Systematic Review and Meta-Analysis

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Effects of perioperative erythropoietin administration on acute kidney injury and red blood cell transfusion in patients undergoing cardiac surgery

A systematic review and meta-analysis

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Abstract

Background: The renoprotective effects of erythropoietin (EPO) are well-known; however, the optimal timing of EPO administration remains controversial. Red blood cell (RBC) transfusion is an independent risk factor for cardiac surgery-associated acute kidney injury (CSA-AKI). We aimed to evaluate the efficacy of EPO on CSA-AKI and RBC transfusion according to the timing of administration.

Methods: We searched the Cochrane Library, EMBASE, and MEDLINE databases for randomized controlled trials. The primary outcome was the incidence of CSA-AKI following perioperative EPO administration, and the secondary outcomes were changes in serum creatinine, S-cystatin C, S-neutrophil gelatinase-associated lipocalin, urinary neutrophil gelatinase-associated lipocalin, length of hospital and intensive care unit (ICU) stay, volume of RBC transfusion, and mortality. The subgroup analysis was stratified according to the timing of EPO administration in relation to surgery.

Results: Eight randomized controlled trials with 610 patients were included in the study. EPO administration significantly decreased the incidence of CSA-AKI (odds ratio: 0.60, 95% confidence interval [CI]: 0.43–0.85, $P = .004$; $I^2 = 52\%$; P for heterogeneity = .04), intra-operative RBC transfusion (standardized mean difference: −0.30, 95% CI: −0.55 to −0.05, $P = .02$; $I^2 = 15\%$, P for heterogeneity = .31), and hospital length of stay (mean difference: −1.54 days, 95% CI: −2.70 to −0.39, P = .009; $I^2 = 75\%$, P for heterogeneity = .001) compared with control groups. Subgroup analyses revealed that pre-operative EPO treatment significantly reduced the incidence of CSA-AKI, intra-operative RBC transfusion, serum creatinine, and length of hospital and ICU stay.

Conclusion: Pre-operative administration of EPO may reduce the incidence of CSA-AKI and RBC transfusion, but not in patients administered EPO during the intra-operative or postoperative period. Therefore, pre-operative EPO treatment can be considered to improve postoperative outcomes by decreasing the length of hospital and ICU stay in patients undergoing cardiac surgery.

Abbreviations: CI = confidence interval, CPB = cardiopulmonary bypass, CSA-AKI = cardiac surgery-associated acute kidney injury, EPO = erythropoietin, GFR = glomerular filtration rate, ICU = intensive care unit, IR = ischemia-reperfusion, MD = mean difference, NGAL = neutrophil gelatinase-associated lipocalin, OR = odds ratio, RBC = red blood cell, RCTs = randomized controlled trials, rHuEPO = recombinant human erythropoietin, SCr = serum creatinine, SMD = standardized mean difference.

Keywords: acute kidney injury, cardiac surgery, erythropoietin, meta-analysis, transfusion

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is defined by a sudden worsening in renal function due to a reduced glomerular filtration rate (GFR) after cardiac surgery.[1,2] CSA-AKI has various etiologies, including cardiopulmonary bypass (CPB), red blood cell (RBC) transfusion, and renal hypoperfusion.[1] Cardiac surgery is frequently related with renal hypoperfusion, resulting from the non-pulsatile perfusion with hemodilution that is associated with CPB.[3] After CPB, ischemia-reperfusion (IR) injury may cause AKI by leading to the opening of mitochondrial permeability transition pores in the kidneys.[3] The pore opening may be a main factor in the pathogenesis of cell injury or cell death after ischemia and reperfusion.[4] The pathophysiological pathways of CSA-AKI also include oxidative stress, inflammation, nephrotoxins, neurohumoral activation, and mechanical factors.[3] Preoperative risk factors for CSA-AKI include advanced age, female sex, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, and reduced left ventricle function.[5]

Allogeneic RBC transfusion has been recognized as an independent risk factor for CSA-AKI.[6,7] Renal IR injury following CPB may be exacerbated by RBC transfusion. The possible pathophysiological mechanism is that transfusion can promote inflammatory responses, impair tissue oxygen delivery, and increase tissue oxidative stress by hemolysis of transfused stored erythrocytes.[8,9] Increased free hemoglobin and iron levels by hemolysis result in AKI following cardiac surgery with CPB.[10,11] Khan et al[12] reported that the patients who received of more than 2 packed RBC units were significantly associated with the risk of AKI compared with those who received 2 or less packed RBC units during cardiac surgery.

Serum creatinine (SCr) level has been used as a biomarker of kidney damage.[13] Other biomarkers, such as cystatin C, interleukin-18, insulin-like growth factor binding protein-7, liver fatty acid-binding protein, and neutrophil gelatinase-associated lipocalin (NGAL) have also been investigated in the prompt detection of AKI.[14] NGAL is a dramatically upregulated gene and overexpressed protein in the kidney following ischemia.[15] Human NGAL is a 25-kDa protein bound to gelatinase from human neutrophils and overexpressed in the kidney following ischemia.[15] NGAL increases early in AKI, and is secreted into the urine through damaged distal tubular epithelial cells after nephrotoxic and ischemic injury.[16] Cystatin C, a low-molecular-weight protein, is eliminated solely by glomerular filtration. Serum cystatin C levels increase before SCr levels increase when the GFR decreases and, therefore, can be used to detect AKI 2 days earlier than when using SCr levels.[17,18]

The reported incidence of CSA-AKI is 5% to 42%.[19] CSA-AKI is independently associated with increased morbidity and mortality, particularly with prolonged duration of hospital and intensive care unit (ICU) stay, and increased cost of care.[2,20–23] Additionally, the mortality rate in CSA-AKI is significantly higher in patients who require hemodialysis.[24] The therapeutic strategies are limited to renal replacement therapy in patients with severe AKI. Therefore, it is essential to prevent and manage the risk of AKI in patients undergoing cardiac surgery.

Erythropoietin (EPO) is a hematopoietic hormone that regulates RBC production. Human EPO was first purified from the urine of a patient with aplastic anemia in 1977, and was used in cloning the gene of human EPO and large-quantity manufacturing of recombinant human EPO.[25] EPO is released into the circulation from renal cortical fibroblasts in response to renal hypoxia.[26] EPO binds to the EPO receptor on erythroid progenitor cells and stimulates erythropoiesis by inhibiting apoptotic cell death of immature erythroblasts.[27] In addition to its hematopoietic effects, EPO has renal protective effects on IR injury through antioxidant, anti-apoptotic, and anti-inflammatory effects in various animal studies.[28–30] Recent clinical studies have demonstrated that EPO has pre-conditioning, anti-apoptotic, and cytoprotective effects on the kidneys.[31–33] However, other clinical studies have reported conflicting results that EPO administration did not reveal a renal protective effect in patients at high risk of AKI undergoing cardiac surgery.[34–36] Until recently, the optimal timing of EPO administration has remained controversial.[37–40] Therefore, we conducted this meta-analysis to evaluate the efficacy of EPO administration in reducing the incidence of AKI and RBC transfusion according to the timing of administration in cardiac surgery.

