE (through OVID), EMBASE (through OVID), the Cochrane Central Registry of Controlled Trials, and the Web of Science from inception to October 2014. Medical subject headings, entry terms, and text word searches included the following terms: “critical illness,” “critical care,” “intensive care,” “ICU,” “severely ill,” “perioperative care,” “perioperative period,” “erythropoietin,” “epoetin,” “EPO,” “erythropoiesis stimulating protein,” “darbepoetin,” “acute kidney injury,” “acute renal injury,” “acute renal insufficiency,” “acute kidney insufficiency,” “acute renal failure,” “acute kidney failure,” “acute tubular necrosis,” “AKI,” “ARF,” and “ATN.” There was no restriction on language or publication date. In addition, other potentially relevant studies were searched from the Clinical Trials database (<http://clinicaltrials.gov/>) for completed trials and the references cited in the retrieved articles and pertinent reviews.

Study Selection Criteria

All titles, abstracts, and full articles were independently searched and evaluated using predesigned inclusion and exclusion criteria by 2 investigators (C.Z. and Z.C.L.). Any discrepancies were resolved by consensus with a third investigator (Q.M.L.) if necessary, which was infrequent.

Studies were included when the following inclusion criteria were met: (1) RCTs, (2) adult patients (age ≥ 18 years) with critical illness or perioperative care, (3) use of EPO for prevention at least in 1 treatment group, (4) control group receiving placebo or usual treatment, (5) reported incidences of AKI in both groups, and (6) for more than 1 publication on the same trial, data from the most recent or complete report were used. Exclusion criteria were as follows: (1) nonrandomized or pseudo-randomized design, retrospective study, case report, and case series; (2) enrolled participants undergoing chronic dialysis therapy, nephrectomy, or transplant surgery (heart, liver, or kidney) due to their complex situations; (3) lack of a control group; (4) studies not addressing the target outcome as mentioned above; and (5) use of EPO as a treatment agent after the occurrence of AKI.

Data Extraction and Risk of Bias Assessment

Two investigators (Q.M.L. and X.X.) independently extracted data from all eligible trials and assessed the risk of bias. Disagreements were resolved through consensus with a third investigator (C.Z.). Data included the first author, publication year, nation of origin, study participants, sample size, whether EPO was used previously, mean age, proportions of male patients, hypertension, and diabetes mellitus, mean baseline hemoglobin and serum creatinine levels, mean blood transfusion volume, treatment regimens of the EPO-based intervention and control groups, definition of AKI, and outcomes measured. The primary outcome was the incidence of AKI, the secondary outcomes included dialysis requirement, 30-day mortality, and the adverse events. When the study had several dosage intervention arms,¹⁴ all EPO

intervention arms were combined as one arm by weighted means. In the case of missing or incomplete data, the corresponding author of the original trial was contacted by e-mail for additional information.

The risk of bias in the eligible trials was assessed according to the Cochrane Collaboration tool (version 5.1.0),²⁰ which included 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. In each item, an answer of “low risk of bias” suggested sufficient and correct information, “high risk of bias” indicated that the item was reported incorrectly, and “unclear risk of bias” meant insufficient or unmentioned details for judgment.

Statistical Analysis

For dichotomous outcomes (the incidence of AKI, dialysis requirement, and mortality), data were pooled as risk ratio (RR) with 95% confidence interval (CI). The between-study heterogeneity was quantified by Cochran’s Q -statistic and the inconsistency index (I^2). If there was significant heterogeneity among studies ($P_{Q\text{-statistic}} < 0.10$ and $I^2 > 50\%$), the random effect model (DerSimonian and Laird method) was adopted to pool the results; otherwise, the fixed effect model (Mantel-Haenszel method) was used. Subgroup analysis was performed based on (1) entirely perioperative care, (2) no use of EPO previously, (3) at least 2 doses of EPO, and (4) patients at high risk for AKI according to each study. Sensitivity analysis was conducted to assess the influence of individual studies on the pooled estimate of effects by withdrawing 1 study at a time. Publication bias was explored by the funnel plot and Egger’s test. An asymmetric funnel plot and $P_{\text{Egger’s test}}$ less than 0.05 indicated a significant publication bias. The assessment for the risk of bias was performed with Review Manager software (version 5.3 from <http://tech.cochrane.org/revman>).

