Systematic Review and Meta-Analysis

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Is blood transfusion associated with an increased risk of infection among spine surgery patients?

A meta-analysis

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Abstract

Background: Blood transfusions are associated with many adverse outcomes among spine surgery patients, but it remains unclear whether perioperative blood transfusion during spine surgery and postoperative infection are related. Recently, many related cohort studies have been published on this topic.

Methods: This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The PubMed, Embase, and Cochrane Library databases were searched for eligible published studies. The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of the studies, and a random-effects model was used to calculate the odds ratios (ORs) with 95% CIs. Sensitivity analyses were conducted to explore the source of heterogeneity.

Results: The final analysis included 8 cohort studies with a total of 34,185 spine surgery patients. These studies were considered to be of high or moderate quality based on their NOS scores, which ranged from 5 to 9. Pooled estimates indicated that blood transfusion increased the infection rate (OR, 2.99; 95% CI, 1.95 to 4.59; $I^2 = 86\%$), which was consistent with the sensitivity analyses.

Conclusions: Our results suggest that perioperative blood transfusion is a risk factor for postoperative infection among spine surgery patients. Further study is necessary to identify other influencing factors and to establish the mechanism underlying this relationship. Additional measures may be needed to reduce unnecessary blood transfusions during spine surgery.

Abbreviations: EBL = estimated blood loss, Hb = hemoglobin, HR = hazard ratio, MD = mean difference, NOS = Newcastle–Ottawa Scale, NSQIP = National Surgical Quality Improvement Program, OR = odds ratio, PRBCs = packed red blood cells, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Keywords: blood transfusion, infection, meta-analysis, spine

1. Introduction

Blood loss is one of the major concerns in spine surgery. Many measures such as stripping skeletal muscles and exposing cancellous bone can cause direct or indirect blood loss and are often accompanied by coagulopathy.[1] As a common method used to solve the problem, blood transfusion involves the intravenous infusion of various blood components to patients, improving the oxygen transport capacity of blood and tissue oxygenation. According to the results of 1 study, 8% to 36% of spine surgery patients required perioperative blood transfusions; these transfusions were generally performed 7 days before to 30 days after surgery.[2] Studies have shown that the factors that influence the need for transfusion are complicated, including the patient's age, preoperative hemoglobin (Hb) level, comorbidities, treatment methods, and duration of surgery.[3,4]

Blood transfusion is essential and beneficial in many cases, but it is still compromised by a series of possible complications. Recently, allogeneic blood transfusion was speculated to be an independent risk factor for bacterial infections in orthopedic surgery, which may result in higher morbidity and worse prognoses, particularly in elderly patients. This hypothesis was supported by several animal models. However, the same result was not observed when syngeneic blood was given.[5,6] Most scholars believe that these observations were due to the immunosuppressive effects of allogeneic transfusions.[7] Other research suggested that fracture patients who received less than 3 units of packed red blood cells (PRBCs) had no significant differences in morbid complications compared to nontransfused patients.[8] It is difficult to confirm the association between blood transfusion and infection. A meta-analysis conducted by Kim provided some useful information showing that allogeneic blood transfusion increased the risk of infection during joint replacement.[9] However, the postoperative infection rate of spine surgery is particularly worthy of attention among orthopedic surgeries because of the long operation time and because swelling and congestion of soft tissue more readily occur. Moreover, the surgery is often accompanied by the placement of internal

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fixation. Thus, once an infection occurs, it is difficult to cure and causes serious harm to patients. However, the relationship between perioperative blood transfusion and postoperative infection in patients who undergo spinal surgery has not been well described.[10]

With advances in technology, blood transfusion practices in spine surgery have undergone significant changes. The use of allogeneic transfusion has substantially decreased, whereas that of autologous and intraoperative autotransfusion has increased.[11] The association between blood transfusion and infection must be systematically evaluated in spine surgery. This meta-analysis was designed to determine whether perioperative blood transfusion increases the infection rate among spine surgery patients, which may help establish more appropriate transfusion policies during spine surgery.

2. Methods

This study was based entirely on published data; thus, no ethical approval or patient consent were required.