2. Methods

The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement[41] was used to perform this systematic review and meta-analysis, and the study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration no. CRD42020189692). Ethical approval was not required because our meta-analysis was based on previously published articles.

2.1. Search strategy

The Cochrane Library, EMBASE, and MEDLINE databases were searched till July 2020 using the following keywords: ("Erythropoietin" OR "hematopoietin" OR "hemopoietin") AND ("groups" OR "trial" OR "placebo" OR "randomized" OR "randomly" OR "controlled clinical trial" OR "randomized controlled trial") NOT ("animals" OR ("humans" AND "animals") NOT ("review" OR "review literature as topic").

The reference lists of the clinical trials were manually investigated to identify additional trials. Randomized controlled trials (RCTs) were included to examine the incidence of postoperative AKI based on perioperative EPO treatment in patients who underwent cardiac surgery. Furthermore, if necessary, the corresponding authors were contacted via email. There were no limitations in the literature search for language in this study.

2.1.1. Study selection. Abstracts and titles were screened independently by 2 authors (HJ Shin and IJ Jun) to identify the appropriate studies. Subsequently, the full texts of the articles were examined to determine whether they contained clinical trials that satisfied the criteria of the review. Any dispute was regulated by consensus with the third author (CH Lim).

2.1.2. Data extraction. The following data were extracted by 2 authors (HJ Shin and CH Lim): trial-associated data (publication year, first author, and sample size), patient demographic data (age, sex, and surgery type), and intervention-associated data (intervention group of EPO, intervention group of control, time of intervention, and prior risk of CSA-AKI). The primary outcome was AKI incidence. The secondary outcomes were the changes in serum NGAL, serum cystatin C, urinary NGAL, and SCr levels, intra-operative and postoperative RBC transfusion requirements, hospital and ICU length of stay, renal replacement, and mortality.

2.1.3. Inclusion and exclusion criteria. The inclusion criteria were as follows: RCTs that included adult patients who underwent cardiac surgery, a placebo group as the comparison, perioperative EPO administration as the intervention, and postoperative AKI incidence as the clinical outcome. The exclusion criteria were case reports, abstracts, reviews, meta-analyses, retrospective studies, duplicate publications, cell lines or animal studies, articles published in languages other than English, and insufficient data.

2.2. Quality and risk-of-bias assessments

The methodological quality and bias risk of each trial was estimated using the revised form of Cochrane risk-of-bias tool for randomized trials (RoB 2) by 2 independent authors (HJ Shin and EJ Ko).[42] RoB 2 is organized into 5 areas as follows: bias owing to deviations from intended interventions, bias occurring because of the randomization process, bias in the collection of the reported results, bias in the outcome assessment, and bias due to missing data of outcome.[42] Each area categorizes clinical trials into high, unclear, and low risks of bias. A high risk of bias may seriously alter the results; unclear risk of bias raises some doubt about the results; and low risk of bias, if present, is unlikely to alter the results seriously.[42] Any disagreements were resolved by consensus with the third author (CH Lim).

2.3. Statistical analysis

RevMan v5.3 (The Cochrane Collaboration, Oxford Software, UK) was used for data analysis and synthesis. Statistical significance was defined as a P value $< .05$. A forest plot with 95% confidence intervals (CIs) based only on the fixed-effects model was used to present the findings. Odds ratios (ORs) with 95% CIs were used for dichotomous outcomes (incidence of AKI, renal replacement, and mortality). Mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were used for continuous outcomes (changes in SCr, serum NGAL, serum cystatin C, and urinary NGAL levels, intra-operative transfusion, postoperative transfusion requirement, and length of hospital and ICU stay). SMDs were used if the measurement unit was different for each study, such as serum NGAL, intra-operative transfusion, and postoperative transfusion requirement. Wan formula was used to calculate the means and standard deviations if the results were expressed as medians and ranges.[43] The grade of heterogeneity between the studies was measured using I^2 statistics. The proposed high, moderate, and low ranges of I^2 values were 75% to 100%, 50% to 75%, and 0% to 50%, respectively. Subgroup analysis was performed according to the timing of EPO administration. Publication bias was investigated using funnel plots. If the funnel plot was symmetrical, publication bias was considered not to exist in this meta-analysis.

3. Results

3.1. Study selection and identification

The search in the MEDLINE, EMBASE, and Cochrane Library databases returned 12,003 studies (4198, 3556, and 4249, respectively), and 2 RCTs were added by manually searching the references. Overall, 12,005 articles were identified during the initial search. Of these, 3649 duplicate studies were excluded, and 8336 studies were excluded after screening the abstracts and titles. The remaining 20 full-text articles were assessed for eligibility. Of these, 2 studies were excluded due to non-cardiac surgery, and 10 studies were excluded due to re-analysis of previous patients. Consequently, 8 RCTs[31–36,44,45] that satisfied the inclusion criteria were included in the systematic review and meta-analysis (Fig. 1).

3.2. Study characteristics

Table 1 summarizes the patient demographics and pre-operative clinical data of the 8 RCTs included. The RCTs were published

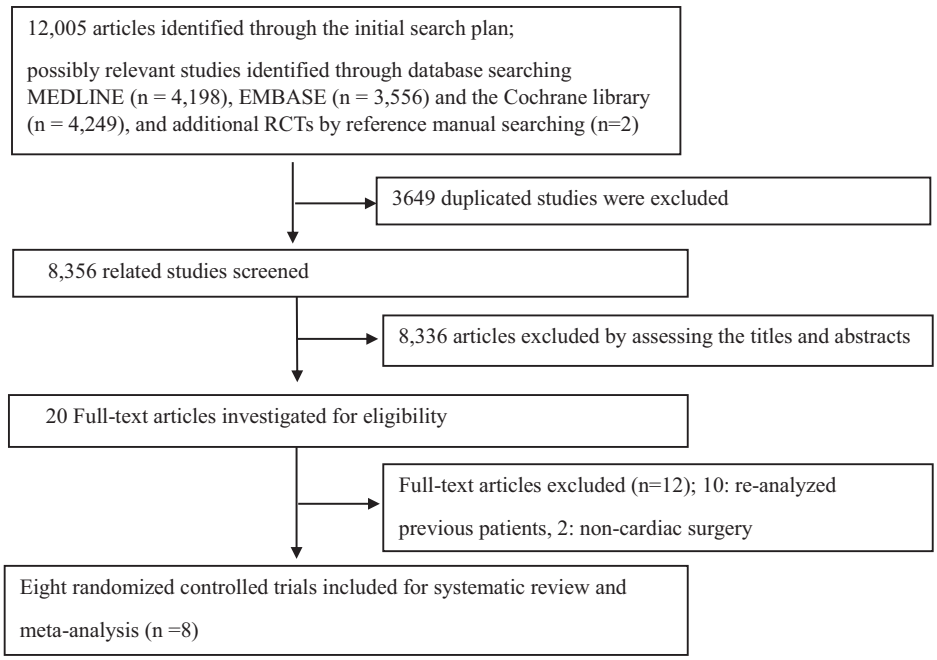

Figure 1. Flow diagram of screening randomized controlled trials that were included in the meta-analysis.

Table 1

Patient demographics and pre-operative clinical data of the 8 randomized controlled trials.

