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Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review

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Abstract

Objectives To determine if hemoglobin level below 7g/dl is a priority trigger for blood transfusion for ICU patients, and even patients with septic shock by conducting a comprehensive system review and meta-analysis, underlying impacts on short-term mortality and adverse effects.

Data sources We performed systematical searches for relevant randomized controlled studies in the Cochrane Library, EMBASE, and PubMed databases up to May 1, 2018. The clinical outcomes, including short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction(MI), and ischemic events, were screened and analyzed after data collection. We applied odds ratios (ORs) to analyze dichotomous outcomes and mean differences to analyze continuous outcomes with a random effects model.

Results Nine RCTs with 3551 patients were included. Compared with a more liberal threshold, an RBC transfusion threshold < 7 g/dl hemoglobin showed no significant difference in short-term mortality (OR: 0.92, 95% CI: 0.70-1.20; *P*=0.52; I^2=47%), length of ICU stay (MD: -0.05, 95% CI: -0.70-0.61, *P*=0.89, I^2=0%), MI (OR: 0.56, 95% CI: 0.30-1.04, *P*=0.07; I^2=0%), or ischemic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%). However, the length of hospital stay was shorter in the group with the threshold < 7 g/dl than that with the more liberal threshold.

Conclusions A RBC transfusion threshold < 7 g/dl hemoglobin is incapable of decreasing short-term mortality in ICU patients according to currently published evidence. Further studies are needed to for determine the optimal RBC transfusion strategy.

Keywords: Red blood cells, Transfusion, Hemoglobin, Intensive care units, Septic shock

Strengths and limitations of this study

1. This meta-analysis focused on the feasibility of a transfusion threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients through only including RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl.

2. In this meta-analysis, we performed an updated and comprehensive analysis that focused on ICU patients with septic shock.

3. The number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl.

4. There was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions.

Introduction

Allogenic red blood cell (RBC) transfusion remains a commonly used and crucial treatment among patients admitted to the intensive care unit (ICU). Undoubtedly, appropriate blood transfusion can benefit critical ill patients by increasing oxygen delivery and reducing oxygen debt, protecting against multiple organ dysfunction [1]. Every year, approximately 75 million units of blood are reportedly obtained worldwide, with higher levels of consumption in the UK, Canada, and US [2, 3]. These data urge the cautious use of RBCs because of the substantial cost and supply shortage. Additionally, the risk of complications, such as volume overload, infection, transfusion reactions, and even increased mortality, also raises concerns about the threshold for RBC transfusion in ICU patients [4-6]. However, the optimal thresholds for RBC transfusion in diverse critical care settings remain controversial.

The results of the Transfusion Requirements in Critical Care (TRICC) study have confirmed the superiority of a restrictive transfusion strategy in controlling the 30-day mortality of critical ill patients with younger age and lower Acute Physiology and Chronic Health Evaluation (APACHE II) score. Indeed, conservative blood transfusion could result in a marked decline in the use of RBCs, which further decreases the in-hospital cost of ICU patients [2, 7]. Recently, various studies have extensively discussed transfusion strategies to optimize the outcomes. For instance, no significance was shown between restrictive and liberal transfusion strategies in terms of adverse effects, as reported by some studies [8, 9]. However, other researchers

found that blood transfusions triggered at a threshold of 7 g/dl are much safer in critically ill patients with cardiovascular diseases [7, 10]. Therefore, the thresholds for blood transfusion should be different for patients with various diseases and need to be carefully evaluated.

Though the benefits of blood transfusions have been discussed by many systematic reviews and meta-analyses, the results remain controversial [6, 8, 9, 11-13]. Different clinical settings, participants, methods, and study designs all account for the diversity of outcomes. In addition, no studies have reported the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or the financial value of a different transfusion strategy. Therefore, we performed a systematic review and meta-analysis in which we investigated differences between the 7 g/dl transfusion threshold and a lower threshold.

