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Liberal blood transfusion strategies and associated infection in orthopedic patients

A meta-analysis

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Abstract

Objective: It remains unclear whether transfusion strategies during orthopedic surgery and infection are related. The purpose of this study is to evaluate whether liberal blood transfusion strategies contribute to infection risk in orthopedic patients by analyzing randomized controlled trials (RCTs).

Methods: RCTs with liberal versus restrictive red blood cell (RBC) transfusion strategies were identified by searching PubMed, Embase, the Cochrane Central Register of Controlled Trials from their inception to July 2019. Ten studies with infections as outcomes were included in the final analysis. According to the Jadad scale, all studies were considered to be of high quality.

Results: Ten trials involving 3938 participants were included in this study. The pooled risk ratio (RR) for the association between liberal transfusion strategy and infection was 1.34 (95% confidence intervals [CI], 0.94–1.90; $P = .106$). The sensitivity analysis indicated unstable results, and no significant publication bias was observed.

Conclusion: This pooled analysis of RCTs demonstrates that liberal transfusion strategies in orthopedic patients result in a nonsignificant increase in infections compared with more restrictive strategies. The conclusions are mainly based on retrospective studies and should not be considered as recommendation before they are supported by larger scale and well-designed RCTs.

Abbreviations: CI = confidence intervals, RBC = red blood cell, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: infection, liberal blood transfusion, meta-analysis, orthopedic patients

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The data used to support the findings of this study are included within the article.

Our goal is to publish this systematic review in a peer-reviewed journal. Since there are no issues about participant privacy, the review will not require ethical approval.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Blood transfusion is commonly administered to patients undergoing orthopedic surgery,[1,2] and subsequent transfusion-related infections frequently occur. Many studies,[3–7] reported that the number of transfused red blood cell (RBC) units can be effectively reduced by using restrictive blood transfusion strategies, but the results show the infectious events are not significantly decreased. A previous meta-analysis,[8] found that the effect of transfusion strategies on infection was marginally significant. Gregersen[9] reported that liberal RBC transfusion strategy was not associated with higher risk of infection among residents undergoing hip fracture surgery. However, Rohde[10] reported that liberal blood transfusion strategies significantly increase infection. A meta-analysis conducted by He[11] provided some useful information showing that liberal blood transfusion is a risk factor for postoperative infection among spine surgery patients. Our previous study[12] demonstrated that liberal RBC transfusion strategies are associated with a 35% increase in infection risk. Thus, it remains controversial whether liberal blood transfusion strategies compared to restrictive blood transfusion strategies may increase infectious events.

Liberal blood transfusion strategies are more widely used for patients who undergo orthopedic surgery, and improper blood transfusion policies may result in infection, which can worsen clinical status, and cause serious harm to patients. Pooling the results of all the available studies will help to assess the efficacy and safety of restrictive versus liberal transfusion strategies for patients undergoing orthopedic surgery. We performed a new update meta-analysis with the purpose of exploring weather liberal transfusion strategies increase the infection risk among orthopedic patients, which may help establish more appropriate transfusion strategies during orthopedic surgery.

2. Methods

2.1. Search strategy and data sources

We searched PubMed (from 1946 to July 2019), Embase (from 1947 to July 2019) and the Cochrane Central Register of Controlled Trials (July 2019) for randomized controlled trials (RCTs) describing the study requirements listed below. We also searched the bibliographies of relevant articles to identify any additional studies. The following Medical Subject Headings (MeSH) and terms were used in searching: "Blood Transfusion," "liberal," "restrictive," "randomized controlled trials," "hip or knee or orthopedic, or fracture".

2.2. Study selection

Studies were considered eligible if they met all of the following criteria:

1. presented original data from an RCT;
2. used 2 comparator groups in which 1 group received a restrictive RBC transfusion strategy and the other received a liberal RBC transfusion strategy;
3. orthopedic patients as the study participants;
4. infections as outcomes;
5. adequate data for the analysis, that the studies can provide mean, standard deviation, sample size, odds ratio (OR), risk ratio (RR), hazard ratio (HR), and its 95% CIs.