2.1. Study search and selection

The PubMed, Embase, and Cochrane Library databases were searched for relevant articles published from inception to July 2017. The key words were as follows: 'spine' or 'vertebra' or 'sacrum' or 'coccyx' AND 'blood transfusion' AND 'infection' or 'toxicema' or 'sepsis' (refer to Appendix Table 1 for details, http://links.lww.com/MD/D80). The search language was limited to English.

Two reviewers independently assessed the titles and abstracts of papers and resolved discrepancies through discussion. If an agreement could not be reached, a final decision was made by a third reviewer. The inclusion criteria were as follows:

1. observational, cohort studies;
2. studies that examined the impact of blood transfusion on the infection rate among spine surgery patients;
3. sufficient data presented to allow further analysis; and
4. data not duplicated in another manuscript (refer to Table 1 for details).

2.2. Data extraction and quality assessment

We used Microsoft Excel (Microsoft Corporation, USA) to extract the following data: first author, study period, country, demographic parameters, estimated blood loss (EBL), operative time, comorbidities, treatment methods, transfusion, study design, covariates, and outcomes of interest. The primary outcome was infection. The other outcomes included length of hospital stay and morbid complications. The quality of the included observational studies was assessed by the Newcastle–Ottawa Scale (NOS) score.[12] The studies were classified as low, moderate, and high quality according to NOS scores of 0 to 3, 4 to 6, and 7 to 9, respectively.

Table 1

Inclusion and exclusion criteria of the current meta-analysis.

Detailed inclusion and exclusion criteria based on PICOS framework	
Populations	Surgical spine patients
Intervention/Exposure	Blood transfusion in perioperative period
Control	No blood transfusion in perioperative period
Clinical outcomes	Infection
Study design	Observational study: cohort studies.
	Studies published in English
Exclusion criteria	Reviews
	No cohort studies
	Conference abstracts

2.3. Statistical analysis

After summarizing the data from each study, we divided the patients into 2 groups: "Transfusion group" and "Non-transfusion group", according to whether they received perioperative blood transfusion during spine surgery. The effects were assessed by adjusted odds ratios (ORs) or the mean difference (MD). ORs were used instead of hazard ratios (HRs) because of the high incidence of events. We pooled individual study data using the Mantel–Haenszel method. Because of the anticipated heterogeneity, we used a random-effects model. Heterogeneity was evaluated by the I^2, Chi^2, and Tau^2 statistics. A value of $I^2 >$ 50% was regarded as significant heterogeneity. A two-sided P-value<.05 was considered statistically significant. To explore possible sources of heterogeneity, we performed sensitivity analyses by omitting each study individually to assess the effect of the individual study. All statistical analyses were conducted with Review Manager 5.3.[13]

3. Results

3.1. Study selection

A total of 1648 related studies were identified in 3 databases. Forty one studies remained after removing duplicates and irrelevant records after further assessment. Five studies were meta-analyses or reviews, 3 studies were not cohort studies, and the remaining studies did not report primary outcomes from which the required data could be extracted. No other eligible studies were identified in the references of the included studies or important reviews. Finally, 8 studies were included in our meta-analysis. The study selection process was performed as described in the flow diagram.

3.2. Study characteristics

The basic information of the 8 studies is shown in Table 2. All studies were retrospective cohort studies except for one ambispective cohort study. The sample size of the included studies ranged from 56 to 13,695. Treatment methods mainly involved various types of spine surgery. Demographic characteristics, comorbidities, preoperative Hb levels, EBL, and operative times showed wide variability across the included studies. The NOS scores of the studies are shown in Appendix Table 2., http://links.lww.com/MD/D80 4 studies were of moderate quality, and 4 were of high quality.

3.3. Infection rate

The pooled analysis suggested that blood transfusion increased the infection rate among spine surgery patients (8 studies; OR, 2.99; 95% CI, 1.95–4.59; Fig. 1), with high heterogeneity ($I^2 = 86\%$). The sensitivity analyses showed that the ORs ranged from 2.65 (95% CI, 1.76–3.99) to 3.27 (95% CI, 1.93–5.54), and the I^2 statistic ranged from 78% to 88%. Two studies

Table 2

Baseline characteristics of the included studies.