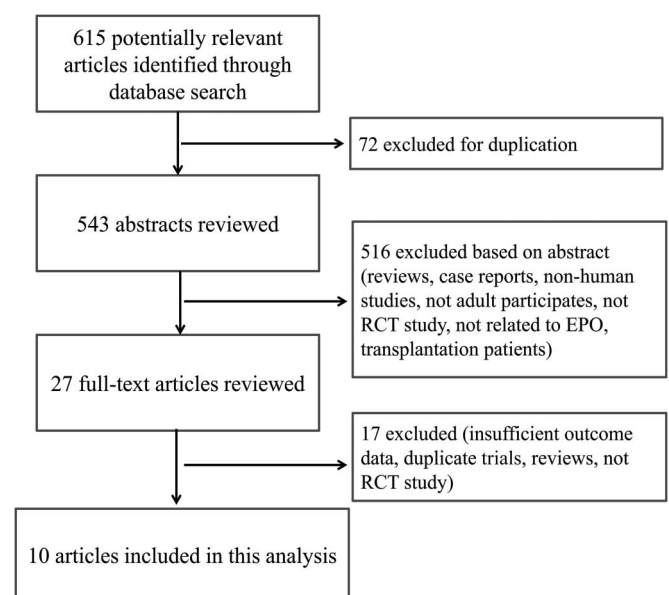


FIGURE 1. Flow diagram of article selection approach.

TABLE 1. Baseline Clinical Characteristics of Included Studies

First Author, yr	Country	Study Participants	No. Participants (EPO/Control)	Prior EPO Use	Mean Age, yr*	Men, %*	HP, %*
Corwin HL, 2002 ⁹	USA	ICU patients	1302 (650/652)	No	51/51	60/64	26/27
Napolitano LM, 2008 ¹⁰	USA	Trauma patients in ICU	793 (402/391)	No	41/40	74/75	NA
Endre ZH, 2010 ¹¹	New Zealand	General ICU or scheduled CPB surgery patients with increased risk of AKI	108 (61/47)	NA	NA	NA	NA
Yoo YC, 2011 ¹²	Korea	Scheduled valvular heart surgery patients with preoperative anemia	74 (37/37)	NA	56/59	35/38	24/38
Oh SW, 2012 ¹³	Korea	Elective CABG patients	71 (36/35)	No	65/69	83/66	83/64
de Seigneux S, 2012 ¹⁴	Switzerland	Elective cardiac surgery patients with risk for AKI	80 (E1: 20/E2: 20/C: 40)†	NA	E1: 69/E2: 67/C: 65	E1: 80/E2: 65/C: 68	E1: 85/E2: 60/C: 65
Tasanarong A, 2013 ¹⁵	Thailand	Elective CABG patients	100 (50/50)	No	63/60	62/52	79/63
Kim JH, 2013 ¹⁶	Korea	Complex valvular heart operation patients with high risk of AKI	98 (49/49)	NA	63/62	59/51	55/49
Kim JE, 2013 ¹⁷	Korea	Thoracic aorta surgery with hypothermic cardiac arrest	63 (31/32)	No	NA	NA	NA
Dardashti A, 2014 ¹⁸	Sweden	Nonemergent CABG	70 (35/35)	No	72/73	80/77	83/86