If the data were duplicated or if the population was analyzed in more than 1 study, we included only the study with the largest sample size and the most comprehensive outcome evaluation. Studies were excluded if they

1. evaluated the effect of transfusion of components other than whole blood or RBC,
2. were reviews, meta-analyses, letters, and conferences.

2.3. Data extraction and quality assessment

Two teams of independent investigators (Y Wang and J Chen) independently evaluated the eligibility of the studies retrieved from the databases based on the selection criteria. These 2 teams independently extracted the following data: the first author's name, year of publication, patients' ages, sample size, hemoglobin thresholds, and infectious outcomes. Any disagreements were resolved either by discussion or consultation with the corresponding author (Y Liu). The assessment of methodological quality was based on the Jadad scale scoring system,[13] in which the maximum score is 5. We defined low quality as a Jadad score < 3.0 and high quality as a score ≥ 3.0. We also referred to the Cochrane Collaboration's tools for guidelines to assess the risk of bias.[14] The main items of the Cochrane evaluation manual include randomization sequence generation, allocation concealment, the implementation of blinding methods, the integrity of the resulting data, selective reporting, the use of intentional therapy analysis if there were losses to follow-up or withdrawal, and other biases.

2.4. Statistical analyses

RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK) was used for systematic review and meta-analysis. We calculated the RR and 95% CIs for each study using the DerSimonian and Laird random-effects model.[15] We computed the pooled RR and 95% CI for any infection in all studies based on the calculated RRs and 95% CIs. Additionally, we also pooled the RR of pneumonia and wound infection for the studies that provided adequate data. Cochran Q and I^2 statistics were used to evaluate statistical heterogeneity.[16] When the P value was $<.1$ and the I^2 value was $> 50\%$, the data were considered to be heterogeneous, and a random-effects model (DerSimonian and Laird method) was applied to estimate the overall summary effect sizes. A fixed-effects model[15,17] as used when no heterogeneity was present in the included studies. To assess the stability of our results, a sensitivity analysis (by omitting each single study in turn) was conducted to estimate the influence of individual studies on the pooled result. We used the Egger test (linear regression method)[18] and Begg test (rank correlation method)[19] to assess potential publication bias.

3. Results

3.1. Search results

The study selection was performed according to the PRISMA flow diagram (Fig. 1). We identified 1420 potential citations (371 from PubMed; 637 from Embase; 412 from the Cochrane Central Register of Controlled Trials Databases) for studies comparing a liberal blood transfusion strategy and a restrictive transfusion strategy for the treatment of orthopedic patients. Then 148 articles were excluded because of duplication. After screening the title and abstract or by further reviewing full-text articles, 38 articles were excluded (see supplementary material, http://links.lww.com/MD/F803), and 10 RCTs with infection as an outcome were ultimately identified.[4–7,9,20–24] A total of 3938 patients were included in the analysis.

Three trials were conducted in Denmark, 1 in the Netherlands, 1 in Canada, 1 in China, 1 in England, and 3 in facilities spanning multiple countries (United States, Scotland, and Canada). The general characteristics of the 10 studies are summarized in Tables 1–3. In these trials, the hemoglobin threshold ranged from 6.4 g/dl to 9.7 g/dl in the restrictive groups and from 8.0 g/dl to 10.0 g/dl in the liberal groups. Baseline hemoglobin levels were comparable between the 2 groups. Patients in the liberal groups received more RBC units than those in the restrictive groups. The studies included were all of high quality (Jadad score ≥ 3.0). The risk of bias for all the 10 studies assessed are shown in Figure 2.

3.2. Meta-analyses

Ten studies with 3,938 patients provided information about infection. The overall pooled RR for the association between transfusion strategy and infection was 1.34 (95% CI, 0.94–1.90; $P = .106$), as shown in the forest plot presented in Figure 3A. Heterogeneity was observed ($P = .085$, $I^2 = 40.8\%$). We also conducted meta-analyses for wound infection and pneumonia. Of the 10 trials, 7 provided data on pneumonia, 6 provided data on wound infection. And the data on pneumonia yielded a pooled RR of 1.25 (95%CI, 0.84–1.85; $P = .264$), whereas the data on wound infection yielded a pooled RR of 1.56 (95%CI, 0.84–2.91; $P = .161$) (Fig. 3B, C, and D).