		Population (EPO/control)						Method			
First author, yr	Country	Sample (n)	Age (yrs)	SCr (mmol/L)	eGFR (mL/min/ 1.73 m^2)	Hb (g/dL)	Risk for CSA-AKI	Surgery type	Intervention (EPO/control)	Administration time	Clinical outcomes
Kim JE, 2016[36]	Korea	60 (31/29)	60.33 ± 33.42/ 64.0 ± 44.45	NA/NA	NA/NA	NA/NA	Yes*	Thoracic aortic surgery with CPB	500 IU/kg of rHuEPO, IV/NS	Intra-operative (after skin incision after anesthesia)	Incidence of AKI, Scr, S-NGAL, hospital and ICU LOS, renal replacement, mortality
Dardashiti A, 2014[35]	Sweden	70 (35/35)	72.4 ± 8.1/ 75.5 ± 10.5	1.35 ± 0.38/ 1.31 ± 0.39	56.3 ± 14.4/ 58.0 ± 14.5	12.91 ± 1.46/ 13.36 ± 1.48	Yes†	CABG with CPB	400 IU/kg of rHuEPO, IV/NS	Pre-operative (before skin incision after anesthesia)	Incidence of AKI, Scr, S-cystatin C, S-NGAL, urinary NGAL, ICU LOS,
Kim JH, 2013[34]	Korea	98 (49/49)	63 ± 10/ 62 ± 10	0.92 ± 0.28/ 0.99 ± 0.27	83 ± 28/77 ± 30	NA/NA	Yes‡	VHS with CPB	300 IU/kg of rHuEPO-α, IV/NS	Pre-operative (before skin incision after anesthesia)	Incidence of AKI, Scr, S-cystatin C, S-NGAL, introp transfusion, postop transfusion, hospital and ICU LOS, renal replacement, mortality
de Seigneux S, 2012[45]	Switzerland	80 (20/20/40)	68.9 ± 12/ 66.5 ± 16.5/ 64.7 ± 14.7	1.05 ± 0.29/ 0.98 ± 0.27/ 0.96 ± 0.30	NA/NA/NA	NA/NA/NA	Yes§	Cardiac Surgery with CPB	20,000 IU/40,000 IU of α-Epoetin, IV/NS	Postoperative	Incidence of AKI, Scr, S-cystatin C, urinary NGAL, hospital and ICU LOS, mortality
Song YR, 2009[44]	Korea	71 (35/36)	64.6 ± 10.7/ 68.9 ± 8.4	1.20 ± 0.38/ 1.08 ± 0.32	61.60 ± 25.20/ 59.30 ± 21.70	13.10 ± 2.30/ 12.60 ± 1.60	No	CABG with (CPB or OP)	300 IU/kg of rHuEPO, IV/NS	Pre-operative (before skin incision after anesthesia)	Incidence of AKI, Scr, intraop transfusion, postop transfusion, hospital and ICU LOS,
Yoo YC, 2011[31]	Korea	74 (37/37)	56 ± 12/ 59 ± 12	NA/NA	NA/NA	11.80 ± 0.80/ 11.60 ± 1.20	Yes‖	VHS with CPB	500 IU/kg of rHuEPO + 100 mL NS with 200 mg iron sucrose, IV/NS	Pre-operative (16–24 hours before surgery)	Incidence of AKI, intraop transfusion, postop transfusion, hospital and ICU LOS, mortality
Tasanarong A, 2013[32]	Thailand	100 (50/50)	63 ± 16/ 60 ± 16	1.05 ± 0.27/ 1.05 ± 0.45	64 ± 29/67 ± 33	12.30 ± 1.70/ 12.20 ± 1.90	No	CABG with CPB	200 IU/kg 3 day before surgery + 100 IU/kg of rHuEPO at surgery, IV/ NS	Pre-operative (3 days before surgery and at operation)	Incidence of AKI, Scr, urinary NGAL, hospital and ICU LOS, renal replacement, mortality
Oh SW, 2012[33]	Korea	71 (36/35)	66.67 ± 10.81/ 70.5 ± 6.96	1.3 ± 0.35/ 1.1 ± 0.31	60.83 ± 15.06/ 73.97 ± 27.60	13.6 ± 2.70/ 12.67 ± 1.86	No	CABG	300 IU/kg of rHuEPO, IV/NS	Pre-operative (before skin incision after anesthesia)	Incidence of AKI

CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, CSA-AKI = cardiac surgery-associated acute kidney injury, eGFR = estimated glomerular filtration rate, EPO = erythropoietin, Hb = hemoglobin, ICU = intensive care unit, IV = intravenous administration, LOS = length of stay, n = sample size, NGAL = neutrophil gelatinase-associated lipocalin, NS = normal saline, OP = off-pump, rHuEPO = recombinant human erythropoietin, SCr = serum creatinine, VHS = valvular heart surgery.

* Described as including pre-operative AKI caused by thoracic aortic aneurysm and dissection.

† Described as pre-operative eGFR less than 60.

‡ Described as including more than 2 of the following criteria: pre-operative creatinine > 1.2 mg/dL, New York Heart Association functional class IV, female, left ventricle ejection fraction < 35%, chronic obstructive pulmonary disease, peripheral vascular disease, or diabetes mellitus.

§ Described as previous chronic kidney disease, hemodynamic impairment, postoperative state, mechanical ventilation, or sepsis.

‖ Described as including pre-operative anemia, which is recognized as a risk factor for postoperative AKI.

between 2009 and 2016, and the sample sizes ranged from 66 to 100, with a total of 610. The studies included adult patients aged >18 years, and the height, weight, and mean age were comparable between the groups. The type of surgery was coronary artery bypass grafting in 4 studies,[32,33,35,44] whereas the other studies included complex valvular, simple valvular, and thoracic aortic surgeries.[31,34,36,45] For subgroup analysis, we divided all RCTs into 2 groups according to the timing of EPO administration based on skin incision. The pre-operative group received EPO before skin incision, while the intra-operative or postoperative group received EPO after skin incision. The patients included in the 6 studies[31–35,44] received EPO pre-operatively. Tasanarong et al[32] administered 2 EPO doses, one 3 days before the surgery and the other during the surgery. Yoo et al[31] administered a dose of 16 to 24 hours before surgery. In the 4 remaining studies, the dose was administered before incision after induction of anesthesia.[33–35,44] The patients included in the 6 RCTs were allocated to the pre-operative EPO administration group.[31–35,44] Kim et al[36] administered EPO after skin incision during the intra-operative period, whereas de Seigneux et al[45] administered EPO only after the surgery. The patients included in the 2 RCTs were divided into intra-operative or postoperative EPO administration group.[36,45]