Study characteristics					Patients characteristics			
Author/year	Study location	Period of enrolment	Study design	Covariates in Multivariable model	Number of patients (Expose/Control)	Age (mean) male (Expose/Control)	Comorbidity	Treatment methods
Aladine et al, 2017	America	2008–2010	Ambispective cohort study	age, sex, and body mass index (BMI), length of surgery, number of vertebral levels involved, EBL, and urinary output	60/100	57.78/56.28 30/50	diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), hyperlipidemia, peripheral vascular disease (PVD), hypertension (HTN), and atrial fibrillation, DVT, PE, hematoma, cardio-pulmonary arrest, and CVA	posterior decompression and fusion.
Christian et al, 2017	Sweden	2012–2015	Retrospective cohort study	levels of surgery, length of surgery, starting and ending hematocrit, EBL, Vancomycin powder (2g)	36/20	64.3/67.3 12/8	–	spine surgery of >8 levels fused with a posterior approach
Daniel et al, 2017	America	2009–2015	Retrospective cohort study	the number of vertebral levels surgically fused, EBL, nadir hemoglobin, duration of surgery, vertebral levels	603/360	59/52 215/194	transient ischemic attack (TIA), cerebrovascular attack (CVA), myocardial infarction (MI), kidney injury, deep venous thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC).	posterior spinal fusion surgery
Purvis et al, 2017	America	2008–2015	Retrospective cohort study	age, preoperative Hb level, estimated blood loss (EBL), total crystalloid fluid use, ASA class	2374/4557	57/50 935/2197	thrombotic event, kidney injury, respiratory event, ischemic event	cervical fusion, lumbar fusion tumor-related surgeries
Ahmed et al, 2016	America	2010–2013	Retrospective cohort study	sex, age, and race, BMI, comorbidities, steroids intake, functional health status, and ASA class.	2407/11288	63.7/58.8 937/5045	DVT, PE, MI	lumbar or thoracic fusion
Janssen et al, 2016	America	2001–2013	Retrospective cohort study	age, sex, race, comorbidity, tobacco use, obesity, duration of surgery, preoperative hemoglobin level, operative treatment,	293/3428	64/54 113/1865	Congestive heart failure, Dementia, Chronic pulmonary disease, Rheumatologic disease, Liver disease, Diabetes, Hemiplegia or paraplegia, Renal disease, tumor, AIDS/HIV	laminectomy or arthrodesis of the lumbar spine.
Kato et al, 2016	Japan	2007–2012	Retrospective cohort study	sex, age, type of hospital, preoperative comorbidities, operative methods, cell saver use and duration of anesthesia	4275/4275	72.7/69 2698/2714	diabetes, cardiovascular diseases, cerebrovascular diseases, and hemodialysis	elective lumbar surgeries
Triulzi et al, 1992	America	1988–1990	Retrospective cohort study	age, gender, operative treatment, hematocrits (Hcts), white cell (WBC), duration of surgery, EBL, comorbidity, days of fever, days on antibiotics	24/85	30.3/32.8 9/41	–	spine surgery

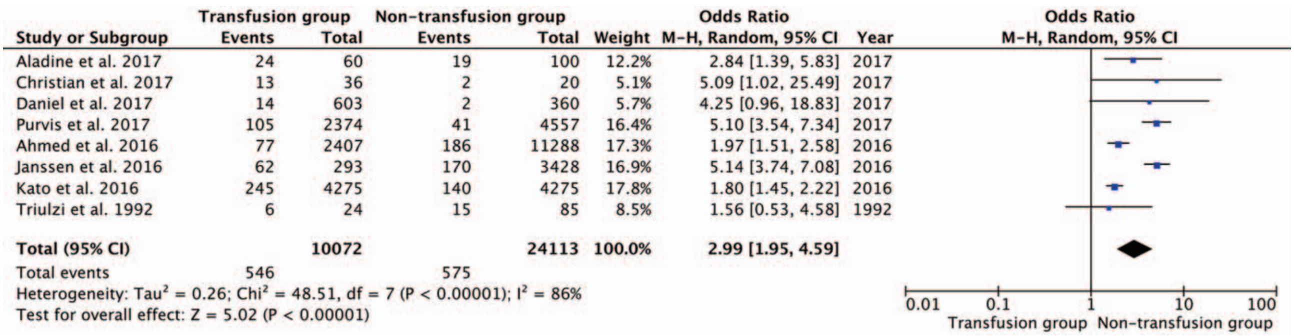

Figure 1. Forest plot summary comparing the infection rate between the Transfusion and Non-transfusion groups. CI=confidence interval, OR=odds ratio.