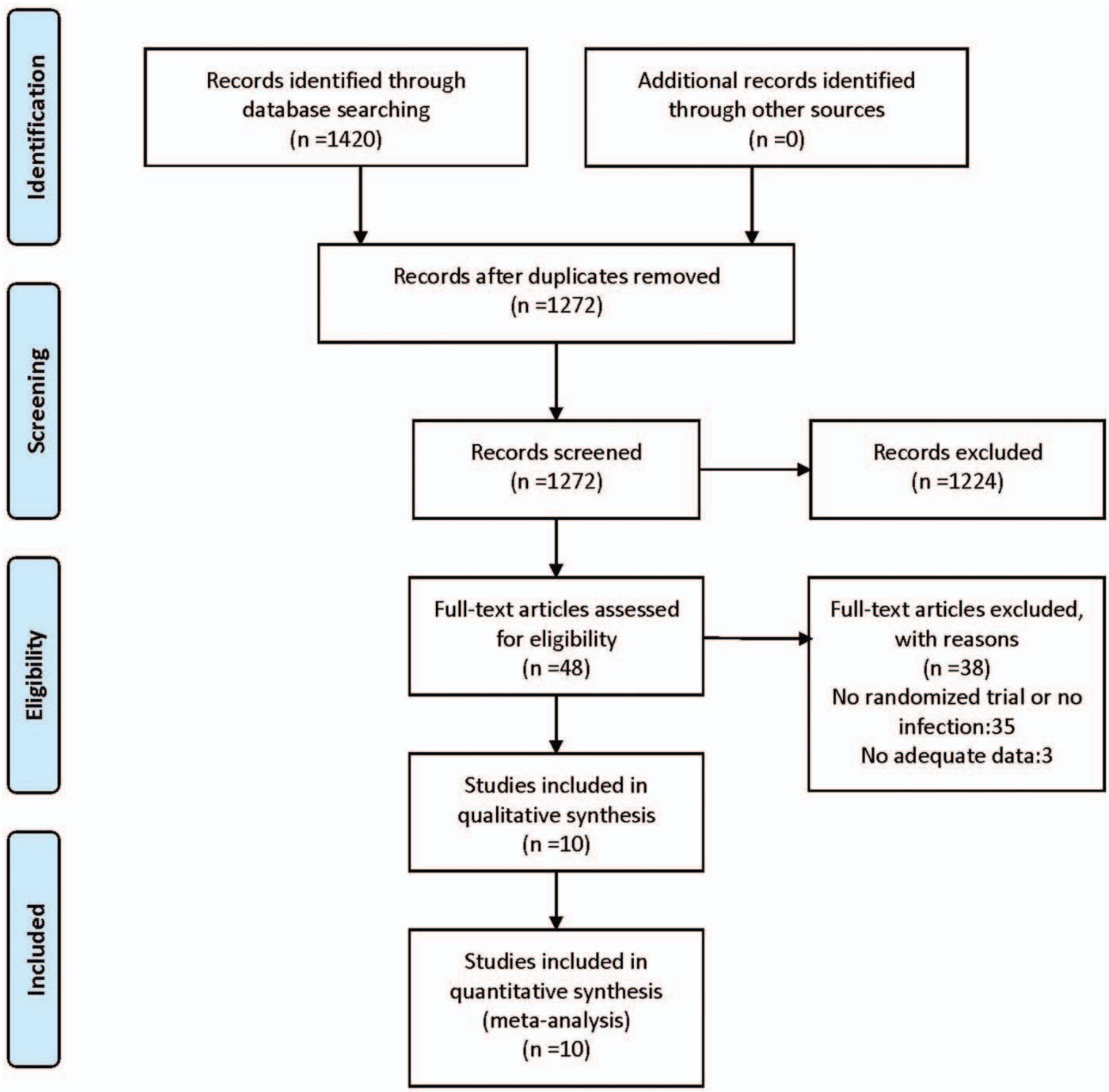

Figure 1. Flow chart of selection of studies for inclusion in meta-analysis.

No publication bias was found according to Begg test ($P=.929$) or the Egger test ($P=.006$; 95%CI, 0.44–1.81) (Fig. 4A and B).