First Author, yr	DM, %*	Mean Baseline Hb, g/dL*	Mean Baseline sCr, mg/dL*	Mean Blood Transfusion, mL*	EPO-based Intervention	Control Group	Definition of AKI
Corwin HL, 2002 ⁹	13/13	10.0/10.0	NA	480/600	40,000 units rHuEPO ih on ICU day 3 and continued weekly until a fourth dose + iron supplement	Placebo + iron supplement	NA
Napolitano LM, 2008 ¹⁰	NA	9.4/9.3	NA	860/860	40,000 units rHuEPO ih between 48-96 h after admission to ICU and continued weekly until a third dose + iron supplement	Placebo + iron supplement	NA
Endre ZH, 2010 ¹¹	NA	NA	NA	NA	Two doses of 500 U/kg EPO iv after admission to ICU and 24 h later	Normal saline	≥0.3 mg/dL or ≥50% increase in sCr levels from baseline, or <0.5 mL·kg ⁻¹ ·h ⁻¹ oliguria for more than 6 h, or dialysis in 7 d
Yoo YC, 2011 ¹²	19/8	11.8/11.6	≤2 for both groups	200/660	500 U/kg rHuEPO iv at 16–24 h before surgery + 200 mg iron sucrose supplement	Normal saline	≥0.3 mg/dL or 50%–200% increase in sCr levels from baseline within 48 h after surgery
Oh SW, 2012 ¹³	40/44	13.1/12.6	1.20/1.08	280/290	300 U/kg EPO iv following induction of anesthesia	Normal saline	≥0.3 mg/dL or ≥50% increase in sCr levels from baseline in the first 72 h after CABG, or <0.5 mL·kg ⁻¹ ·h ⁻¹ of oliguria for more than 6 h

(continued on next page)

TABLE 1. (Continued) Baseline Clinical Characteristics of Included Studies

First Author, yr	DM, %*	Mean Baseline Hb, g/dL*	Mean Baseline sCr, mg/dL*	Mean Blood Transfusion, mL*	EPO-based Intervention	Control Group	Definition of AKI
de Seigneux S, 2012 ¹⁴	E1: 25/E2: 20/C: 35	E1: 10.0/E2: 9.8/C: 9.8	E1: 1.05/E2: 0.98/C: 0.96	NA	E1 or E2 iv when arrival to the ICU	Normal saline	Serum creatinine criteria of AKIN classification from ICU admission to the following wk
Tasanarong A, 2013 ¹⁵	27/34	12.3/12.2	1.05/1.05	NA	200 U/kg rHuEPO iv 3 d before surgery and 100 U/kg rHuEPO at the time of surgery	Normal saline	≥0.3 mg/dL or ≥50% increase in sCr levels from baseline within the first 48 h after surgery
Kim JH, 2013 ¹⁶	33/16	NA	0.92/0.99	122/219	300 U/kg rHuEPO- α iv after anesthetic induction	Normal saline	≥0.3 mg/dL or ≥50% increase in sCr levels from baseline within 48 h after surgery
Kim JE, 2013 ¹⁷	NA	NA	NA	NA	500 U/kg EPO iv before surgery	Normal saline	RIFLE Criteria for 7 d postoperatively
Dardashti A, 2014 ¹⁸	34/43	12.9/13.4	1.35/1.31	NA	400 U/kg EPO iv before surgery	Normal saline	RIFLE Criteria for 4 d postoperatively

*Data are presented as EPO/control.

†E1: 20,000 units α -epoetin subgroup treatment; E2: 40,000 units α -epoetin subgroup treatment; C: control group.

AKIN, acute kidney injury network; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DM, diabetes mellitus; Hb, hemoglobin; HP, hypertension; ih, intravenous administration; iv, intravenous administration; NA, not available; rHuEPO, recombinant human erythropoietin; RIFLE, Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End stage kidney disease; sCr, serum creatinine.

All statistical analyses were conducted using the Stata/SE 12.0 software (Stata Corporation, College Station, TX). A *P* value less than 0.05 by a 2-sided test was considered to be statistically significant.