(Purvis et al, 2017 and Janssen et al, 2016) were identified as the source of statistical heterogeneity (refer to Table 2 for details). We found that removing either 1 of the studies did not significantly reduce heterogeneity: I^2 = 82% when we removed the study by Purvis et al 2017, and I^2=78% when we removed the study by Janssen et al 2016 (Appendix Fig. 1 and Appendix Fig. 2, http://links.lww.com/MD/D80). However, when both studies were removed, no heterogeneity was observed among the 6 remaining studies, but the result was not substantially changed (I^2 = 0%; OR, 1.93; 95% CI, 1.65–2.26; Fig. 2). Since only 8 studies were included, a funnel plot was not appropriate for this study.

3.4. Other outcomes

To further understand the impact of blood transfusion on spine surgery patients, we also analyzed the length of hospital stay and morbid complications. According to the results, blood transfusion was associated with a longer hospital stay (4 studies; MD, 3.55; 95% CI, 1.97–5.14; Fig. 3) and a higher rate of morbid complications (5 studies; OR, 2.65; 95% CI, 1.23–5.71; Fig. 4) among spine surgery patients. The studies showed high heterogeneity (I^2 = 73% in Fig. 3 and I^2 = 98% in Fig. 4); however, the results were consistent in the sensitivity analyses. When we separately removed the studies to investigate the sources of heterogeneity, the results were as follows: MD, 2.76; 95% CI, 1.63 to 3.90 (Fig. 5) and MD, 2.80; 95% CI, 2.35 to 3.35 (Fig. 6). Therefore, the results still fully indicated the adverse effects of blood transfusion on patient prognosis.

4. Discussion

This review was performed by strictly following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The results showed that perioperative

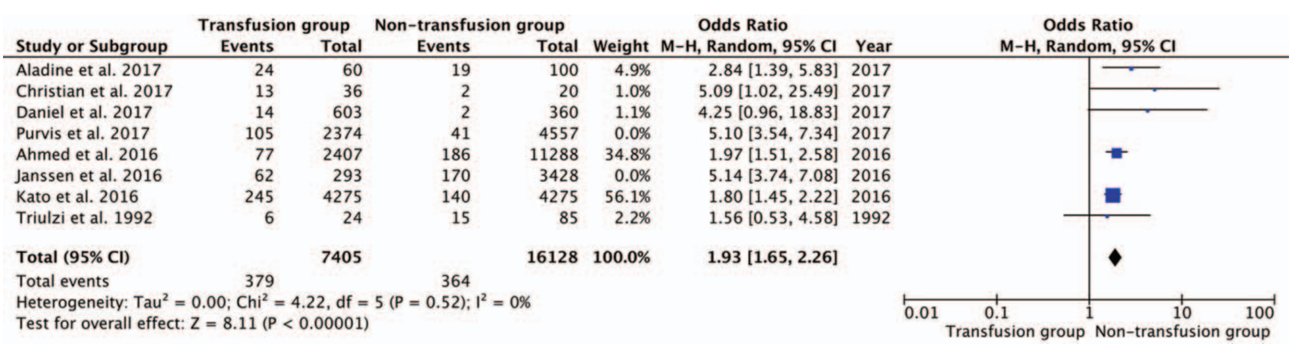

Figure 2. Forest plot summary comparing the infection rate between the Transfusion and Non-transfusion groups (after removal of studies with high heterogeneity). CI=confidence interval, OR=odds ratio.

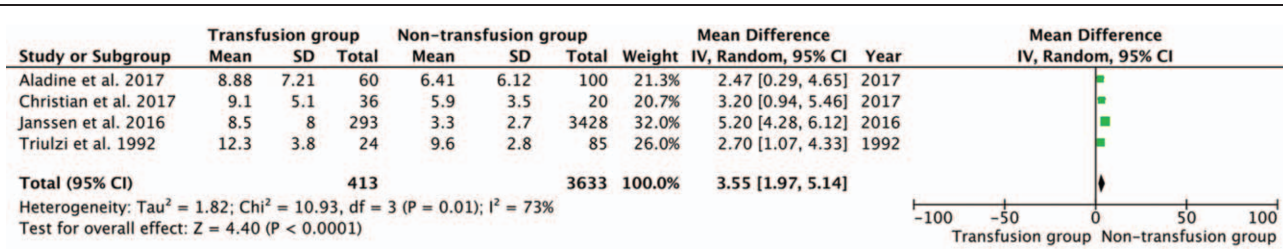

Figure 3. Forest plot summary comparing the length of hospital stay between the Transfusion and Non-transfusion groups.