The EPO doses ranged from 300 to –500 IU/kg (Table 1). All the studies described AKI in accordance with the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria[35,36] or Acute Kidney Injury Network criteria.[31–34,44,45] Six of the clinical trials detected AKI on the basis of SCr diagnostic standard, such as increase of 0.3 mg/dL from baseline or more than 50% increase in SCr level.[31–34,44,45] Dardashti et al[35] detected AKI based on RIFLE criteria and a decrease in estimated GFR >25%. Five of the clinical trials included patients with previous risk factors of CSA-AKI.[31,34–36,45] The patients included by Kim et al[36] had pre-operative AKI caused by thoracic aortic aneurysm and dissection. The patients included by Dardashti et al[35] had previous renal damage with an estimated GFR <60%. The patients included by de Seigneux et al[45] had a prior risk of AKI due to mechanical ventilation, sepsis, previous chronic kidney disease, postoperative status, or hemodynamic impairment. The patients included by Kim et al[34] had a prior risk of AKI and met 2 or more of the following criteria: age >65 years, New York Heart Association functional class IV, chronic obstructive pulmonary disease, left ventricular ejection fraction <35%, pre-operative creatinine level >1.2 mg/dL, pulmonary vascular disease, female sex, and diabetes mellitus. The patients included by Yoo et al[31] had pre-operative anemia, which is recognized as a risk factor for postoperative AKI.[46]

3.3. Methodological quality and risk of bias

Figure 2 illustrates the risk of bias in the included RCTs according to the revised form of Cochrane risk-of-bias tool for randomized trials (RoB 2).[42] The patients who underwent cardiac surgery were randomly assigned to each group in all the studies. The risk of randomization bias was low (5 of 8) or unclear (3 of 8). The risk of missing outcome data bias and deviation from the intended intervention bias was low in all 8 studies. The risk of outcome measurement bias was low (7 of 8) or high (1 of 8), while the risk of selection of the reported results was low (5 of 8) or high (3 of 8).pt

3.4. Primary outcome

EPO administration was significantly associated with a decrease in the incidence of AKI compared with controls (OR: 0.60, 95% CI: 0.43–0.85, $P=.004$). Statistical heterogeneity was moderate among the studies ($I^2=52\%$, P = .04) (Fig. 3). Subgroup analysis suggested that pre-operative EPO treatment was associated with a significant decrease in the incidence of CSA-AKI (OR: 0.49, 95% CI: 0.33–0.73, $P=.0005$). The level of heterogeneity was low among the studies ($I^2=46\%$, $P=.10$). However, EPO treatment was not associated with a decrease in the incidence of CSA-AKI in the intra-operative or postoperative group (OR: 1.22, 95% CI: 0.58–2.54, $P=.60$) (Fig. 3).

3.5. Secondary outcomes

Compared with controls, EPO treatment was significantly associated with a reduction in the levels of urinary NGAL (MD: −12.40 ng/mL, 95% CI: −19.42 to −5.37, $P=.005$; $I^2=74\%$, $P=.02$; Fig. 4D), intra-operative RBC transfusion (SMD: −0.30, 95% CI: −0.55 to −0.05, $P=.02$; $I^2=15\%$, heterogeneity $P=.31$; Fig. 5A), postoperative RBC transfusion (SMD: −0.30, 95% CI: −0.61 to −0.00, $P=.05$; $I^2=82\%$, $P=.02$; Fig. 5B), and hospital length of stay (MD: −1.54 days, 95% CI: −2.70 to −0.39, $P=.009$; $I^2=75\%$, $P=.001$; Fig. 6A).

3.5.1. Change in SCr level. SCr levels were reported in 6 studies[32,34–36,44,45] that included 479 patients. EPO administration did not reduce SCr levels compared to controls (MD: −0.06 mg/dL, 95% CI: −0.15 to 0.02, $P=.13$). The level of heterogeneity was moderate between the studies ($I^2=64\%$, $P=.02$) (Fig. 4A). Subgroup analysis for changes in SCr levels demonstrated that pre-operative EPO treatment was significantly associated with a decrease in SCr level (MD: −0.15 mg/dL, 95% CI: −0.26 to −0.04, $P=.007$; $I^2=64\%$, $P=.04$). However, EPO treatment was not associated with a decrease in SCr level in the intra-operative or postoperative group (MD: 0.04 mg/dL, 95% CI: −0.08 to 0.17, $P=.48$; $I^2=0\%$, $P=.56$) (Fig. 4A).

3.5.2. Change in serum cystatin level. Serum cystatin C levels were reported in 3 studies[34,35,45] that included 248 patients. EPO administration had no impact on the decrease in serum cystatin C levels compared to controls (MD: 0.10 mg/L, 95% CI: −0.02 to 0.22, $P=.11$). The level of heterogeneity was low among the studies ($I^2=0\%$, $P=.60$) (Fig. 4B).

3.5.3. Change in serum NGAL level. Serum NGAL levels were reported in 3 studies[34–36] that included 228 patients. EPO treatment had no effect on the reduction of serum NGAL levels compared with controls (SMD: −0.19, 95% CI: −0.45 to 0.07, $P=.16$). The level of heterogeneity was low between the studies ($I^2=0\%$, $P=.65$) (Fig. 4C).

3.5.4. Change in urinary NGAL level. Urinary NGAL levels were reported in 3 studies[32,35,45] that included 250 patients. EPO treatment was associated with a significant reduction in urinary NGAL levels compared with controls (MD: −12.40 ng/mL, 95% CI: −19.42 to −5.37, $P=.0005$). The level of heterogeneity was moderate between the studies ($I^2=74\%$, $P=.02$) (Fig. 4D).

3.5.5. Intra-operative RBC transfusion. Intra-operative RBC transfusion was reported in 3 studies[31,34,44] that included 243 patients. In these studies, EPO was administered pre-operatively.