RESULTS

A flow diagram of the study selection is demonstrated in Figure 1. The initial search yielded 615 citations, of which 72 were duplicate studies that were excluded. After reviewing the titles and abstracts of 543 citations, 516 articles were removed because of irrelevant content. Upon review of the full text of 27 articles, ten eligible RCTs with 2759 participants were identified for this meta-analysis.^{9–18}

Study and Patient Characteristics

The detailed characteristics are summarized in Table 1. The included studies spanned from 2002 to 2014, and with the exception of 2 articles,^{9,10} the sample size of all other studies was relatively small (63–108 participants). Four trials were conducted in Korea,^{12,13,16,17} 2 in the United States,^{9,10} and the others in New Zealand,¹¹ Switzerland,¹⁴ Thailand,¹⁵ and Sweden.¹⁸ Napolitano et al¹⁰ reanalyzed the data from critically ill trauma patients in EPO-2 trial,⁹ which had been included in this meta-analysis, so only the part of EPO-3 trial was included in this analysis. The intention to treat of participants in 1 study included AKI patients on randomization,¹¹ and for the objective of this meta-analysis, the data of the subgroup not AKI on randomization were used in this analysis. One study¹³ was the follow-up of a previous trial²¹; therefore, the incidence

of AKI was extracted from the former, and the baseline data were extracted from the latter. All studies enrolled participants from single-site center except 3.^{9–11} With respect to the participants setting, 8 studies were performed in perioperative period, 6 of which were conducted in patients with elective cardiac surgery,^{12–16,18} one assessed patients undergoing thoracic aorta surgery with hypothermic cardiac arrest,¹⁷ and the rest one partly included patients with scheduled cardi thoracic surgery.¹¹

Six studies excluded patients who used EPO previously,^{9,10,13,15,17,18} whereas other studies did not specify this issue. In 3 of the 10 studies, a high risk for developing AKI, the definitions of which were not the same, was included in the enrollment criteria.^{11,14,16} In 8 studies, baseline end-stage renal disease or dialysis was set as a compulsory exclusion criterion.^{9–13,15,16,18} When reported, mean baseline hemoglobin levels ranged from 9.3 to 13.1 g/dL,^{9,10,12–15,18} and mean baseline serum creatinine levels varied from 0.92 to 1.35 mg/dL.^{13–16,18} The type of erythropoiesis-stimulating agent used in all of the intervention groups was EPO- α or - β , but not darbepoietin. The one-time EPO dosage was either fixed as 20,000 units or 40,000 units in 3 studies^{9,10,14} or was based on participant weight ranging from 100 units/kg to 500 units/kg in the other 7 studies. The participants in 6 studies received only a single administration of EPO^{12–14,16–18}; however, participants received at least 2 doses in the other studies. Two studies provided supplementary iron therapy to both the intervention and control groups,^{9,10} and 1 study provided an iron sucrose supplement only to the intervention group.¹² There was considerable variation in the definition of AKI across these studies, which was not clear in 2 studies.^{9,10}

Risk of Bias Assessment

The quality of the included studies is presented in Figure 2. All ten studies reported randomization, but 7 studies described the methods of randomization,^{9–12,14,16,18} and only 4 studies showed the details of concealed allocation.^{11,13,15,18} All studies reported double blinding and no or few missing outcome data with the reason. Eight studies provided the clinical trial registration number online with a low risk of bias in selective outcome reporting.^{10,11,13–18} Because of the unbalanced use of iron supplementation in 2 groups, 1 study exhibited a high risk of bias in the item “other biases.”¹²

Effect of EPO on AKI Prevention

All ten eligible RCTs reported that the overall incidence of AKI was 10.57% (147 of 1391 participants) in the EPO-based intervention group and 10.38% (142 of the 1368 participants) in the control group. Pooled analysis using a fixed effect model showed that there was no significant difference for preventing the development of AKI between the EPO and control groups (RR, 0.97; 95% CI, 0.79–1.19; *P* = 0.782), as shown in Figure 3A. Meanwhile, the test for between-study heterogeneity among the included trials was not significant (*I*² = 20.2% and *P* = 0.257).