Sensitivity analysis was performed to evaluate the robustness of our investigation by individually omitting all studies from the pool. After omitting the study published by Gregersen in 2015, the pooled RR of infection was 1.63 (95%CI, 1.17–2.26; $P=.004$), and heterogeneity was not observed ($P=.886$, $I^2=0.0\%$) (Fig. 2C).

4. Discussion

This pooled analysis of RCTs was performed to describe weather liberal RBC transfusion strategies contribute to the infection risk compared to restrictive RBC transfusion strategies in orthopedic patients. Although our study could not demonstrate a statistically significant difference between the 2 RBC transfusion strategies, there was a trend towards worse infection risk for liberal RBC transfusion strategies. These findings are different to those of other recent meta-analyses.[10,12,25] When we restricted the data to wound infection or pneumonia, we also did not find statistically significant results. The findings in our previous study[12] showed that liberal RBC transfusion strategies were associated with a 35% increase in infection risk in orthopedic patients; the results in Rohde study[10] showed that liberal RBC transfusion strategies were associated with a 30% increase in

Table 1

Characteristics of the 10 RCTs included in the final analysis of transfusion strategies and infection risk.

Study, year	Age (years)	Country	Surgery	Transfusion threshold		RCT Size	Infection	No. of infections				Jadad score
				R	L			Events (R)	Total (R)	Events (L)	Total (L)	
Carson 1998	82.3±9.5	US and Scotland	hip fracture repair	Hb <8.0 g/dl or symptomatic anemia	Hb <10.0 g/dl	84	Chest infection	0	42	2	42	3
Grover 2006	≥55	southeast England	elective lower limb joint replacement	Hb <8.0 g/dl, maintenance range, 8.0–9.5 g/dl	Hb <10.0 g/dl, maintenance range, 10.0–12.0 g/dl	218	Pneumonia	2	109	3	109	3
							Wound infection	2	109	2	109	
Foss 2009	≥65	Denmark	hip fracture repair	Hb <8.0 g/dl	Hb<10.0 g/dl	120	Pneumonia	1	60	2	60	5
							Wound infection	0	60	3	60	
							All Infections	6	60	11	60	
So-Osman 2010	≥18	Dutch	hip or knee replacement	Threshold range, 6.4–9.7 g/dl	Varied by hospital, age and condition of patients, symptoms and time	619	All infections	18	299	31	304	4
Carson 2011	≥50	US and Canada	hip fracture repair	Symptomatic anemia or if Hb <8.0 g/dL	Hb <10.0 g/dl	2016	Wound infection	8	1007	14	1005	5
Parker 2013	≥60	Canada	hip fracture surgery	8.0–9.5 g/dl and symptomatic anemia	8.0–9.5 g/dl	200	Pneumonia	2	100	5	100	5
							Wound infection	3	100	1	100	
							All infections	6	100	6	100	
Gruber-Baldini 2013	≥50	US and Canada	hip fracture repair	Symptoms or ≤8 g/dL	≤10 g/dl	139	Infections	3	72	3	66	4
Fan 2014	> 65	China	hip replacement	Symptomatic anemia or Hb <8.0 g/dl,	maintenance≥10 g/dl	192	Pneumonia	3	94	3	92	5
							Wound infection	2	94	3	92	
							All infections	8	94	10	92	
Kamilla 2014	≥18	Denmark	hip revision surgery	Hb of 7.3 g/dl	Hb of 8.9 g/dl	66	Pneumonia	0	30	4	33	3
							Surgical site infection	0	30	1	33	
Gregersen 2015	≥65	Denmark	hip fracture	Hb<9.7 g/dl	Hb<11.3 g/dl	284	Pneumonia	30	144	28	140	4
							All infections	104	144	93	140	

R represents restrictive blood transfusion strategies; L represents liberal blood transfusion strategies. Hb = hemoglobin, RCTs = randomized controlled trials.

Table 2

RBC transfused and baseline hemoglobin in the 10 RCTs groups.