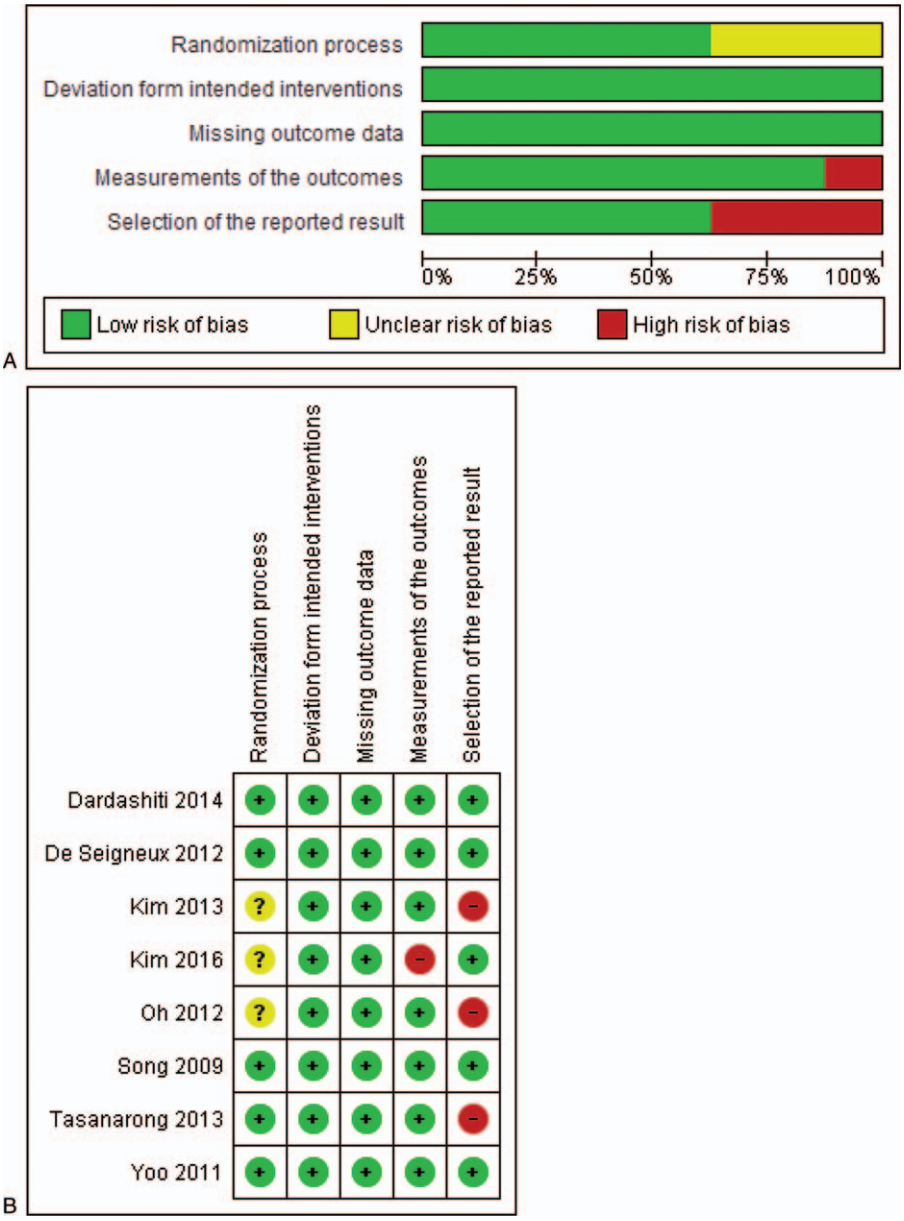

Figure 2. Summary of risk-of-bias assessment. (A) Risk-of-bias graph. (B) Risk-of-bias summary.

EPO treatment was associated with a significant reduction in the total volume of intra-operative RBC transfusion compared with controls (SMD: −0.30, 95% CI: −0.55 to 0.05, $P=.02$). The level of heterogeneity was low between the studies ($I^2=15\%$, $P=.31$) (Fig. 5A).

3.5.6. Postoperative RBC transfusion. Postoperative RBC transfusion was reported in 2 studies[31,34] that included 172 patients. In these studies, EPO was administered pre-operatively. EPO administration substantially reduced the total volume of postoperative RBC transfusion compared to controls (MD: −0.30, 95% CI: −0.61 to 0.00, $P=.05$). The level of heterogeneity was high between the studies ($I^2=82\%$, $P=.02$) (Fig. 5B).

3.5.7. Hospital length of stay. The length of hospital stay was reported in 6 studies[31,32,34,36,44,45] that included 483 patients. EPO treatment was associated with a significant decrease in the length of hospital stay (MD: −1.54 days, 95% CI: −2.70 to −0.39, $P=.009$). The level of heterogeneity was high between the studies ($I^2=75\%$, $P=.001$) (Fig. 6A). Subgroup analysis for the hospital length of stay suggested that pre-operative EPO administration was significantly associated with reduced hospital length of stay (MD: −1.73 days, 95% CI: −2.93 to −0.53, $P=.005$; $I^2=81\%$, $P=.001$). However, EPO treatment was not associated with reduced hospital length of stay in the intra-operative or postoperative group (MD: 0.79, 95% CI: −3.50 to 5.07, $P=.59$; $I^2=63\%$, $P=.10$) (Fig. 6A).

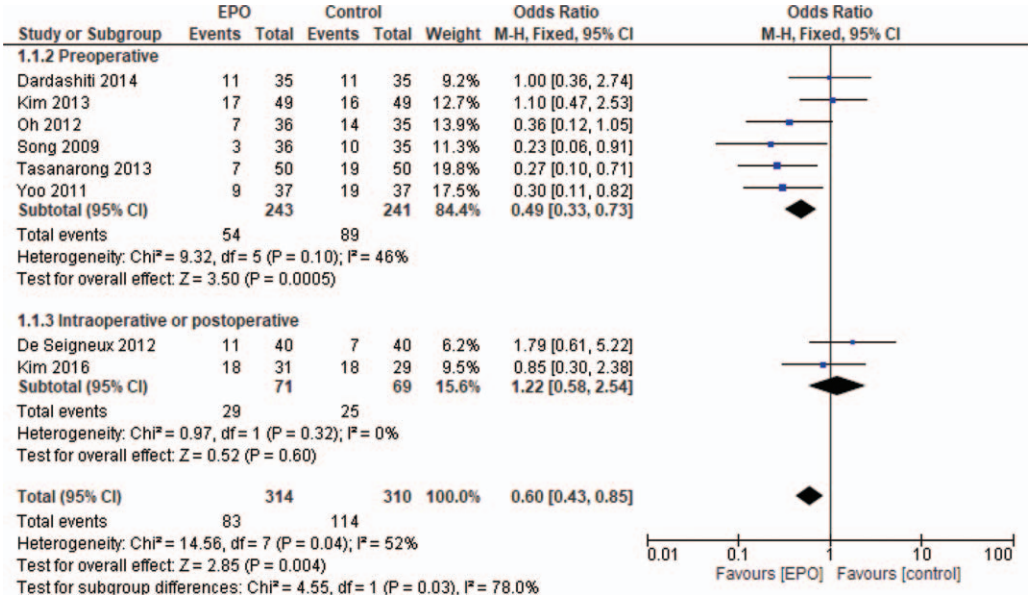

Figure 3. Forest plot of the incidence of CSA-AKI with subgroup analysis according to the timing of EPO administration. CSA-AKI = cardiac surgery-associated acute kidney injury, EPO = erythropoietin.

3.5.8. ICU length of stay. The ICU length of stay was reported in 7 studies[31,32,34–36,44,45] that included 553 patients. EPO administration did not decrease the length of ICU stay (MD: −0.28 hours, 95% CI: −0.58 to 0.02, $P = .07$). The level of heterogeneity was high among the studies ($I^2 = 82\%$, $P < .00001$) (Fig. 6B). Subgroup analysis for ICU length of stay revealed that pre-operative EPO treatment was significantly associated with reduced ICU length of stay (MD: −0.40 days, 95% CI: −0.71 to −0.08, $P = .01$; $I^2 = 84\%$, $P < .0001$). However, EPO treatment was not associated with reduced ICU length of stay in the intra-operative or postoperative group (MD: 0.73, 95% CI: −0.20 to 1.66, $P = .12$; $I^2 = 74\%$, $P = .05$) (Fig. 6B).

3.5.9. Renal replacement. The incidence of postoperative renal replacement was reported in 3 studies[32,34,36] that included 258 patients. EPO treatment was not associated with a reduction in the incidence of postoperative renal replacement compared to controls (OR: 0.65, 95% CI: 0.23 to 1.84, $P = .42$). The level of heterogeneity was low between the studies ($I^2 = 0\%$, $P = .37$) (Fig. 6C).