Stratified analyses of studies with entirely perioperative care demonstrated no significant difference between the EPO and control groups using a fixed effect model (RR, 0.86; 95% CI, 0.66–1.12; *P* = 0.260; *I*² = 33.9%; *P* = 0.169).^{12–18} Among studies that excluded patients with prior EPO use, similar

result of RR was obtained (RR, 0.89; 95% CI, 0.66–1.21; *P* = 0.467; *I*² = 23.3%, *P* = 0.259).^{9,10,13,15,17,18} Among patients who received at least 2 doses of EPO^{9–11,15} or were at high risk of AKI according to each study,^{11,14,16} the prevention of AKI remained nonsignificant (RR, 0.99; 95% CI, 0.73–1.35; *P* = 0.962; *I*² = 44.3%, *P* = 0.145 and RR, 1.22; 95% CI, 0.89–1.67; *P* = 0.215; *I*² = 0%, *P* = 0.805, respectively). The sensitivity analysis after exclusion of 1 study at a time demonstrated that the above pooled result was robust and did not change much depending on any single study (Fig. 4). It should be noted that after removing the study,¹² which gave iron supplement only to EPO intervention group, the overall RR was 1.02 (95% CI, 0.82–1.27; *P* = 0.824) without statistical significance.

The funnel plot and Egger’s test analysis indicated that there was no evidence of publication bias for the AKI outcome (Fig. 5A for funnel plot; *P* = 0.346 for Egger’s test).

Effect of EPO on Dialysis Requirement

The dialysis requirement was reported in 7 studies^{11,13–18} totaling 590 analyzable patients, and in 3 of these studies, no patient was treated with dialysis in either group.^{13,14,18} The overall incidence of dialysis was 2.65% (8 of the 302 participants) in the EPO-based intervention group and 3.82% (11 of the 288 participants) in the control group. By meta-analysis for 4 studies using a fixed effect model,^{11,15–17} there was no significant difference of mortality between the EPO and control groups (RR, 0.72; 95% CI, 0.31–1.70; *P* = 0.457)

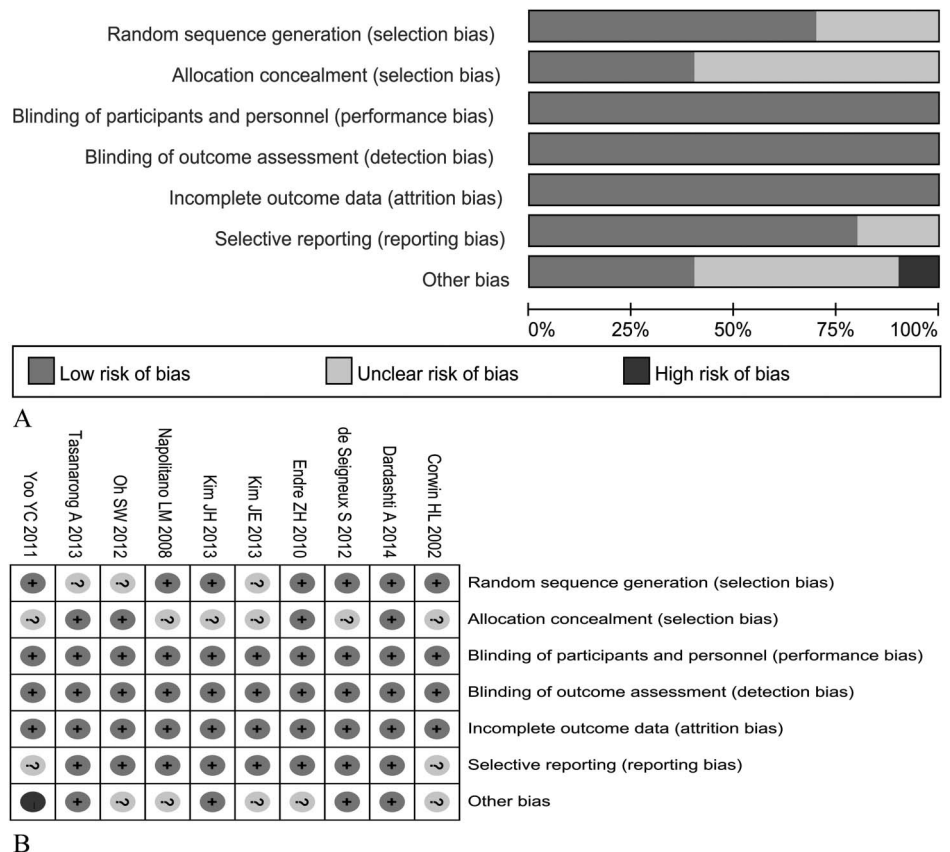


FIGURE 2. Risk of bias in included studies. A, Risk of bias graph demonstrates the percentages of included studies for each item in the tool; (B) risk of bias summary illustrates the review author’s judgments with a cross-tabulation for each eligible study.