Study, year	RBC Transfused (R)	RBC Transfused (L)	Baseline Hemoglobin(R)	Baseline Hemoglobin(L)
Carson 1998	0 (Median) (IQR 0–2) units 19 (45.2%) of patients received RBC transfusion	2 (median) (IQR 1–2) 41 (97.6%) of patients received RBC transfusion	(9.1 ± 0.6) g/dl	(9.1 ± 0.6) g/dl
Grover 2006	0 (Median) (Range 0–5) units 37 (34%) patients were transfused a total of 89 red cell units	0 (Median) (Range 0–10) units 46 (43%) patients received a total of 119 units	(13.1 ± 1.22) g/dl	(13.6 ± 1.22) g/dl
Foss 2009	1 (Median) (IQR 1–2) units 22 (37%) patients received transfusions	2 (Median) (IQR 1–2) units 44 (74%) patients received transfusions	No available but graphed	No available but graphed
So-Osman 2010	0.78 (Mean) ± 1.4 (SD) 105 (35%) of patients received RBC transfusion	0.86 (Mean) ± 1.6 (SD) 93 (31%) of patients received RBC transfusion	(13.7 ± 1.4) g/dl	(13.7 ± 1.4) g/dl
Carson 2011	0 (Median) (IQR 0–1) units 413 (41%) patients were transfused a total of 652 units	2 (Median) (IQR 1–2) units 970 (97%) patients were transfused a total of 1866 units	(11.3 ± 1.5) g/dl	(11.3 ± 1.5) g/dl
Parker 2013	No one received a blood transfusion	All patients received a blood transfusion with a mean of 1.9 units	11.8 g/dl	11.5 g/dl
Gruber-Baldini 2013	0 (Median) units 33(45.8%) patients were transfused a total of 53 units	2 (Median) units 63 (95.4%) patients were transfused a total of 115 units	(11.9 ± 1.7) g/dl	(11.9 ± 1.3) g/dl
Fan 2014	41(43.6%) patients received a blood transfusion	52 (56.5%) patients received a blood transfusion. More units transfused (*P* = .03)	(12.0 ± 1.1) g/dl	(11.8 ± 1.2) g/dl
Kamilla 2014	11 patients received a blood transfusion	16 received a blood transfusion	13.4 (10.2–15.0) g/dL	13.8 (10.5–16.3) g/dL
Gregersen 2015	1 (IQR 1–2) units	3 (IQR 2–5) units	(10.4 ± 1.31) g/dl	(10.3 ± 1.44) g/dl

R represents restrictive blood transfution strategies; L represents liberal blood transfution strategies. RBC = red blood cell, RCTs = randomized controlled trials.

infection risk; however, our present findings include more recent evidence with data from 2 up-to-date additional RCTs show that liberal RBC transfusion strategies are not associated with an increase in infection risk. And the findings of the present study are more thorough.

Anemia is common in patients who have undergone major orthopedic surgery, and RBC transfusion strategy is commonly used to treat anemia, particularly for patients showing symptoms or with low hemoglobin concentrations.[6,23] Transfusion-related adverse events are rather common and transfusion may affect infection risk by altering immune function,[26] so decreasing blood transfusion may be beneficial for orthopedic patients in some cases. Some previous studies[20–23] demonstrated that liberal transfusion strategies could effectively increase the number of units transfused, and Williams' study[27] reported that the number of units of RBCs transfused under a liberal transfusion strategy was 2.9 times greater than that under a restrictive transfusion strategy. All studies included in our pooled analysis also showed that the number of units of RBCs transfused was significantly increased under a liberal strategy; although no significant increase in the risk of infection was found, the trend toward a rise was apparent in each of these studies. In our

Table 3

Infection outcome definition of the 10 RCTs included in the final analysis.