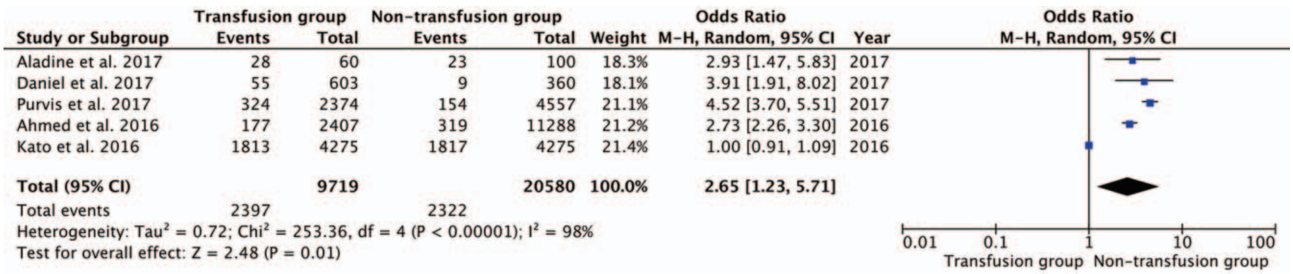

Figure 4. Forest plot summary comparing morbid complications between the Transfusion and the Non-transfusion groups.

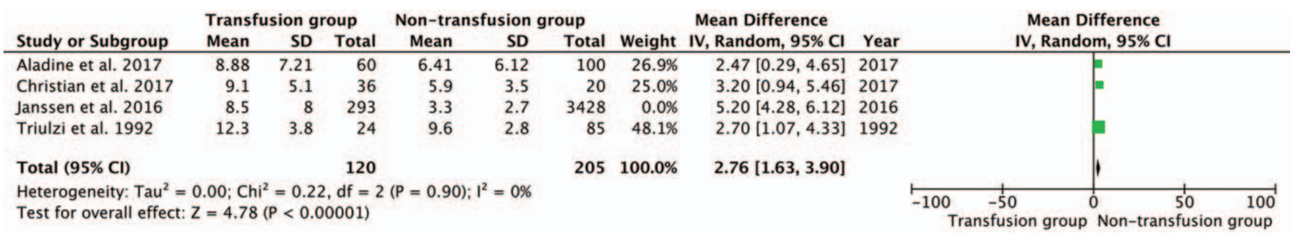

Figure 5. Forest plot summary comparing the length of hospital stay between the Transfusion and Non-transfusion groups (after removal of studies with high heterogeneity).

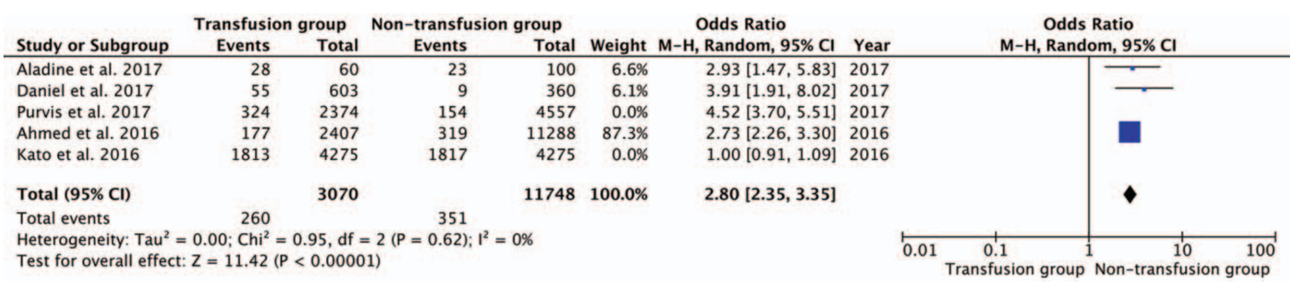

Figure 6. Forest plot summary comparing morbid complications between the Transfusion and Non-transfusion groups (after removal of studies with high heterogeneity).