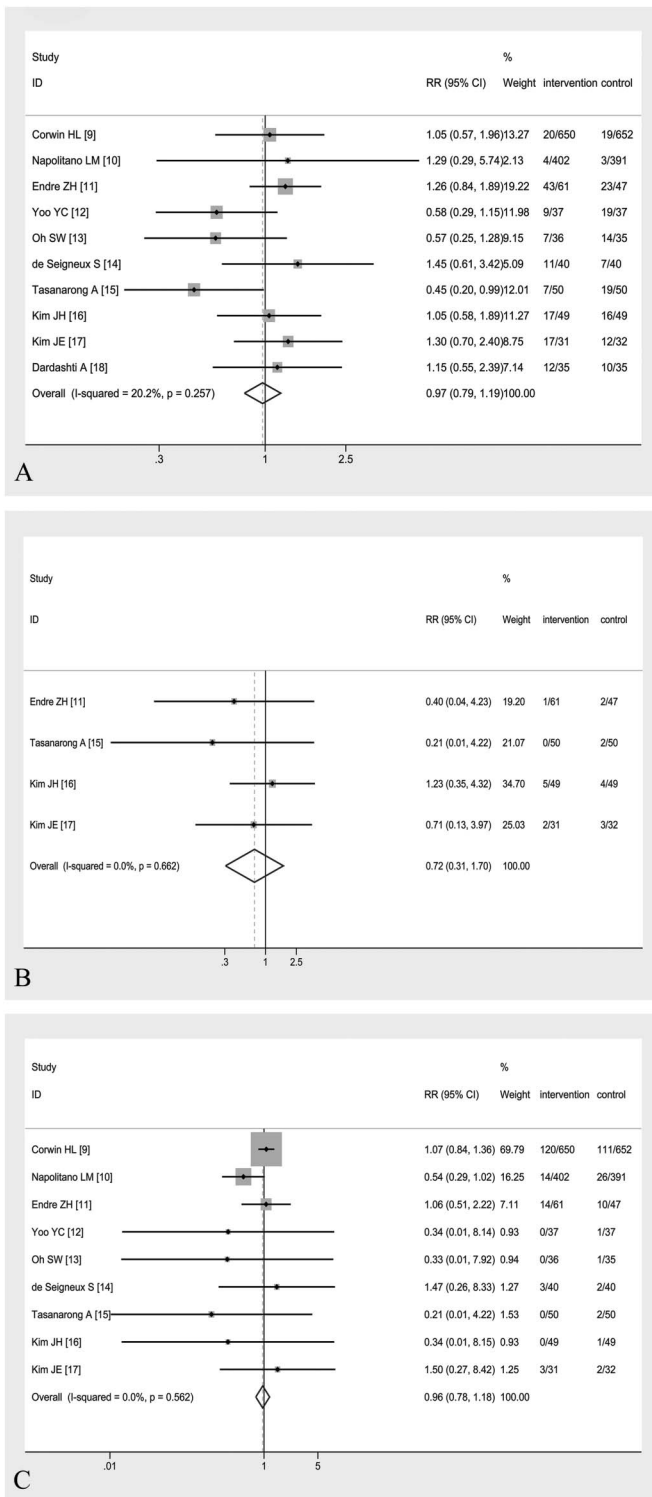


FIGURE 3. Forest plots of RR estimates with the corresponding 95% CI for (A) the incidence of AKI, (B) dialysis requirement, and (C) mortality in patients receiving EPO therapy versus control. The columns of intervention and control were presented as number of events/number of participants.