3.5.10. Mortality. Mortality was reported in 5 studies[31,32,34,36,45] that included 412 patients. EPO treatment was not associated with a decrease in mortality compared to controls (OR: 0.66, 95% CI: 0.24–1.83, $P = .43$). The level of heterogeneity was low between the studies ($I^2 = 0\%$, $P = .75$) (Fig. 6D). Subgroup analysis for mortality revealed that EPO treatment was not associated with a decrease in mortality in both the pre-operative and intra- or postoperative groups.

3.6. Publication bias

Publication bias was presented using the funnel plot in Figure 7. The funnel plot was symmetrical, and no publication bias was observed in this meta-analysis.

4. Discussion

Our findings suggest that EPO administration may have a role in decreasing the incidence of CSA-AKI, intra-operative RBC transfusion, urinary NGAL, and length of hospital stay. Subgroup analyses revealed that pre-operative administration of EPO significantly decreased the incidence of CSA-AKI, intra-operative RBC transfusion, SCr, and length of hospital and ICU stay. However, EPO administration was not associated with a reduction in the incidence of renal replacement or mortality.

The pathophysiological pathways of CSA-AKI involve multiple factors, including IR injury resulting from extracorporeal circulation, inflammation, oxidative stress due to ischemia and hypoxia, neurohormonal activation, endogenous and exogenous nephrotoxins, and metabolic factors.[3,24] The possible mechanisms by which EPO decreases the incidence of CSA-AKI can be clarified as follows. EPO has been reported to protect the kidney by exerting antioxidant, anti-inflammatory, and anti-apoptotic effects.[47–49] EPO also has beneficial effects on renal ischemic injury by activating signaling kinases (Akt, signal transducer and activator of transcription (STAT)-5, and mitogen-activated protein kinase) that are related to the inhibition of apoptosis.[50–52] EPO has direct antioxidant effects, such as reducing intracellular oxidative stress and attenuating oxidative stress-related renal injury through upregulation of heme oxygenase-1.[53]

The optimal timing of EPO treatment in cardiac surgery is an important issue. In an experimental study, Zhang et al[37] reported that EPO pre-treatment decreased the incidence of renal IR injury by attenuating inflammation related to the activation of phosphatidylinositol-3-kinase (PI3K)/Akt signaling through EPO receptor activation. Pre-treatment with EPO initiates negative feedback pathways, which reduce inflammatory responses and inhibit increased immune response after severe renal tissue injury.[37] Shen et al[38] also demonstrated that pre-treatment with EPO decreased the incidence of acute kidney tubular injury

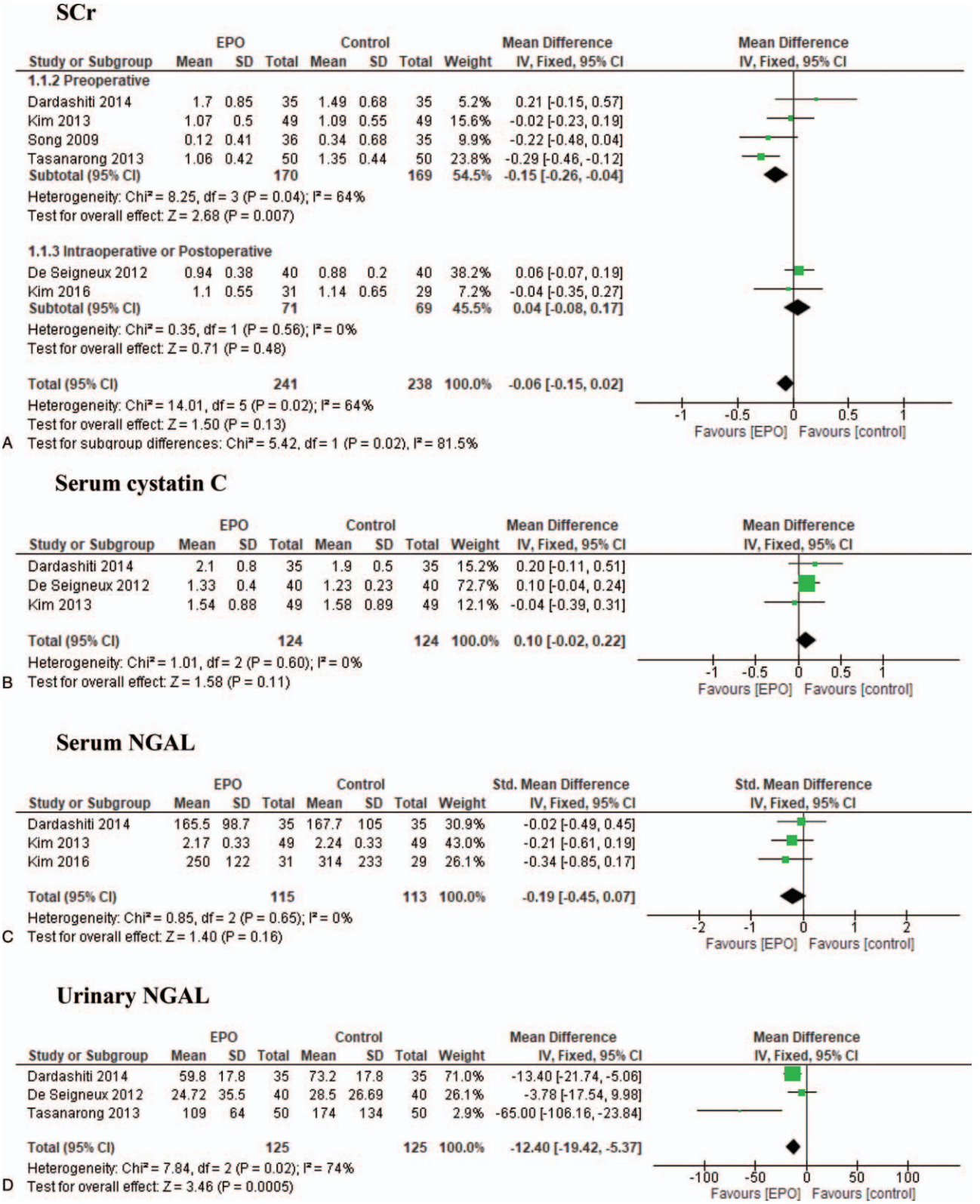

Figure 4. Forest plot of the changes in SCr, serum cystatin C, serum NGAL, and urinary NGAL. NGAL = neutrophil gelatinase-associated lipocalin, SCr = serum creatinine.