Study, year	Definition
Carson 1998	used a modified Centers for Disease Control and Prevention (CDC) case definition of pneumonia: chest radiograph with new or progressive infiltrate, consolidation, or cavitation and any of the following: new onset of purulent sputum or change in character of sputum, or the isolation of the organism from blood culture, transtracheal aspirate, bronchial brushings, or biopsy. Did not consider a patient with rales and purulent sputum to have pneumonia, nor did use pleural effusion in chest radiograph definition.
Grover 2006	new infections requiring antibiotic therapy
Foss 2009	Any infectious complication such as pneumonia, sepsis and wound infection
So-Osman 2010	the CDC criteria according to Horan study (Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Grace Emori T (1992) CDC definitions of nosocomial surgical site infections, 1992: A modification of CDC definitions of surgical wound infections. American Journal of Infection Control 20: 271–274.)
Carson 2011	Wound infection; chest radiograph with new or progressive infiltrate
Parker 2013	Any infectious complication such as pneumonia, superficial wound infection, deep wound infection and septicaemia with septic shock.
Gruber -Baldini 2013	Any infections
Fan 2014	Any infectious complication such as pneumonia, superficial wound infection, and urinary tract infection
Kamilla 2014	Infectious complication such as pneumonia, surgical site infection.
Gregersen 2015	all infections (pneumonia, urinary tract infection, and other infections) within 10 days

CDC = centers for disease control and prevention, RCTs = randomized controlled trials.

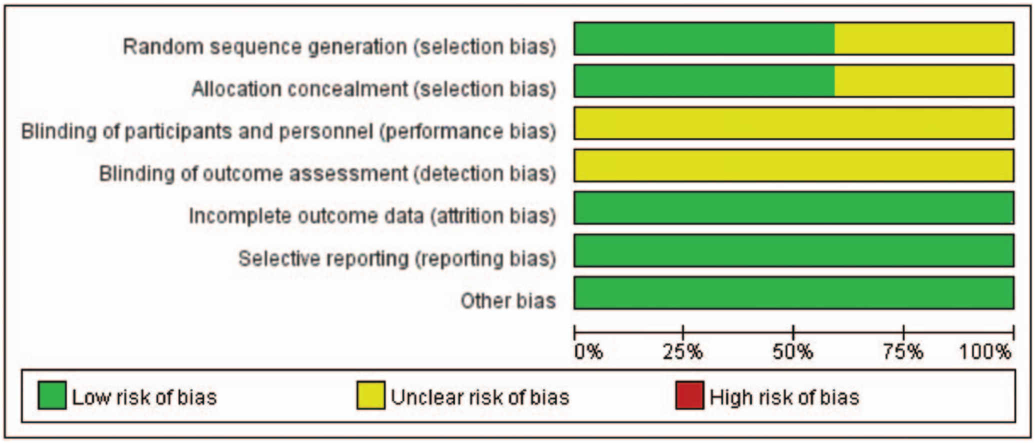

Figure 2. Risk of bias assessments for included studies.

previous meta-analysis, we observed that liberal blood transfusion strategies could significantly increase the risk of transfusion-associated infection.

Publication bias was not observed in our pooled analysis. According to the sensitivity analysis, the combined results were unstable. Gregersen study[9] reported high infection risk in both liberal blood transfusion strategy and restrictive blood transfusion strategy; after we omitted the trial, we found the pooled results were unstable, which indicated that our results were likely due to differences of the infection definition across randomized groups. The combined results after omitting the other trials were stable and robust according to the sensitivity analysis. Heterogeneity was found in our analysis, and the source of heterogeneity was found coming from Gregersen study; after we omitted Gregersen study, we found that heterogeneity was disappeared; therefore, we think that the different standard of infection definition maybe the factors of the heterogeneity. As our previous meta-analysis, all of the