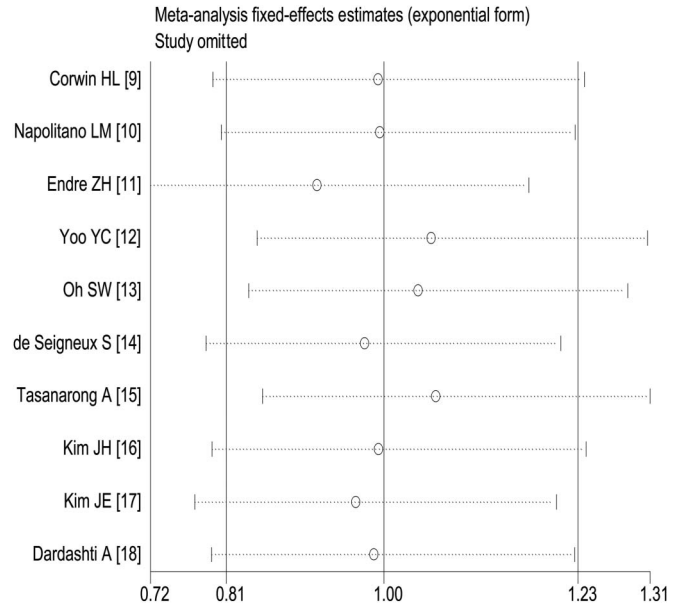


FIGURE 4. The sensitivity analysis by removing each individual study at a time is shown on the pooled effect size of the incidence of AKI.

without significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.662$), as shown in Figure 3B. Because there were only 4 articles in the literature with the effective data, the publication bias was not investigated.

Effect of EPO on Mortality

The ten included studies demonstrated that overall mortality was 11.07% (154 of the 1391 participants) in the

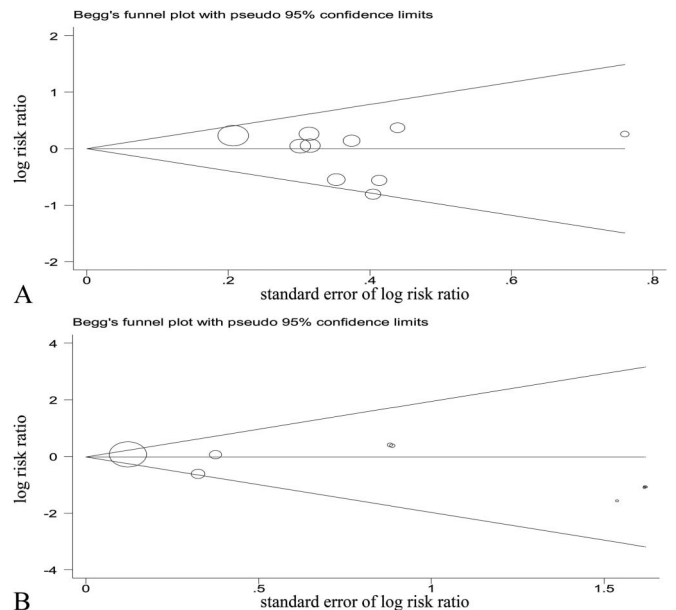


FIGURE 5. The funnel plots for publication bias tests of studies assessing the effect of EPO on (A) the incidence of AKI and (B) mortality.

EPO-based intervention group and 11.40% (156 of the 1368 participants) in the control group. Mortality was ascertained in-hospital in 3 studies,^{13,15,16} at 30 days in 5 studies,^{9–12,14} and unclear in the remaining study.^{17,18} Pooled analysis using a fixed effect model showed that there was no significant difference of mortality between the EPO and control groups (RR, 0.96; 95% CI, 0.78–1.18; $P = 0.705$) without significant between-study heterogeneity ($I^2 = 0\%$, $P = 0.562$), as shown in Figure 3C. Meanwhile, there was no evidence of publication bias for the mortality outcome (Fig. 5B for funnel plot; $P = 0.162$ for Egger's test).