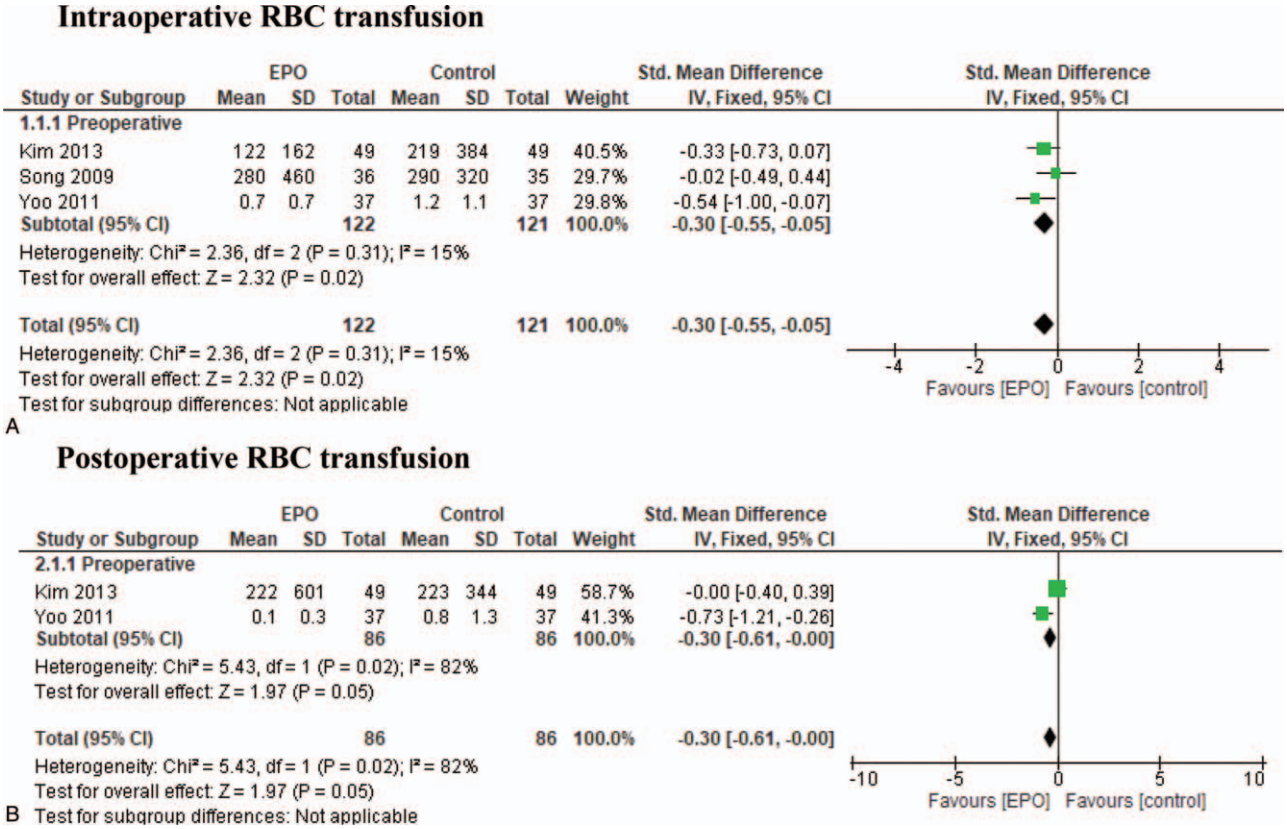

Figure 5. Forest plot of the RBC transfusion. RBC = red blood cell.

by re-establishing the emergence and role of transient receptor potential channel 6 in the collecting ducts. In contrast, in another animal study, delayed administration of EPO following ischemic injury also demonstrated renoprotective effects.[40] However, most studies have demonstrated that the administration of EPO before ischemic injury was more effective in decreasing the incidence of renal injury.[37–39] Therefore, we performed subgroup analysis on all RCTs according to the timing of EPO administration as pre-operative and intra- or postoperative groups. Our subgroup analysis revealed that pre-operative EPO treatment significantly reduced the incidence of CSA-AKI; however, intra-operative or postoperative EPO treatment did not show the same association. Pérez-Oliva et al[54] reported the comparative effects of 2 recombinant human erythropoietin (rHuEPO) formulations on basal concentrations. After subcutaneous administration of a single 100 IU/kg rHuEPO-alpha dose, maximum concentrations up to 200 mIU/mL were measured. One hundred twenty hours after subcutaneous injection, EPO levels returned to baseline. The mean life of rHuEPO-alpha was 22.5 hours. The maximum concentration was 112.7 mIU/mL at a maximum time of 18.1 hours. The mean life before excretion of rHuEPO-beta is 4 to 12 hours when administered intravenously.[54] However, no clinical studies have identified the optimal timing of EPO administration to show the renoprotective effect in patients undergoing cardiac surgery. Large-scale RCTs and elaborate experimental studies are needed to evaluate the pharmacokinetic properties and potential mechanism of renal protection of EPO according to the timing of administration.

Our meta-analysis additionally demonstrated that EPO treatment did not significantly decrease serum cystatin C level, serum NGAL level, incidence of renal replacement, and mortality. NGAL levels are almost undetectable in urine samples of patients with normal renal function and are increased early in the course of AKI. However, recent studies have reported that the diagnostic function of serum NGAL level is significantly affected by the baseline kidney function.[55,56] Our findings demonstrated that EPO treatment did not decrease the serum NGAL and cystatin C levels in patients with previous risk factors for AKI. AKI definition is also an important factor. Therefore, we performed a sensitivity analysis according to AKIN and RIFLE criteria which are the 2 types of AKI definition. As a result, there was no difference from the current results and the trend was the same. Additionally, our findings revealed that EPO administration was not associated with a reduction in the incidence of mortality and renal replacement. By the way, there were studies with zero-events among studies for mortality and renal replacement. Therefore, we also performed meta-analysis using Peto method.[57] As a result, there was no difference from our previous results. The incidence of renal replacement was reported in the studies by Tasanarong et al,[32] Kim et al,[34] and Kim et al[36]; 2 of these studies included patients with previous risk factors for AKI.[34,36] Patients with high risk factors for AKI are commonly affected by inflammation-related illnesses. However, the anti-inflammatory effects of EPO remain controversial in clinical studies. The ineffectiveness of EPO administration may be due to comorbidities in patients with high-risk factors for AKI.[58–60]