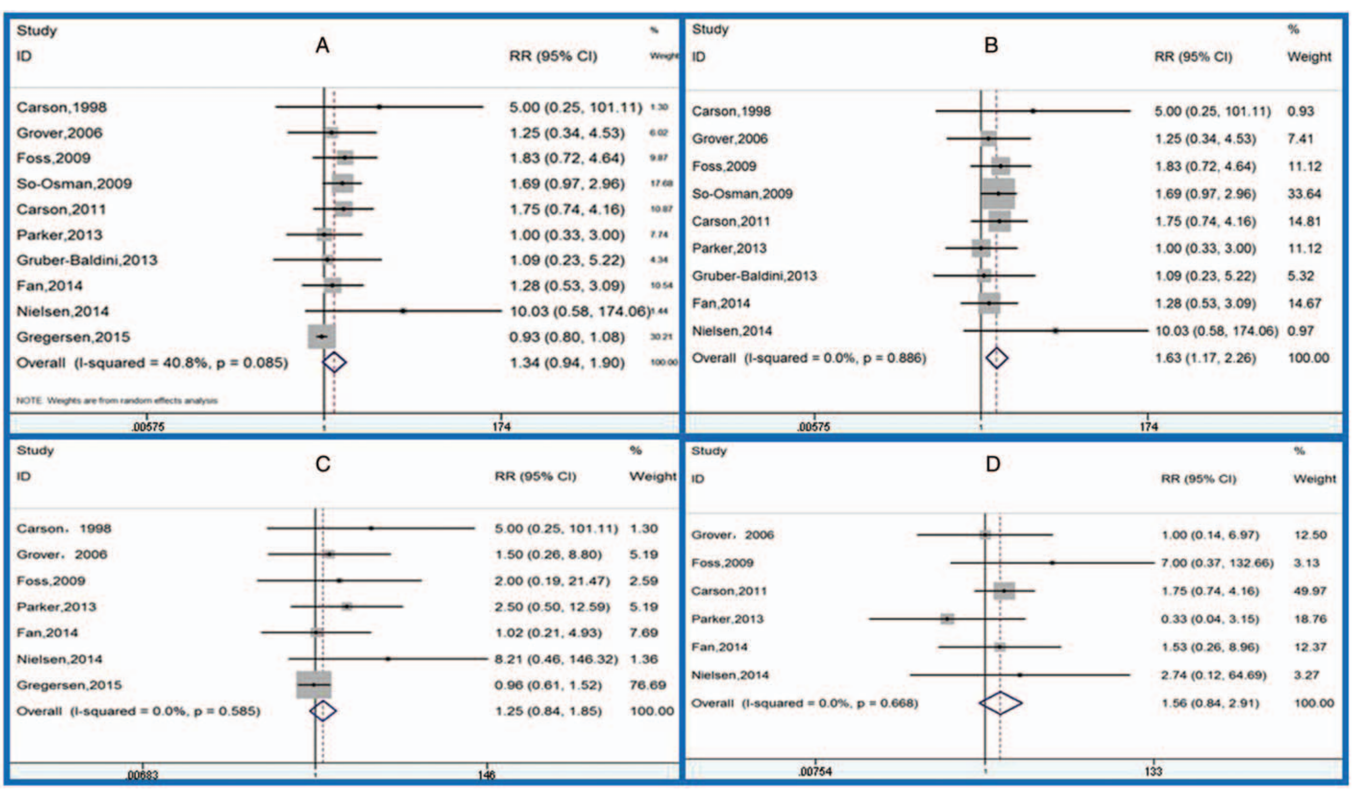

Figure 3. Forest plot. (A): Forest plot of RRs with CIs for the use of transfusion strategies and the risk of infections according to the 10 RCTs in the random effects model meta-analysis; (B): Forest plot for RCTs after omitting Gregersen trial in a fixed-effects model meta-analysis; (C): Forest plot for pneumonia risk according to 7 RCTs in a fixed-effects model meta-analysis; (D): Forest plot for wound infection risk according to 6 RCTs in a fixed-effects model meta-analysis.