blood transfusion increased the risk of infection among spine surgery patients, which has also been supported by other studies. Many studies have observed a relationship between blood transfusion and superficial wound infections. Some small case-control studies have suggested that blood transfusion increases surgical site infection after spine surgery, but the number of such studies was too small to perform a separate analysis. To ensure the consistency of the included studies, we did not include these studies in our analysis. For other surgical procedures such as joint replacement, some evidence suggests that blood transfusion is related to increased infection rates. However, significant differences exist between arthroplasty and spine surgery. Spine surgery often involves less blood loss, and the subsequent infection is greatly affected by the surgical site, surgical route, and other confounding factors, which increases the difficulty of identifying the relationship between blood transfusion and infection.[14,15,16]

The increased infection rate caused by blood transfusion is usually attributed to transfusion-related immunosuppression.[7] However, the mechanism responsible for this relationship remains unknown. Other possible factors including transfusion errors and transfusion-transmissible infections also cause serious risks, but they seldom occur and are entirely preventable.[17]

Many potential confounding factors might have affected our results. For example, the use of a urinary catheter, which was usually in place longer than 120 minutes, might increase the infection rate among surgical patients.[2] The different infection rates between the Transfusion group and the Non-transfusion group could also be explained by the difference in blood loss.

Moreover, our results suggested a relationship between blood transfusion and other interesting outcomes including the length of hospital stay and morbid complications in spine surgery patients. Together, these factors revealed the adverse effects of blood transfusions on patient prognosis, but the relationship among these factors is still unclear. Because of the lack of standardization of transfusion protocols in the database, the results might be biased, and additional relevant studies are required.

Recently, a related systematic review suggested an association between allogeneic transfusion and infection in spine surgery patients based on several low-strength studies with a high or moderately high risk of bias. The risk was not consistent for different infection types.[18] However, to improve the accuracy of the results, we conducted an independent study on this issue by searching additional databases, optimizing the search strategy, and restricting the type of studies to cohort studies with high quality based on the NOS.

Identification of risks related to blood transfusion will lead to stricter transfusion policies. The American Association of Blood Banks recommends that blood transfusion should be considered for stable patients with Hb levels less than 7 g/dl, surgical patients with Hb levels less than 8 g/dl, or patients with symptoms such as chest pain, unresponsive tachycardia, or congestive heart failure.[19] As our results show, more restrictive transfusion policies should be considered for spine surgery to maximize clinical benefits and avoid unnecessary risks. Meanwhile, additional, relevant, randomized controlled trials should be conducted. Alternative measures that reduce blood transfusions, including reinfusion, cell salvage techniques, and preoperative blood donation, should be advocated.

However, our research has some inevitable limitations. First, the statistical heterogeneity was significant ($I^2 = 86\%$), and we found that the sources of statistical heterogeneity mainly included two studies: Purvis et al, 2017 and Janssen et al, 2016. Unfortunately, we could not identify the specific causes of heterogeneity. However, there were several clinical and methodological differences across the included studies, such as demographic characteristics, comorbidities, treatment methods, and study design. Second, the results were based only on observational studies, which might distort the actual effects of blood transfusion because of the potential confounding bias and selection bias. Much of the data were obtained from the National Surgical Quality Improvement Program (NSQIP) database, which lacks certain parameters of interest including EBL, adverse reactions, and other clinical outcomes. Moreover, different hospital protocols might be used in each institution, and these were not available in the NSQIP database.[20] Third, a funnel plot was not produced because of the limited number of studies; therefore, we could not exclude possible publication bias. Overcoming these deficiencies will require more relevant research, more detailed raw data, and further analysis and summary of such data in the future.

5. Conclusions

The current evidence indicates that perioperative blood transfusion increases the risk of postoperative infection among spine surgery patients. Because of the high heterogeneity among studies, the results should be interpreted cautiously, and more randomized, controlled, high-quality studies are necessary to clarify the influence of other factors, such as EBL and operative time, on infection.

Author contributions

Conceptualization: Yu-Kun He, Hua-Ding Lu.
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