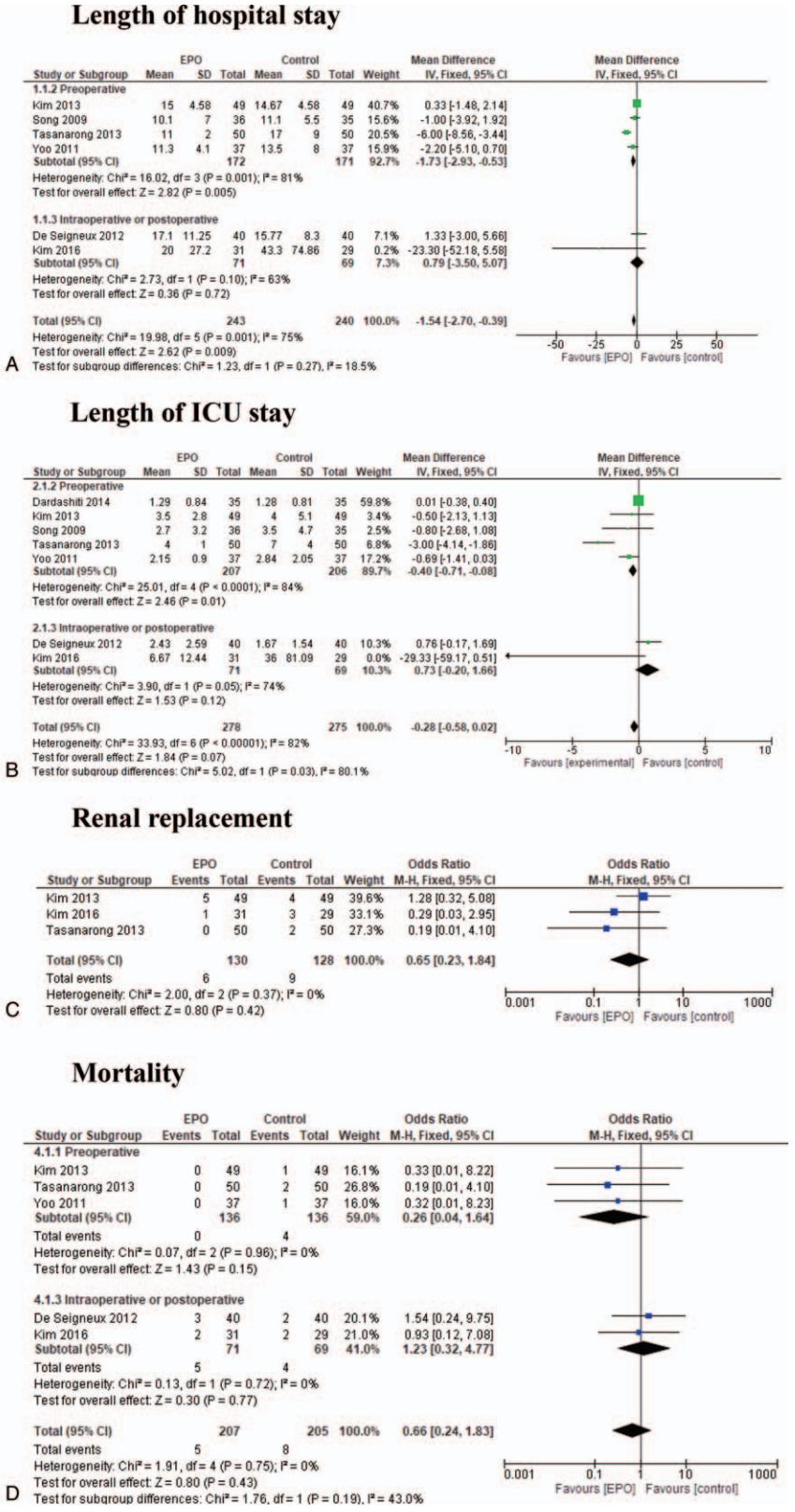

Figure 6. Forest plot of the clinical outcomes with subgroup analyses according to the timing of EPO administration. EPO = erythropoietin.

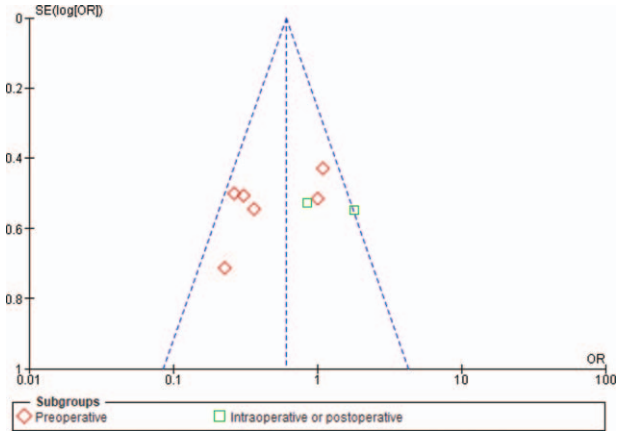

Figure 7. Funnel plot investigating publication bias of AKI incidence; 95% CI is indicated by diagonal lines. AKI = acute kidney injury, CI = confidence interval.

RBC transfusion is an independent risk factor for AKI after cardiac surgery.[6,7] Up to 30% of the transfused RBCs are hemolyzed within 1 hour of the transfusion, releasing free hemoglobin into the circulation or removed from the circulation by macrophages.[61,62] Free hemoglobin level in the plasma has also been demonstrated to be an independent predictor for AKI after CPB.[6,63] Free hemoglobin can produce endothelial injury and impair vascular function through nitric oxide scavenging.[64] Free iron can also cause renal tubulotoxicity through generation of reactive oxygen species.[65] Consequently, RBC transfusion promotes the inflammatory response, reduces tissue oxygen supply, and increases renal tissue oxidative stress.[10] These reactions eventually lead to AKI after cardiac surgery with CPB.[11]

EPO is the main regulator of erythropoiesis.[25–27] EPO has hematopoietic properties activated by hypoxia and promotes erythroid progenitor cells in the bone marrow to increase the number of mature RBCs.[66] Our findings demonstrated that pre-operative EPO reduced the amount of intra-operative RBC transfusion. Yoo et al[31] reported that intravenous administration of 500 IU/kg EPO with 200 mg iron supplementation 16 to 24 hours before surgery significantly decreased the incidence of perioperative RBC transfusion and postoperative AKI in patients who underwent valvular heart surgery. Weltert et al[67] also reported that treatment with a high dose of EPO (80,000 IU) 2 days before cardiac surgery effectively reduced the incidence of perioperative allogeneic RBC transfusion. Our findings were consistent with the results of a previous meta-analysis by Alghamdi et al[68] evaluating the effectiveness of EPO in reducing the risk of exposure to blood transfusion in cardiac surgery. Our findings suggest that pre-operative administration of EPO could reduce the intra-operative RBC transfusion requirement, which consequently might decrease the incidence of CSA-AKI. Therefore, EPO administration prior to cardiac surgery may be helpful to reduce the incidence of CSA-AKI.

This study has several limitations. First, only 8 RCTs with a total of 610 patients were included, of which 5 were conducted in 1 country and 3 RCTs in other countries. It seems to be a serious bias from limited countries. However, in Europe, the United States, and other countries, indications for the use of EPO are anemia due to chronic kidney disease and chemotherapy in cancer patients. Therefore, research may have been limited because state approval was required for the use of EPO in cardiac surgery patients. Second, we did not conduct a subgroup analysis of previous risk factors for AKI. The patients included in the 5 RCTs in our meta-analysis had high risk factors for AKI in the pre-operative period. Several comorbidities may reduce the effect of EPO in patients with high-risk factors for AKI.[58–60] Third, whether the reduced incidence of CSA-AKI was due to the renoprotective effects of EPO or the decreased RBC transfusion remains unclear. Further randomized studies and meta-analyses are required to verify the efficacy of EPO on CSA-AKI and RBC transfusion according to the timing of administration.

In conclusion, our findings suggest that pre-operative EPO treatment may decrease the incidence of CSA-AKI and RBC transfusion, but not in patients administered EPO during the intra-operative or postoperative period. Consequently, pre-operative EPO treatment can be considered to improve postoperative outcomes by decreasing the length of hospital and ICU stay in patients undergoing cardiac surgery. Further high-quality, large-scale RCTs will be needed to evaluate the efficacy and potential mechanism of renal protection of EPO according to the timing of administration.

Author contributions

Conceptualization: Hyeon Ju Shin, Choon Hak Lim.
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Supervision: Choon Hak Lim.
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Writing – review & editing: Choon Hak Lim.

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