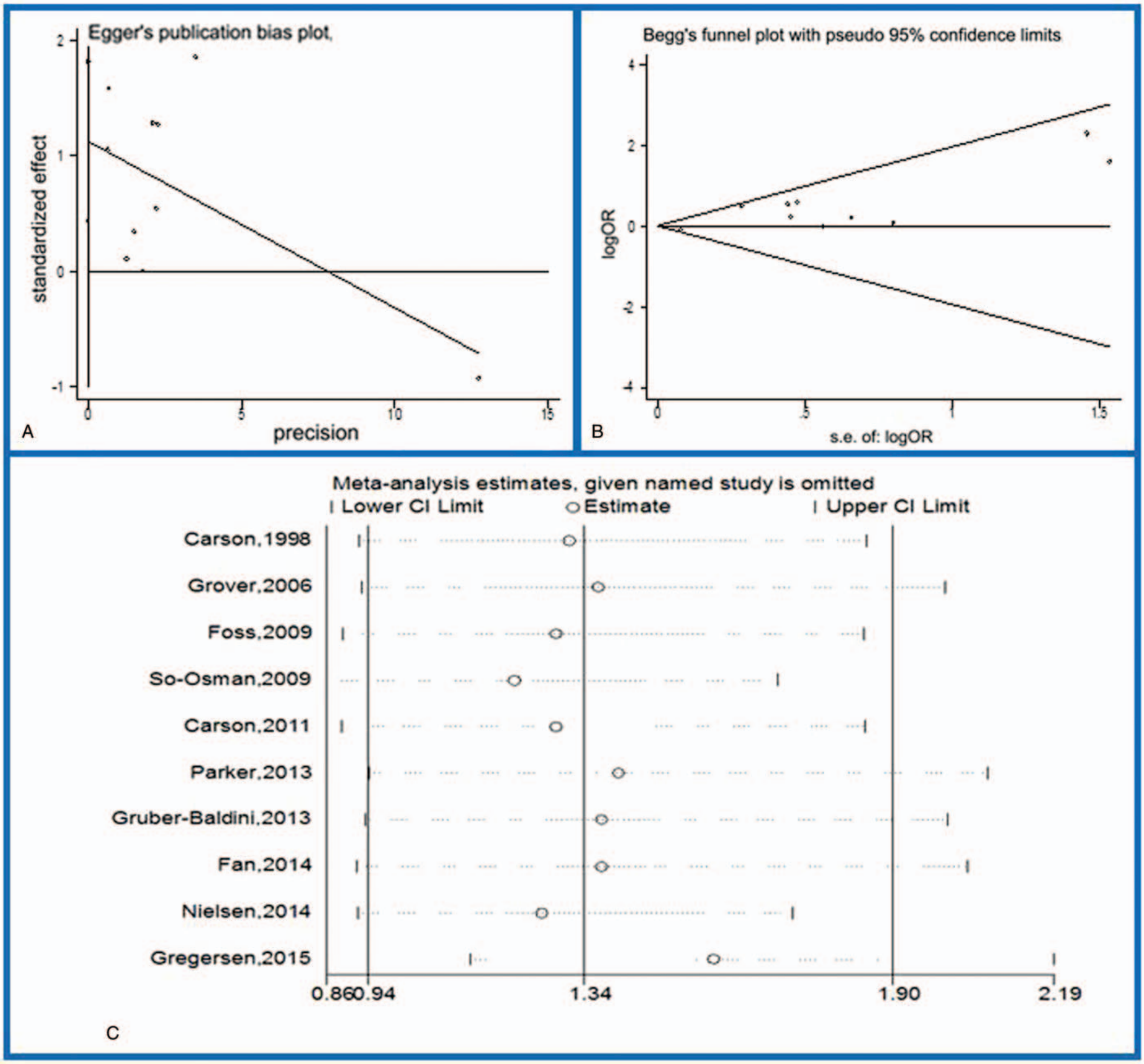

Figure 4. (A): Egger funnel plot of the 10 RCTs; (B): Begg funnel plot of the 10 RCTs; (C): Sensitivity analysis of the 10 RCTs.

included studies adopted a randomized controlled design, and all studies were of good quality.

Despite the advantages, several limitations of our pooled analysis should be acknowledged. First, all eligible RCTs were restricted to those published in the English language, which may limit the result. Second, the number of patients in all of included studies was really small, which may lead to underpowered results. Third, the pooled results may be overestimated for the unpublished gray studies with nonsignificant results. Fourth, the results of our pooled analysis were unstable; heterogeneity was found for that infectious outcomes varied across the included studies. Fifth, for the included studies, types of the listed infections were different, which may cause imprecise results. Sixth, Criteria for restrictive and liberal strategies was different, thus more studies with the same criteria are needed. Finally, larger-scale RCTs are needed, and our meta-analysis findings should be interpreted with caution.

5. Conclusion

We conducted a meta-analysis of RCTs and found that a liberal transfusion strategy resulted in a nonsignificant increase in infections compared with a more restrictive strategy in orthopedic patients. However, liberal RBC transfusion strategies toward a worse infection risk trend. Larger scale and well-designed RCTs are still needed to aid clinicians in choosing an optimal transfusion strategy for patients undergoing orthopedic surgery.

Author contributions

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Writing – review & editing: Ying Wang.

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