Adverse Events

Six studies demonstrated that none of the patients who received the EPO intervention suffered from adverse events, which were associated with the use of drug, throughout the study period, such as hypertension, symptomatic thrombosis, myocardial infarction, stroke, headache, and seizures.^{12–16,18} One study did not report adverse events,¹⁷ and 1 study reported adverse events for the entire participants without specifically describing the specific group.¹¹ Corwin et al⁹ showed that the incidence of deep thrombophlebitis was 2.15% (14/650) among the EPO intervention group and 2.30% (15/652) in the control group without significant difference. Napolitano et al¹⁰ reported that the incidence of clinically relevant thrombovascular events was 16.42% (66/402) in the EPO intervention group and 12.53% (49/391) in the control group with an RR of 1.31 (95% CI, 0.93–1.85).

DISCUSSION

In this present meta-analysis of 10 RCTs with 2759 participants, we found that compared with placebo, prophylactic EPO therapy for patients who are critically ill or under perioperative care was not associated with a significant reduction in the incidence of AKI, dialysis requirement, or mortality. Meanwhile, the effect of EPO on AKI prevention was consistent with the above result for the stratified analyses on patients with entirely perioperative care, no previous EPO use, or more than 1 dose of EPO. In addition, EPO therapy was not associated with adverse events in these studies, which appeared to be safe in this kind of patients.

AKI is a frequent and serious complication occurring in the critically ill or surgical patients and is associated with increased length of hospital stay, occurrence of end-stage renal disease, and mortality.²² Ischemia and reperfusion injury, inflammation, oxidative stress, apoptosis, etc. have all been demonstrated as crucial factors in the development of AKI.²³ Recently, results from several animal studies indicated that EPO exerts a renoprotective effect against AKI induced by cardiopulmonary bypass or sepsis through mechanisms of reducing ischemia/reperfusion injury, inhibiting apoptosis, and alleviating inflammatory responses.^{8,24,25} However, the benefits of EPO in these animal studies were not reproducible in clinical trials or in this meta-analysis. There are several plausible reasons for this discrepancy. First, many patients included in these trials suffered from some comorbidities, such as hypertension, diabetes, dyslipidemia, or ischemic heart disease and had complicated

pathophysiological conditions, which might reduce the effects of EPO.^{26,27} Second, compared with animal experiments, the dosage of EPO in clinical studies is relatively lower, which might be unable to obtain therapeutic effects. Third, the variable time of EPO treatment in clinical studies is not the same as animal experiments, and the optimal time has not been established.

This meta-analysis has several strengths as following. Only 1 EPO intervention study was enrolled in a previous meta-analysis without estimating the risk of AKI,²⁸ and 9 additional RCTs with over 2600 participants were included into our meta-analysis. The majority of trials in this analysis had good or moderate methodological quality, which indicated that the results were not susceptible to be influenced by the biases of original researches. Meanwhile, most trials investigated the effect of EPO on clinically hard end points such as dialysis requirement and short-term mortality. Both the between-study heterogeneity and publication bias were relatively minimal without statistical significance, which made the pooled effect size less likely to be affected. In addition, the appropriate stratified analyses and sensitivity analyses, which removed one study at a time, were performed with consistent results. Therefore, the results of our meta-analysis are reliable with cautiously speaking.

There are several limitations of this study that should be taken into account. First, several inclusion trials might not have sufficient sample size with designed only at the single-center level.^{12–17} In the future, more large multicenter RCTs with adequately participants will be needed to elucidate the prevention role of EPO. Second, there were differences in patient selection, treatment regimen, and the definition of AKI across these trials. An accepted uniform EPO study protocol would reduce the degree of variation among the studies. Finally, our meta-analysis was based on aggregated data, not on individual patient-level data. As a consequence, the results might be less accurate and could not be adjusted for certain confounding factors, such as age, comorbidities, and laboratory parameters, which might influence the true therapeutic effect of EPO.

CONCLUSIONS

In summary, this meta-analysis, based on currently available RCT evidence, suggests that prophylactic EPO treatment of patients with critical illness or under perioperative care does not reduce the incidence of AKI, dialysis requirement, or death. Considering the limitations of this study, larger scale, well-designed multicenter RCT studies using optimal doses and administration times are needed to investigate the role of EPO in AKI prevention.

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