Septic shock is commonly recognized as a substantial threat to ICU, and it is related to high hospital costs and poor outcomes [14]. It presents with insufficient tissue perfusion, like hypovolemic shock, followed by the disruption and dysfunction of cellular metabolism, but it cannot be reversed by prompt fluid resuscitation and the administration of vasoactive drugs. Blood transfusion is frequently administered as a treatment for patients with septic shock, but the protocol for transfusion is different in patients with septic shock than in patients with other critical illnesses [15-17]. In fact, there is still a lack of conclusive data regarding the rational transfusion threshold for patients with septic shock [17, 18]. Thus, in the present study, a subgroup analysis was further performed with patients with or without septic shock.

Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[19].

Search strategy and information sources

Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. Relevant studies up to May 1, 2018, were searched for with the terms 'red blood cell', 'RBC', 'restrictive', 'liberal', 'trigger', 'threshold', 'blood transfusion'. In addition, ongoing trials and conference abstracts were identified to obtain additional evidence. We also obtained references by searching the reference lists of reviews and trial registries. There was no language restriction for the search process.

Eligibility and exclusion criteria

This meta-analysis included randomized controlled trials (RCTs) among adult ICU patients (age>18 years) who underwent allogenic RBC transfusion. The recruited studies had to compare two distinct blood transfusion thresholds, a restrictive threshold and a liberal one. The definition of transfusion thresholds in this systematic review was based on hemoglobin or hematocrit levels. Blood transfusion initiated at hemoglobin thresholds below 7 g/dl were termed restrictive strategies, while the

liberal transfusions were conducted at hemoglobin thresholds between 8.5 and 10 g/dl. Other types of studies, including observational, cohort and case-control, were excluded. Trials with pretransfusion hemoglobin concentrations higher than 7 g/dl were eliminated as well. Only ICU patients were considered, while participants in other hospital departments with critical illnesses were not eligible.

Study selection

Two reviewers (RQY and CR) independently screened the titles and abstracts of the relevant trials. If the abstract of a potentially eligible article failed to provide adequate information, the full-text version was then screened to determine its eligibility. Differing opinions between the two authors were settled by discussion and consensus. If a consensus could not be reached, a consulting group including two experts (ZFX and YMY) resolved the disagreements.

Data collection

Two reviewers (RQY and CR) extracted the data from all eligible trials with a standardized and predesigned form. First author, year of publication, baseline characteristics, the total number of included patients and the clinical settings were recorded. The clinical outcomes (short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events) and study design were also obtained.

Risk of bias assessment

The Cochrane Collaboration tool was used to evaluate the risk of bias of the RCTs. The randomization sequence, allocation concealment, blinding of personnel and participants, risk of incomplete outcome data, selective reporting bias and other sources of bias were assessed independently by two authors. Each clause was rated as 'low', 'high' or 'unclear' bias. The summarized risk of bias of each RCT was ranked as low, moderate or high.

Grading quality of evidence

The quality of evidence of each outcome was evaluated in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods. This procedure was conducted with GRADE Pro software 3.6 (McMaster University 2014, Hamilton, Canada).

Outcomes

The primary endpoint was all-cause short-term mortality, which was preferentially analyzed by 28-day or 30-day mortality. In the case of unreported short-term mortality, we contacted the authors for the original data or considered the closest available mortality data. Secondary outcomes included the following indicators: length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events.

Data synthesis and analysis

The statistical analysis was conducted with ReviewManager (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We applied odds ratios (ORs) to analyze dichotomous outcomes and mean differences for continuous outcomes. The pooled results were calculated with 95% confidence intervals (CIs). A random effects model combined with the Mantel-Haenszel (M-H) method was used. For the publication bias, the funnel plot of the pooled short-term mortality data was scanned visually by reviewers. Besides, by using Stata software, version 12, we performed Begg's and Egger's tests to further assess the possible publication bias. A sensitivity analysis was also performed by means of excluding each study one at a time from the pooled effect. Additionally, we performed a subgroup analysis based on the M-H model to determine the difference between septic shock and nonsepsis groups.

Results

Search results and the characteristics of the included studies

This systematic review and meta-analysis identified 4385 relevant citations; we removed duplicates and then scanned the titles and abstracts of 4346 studies. Eventually, the full-text articles for 39 trials were reviewed, and 9 RCTs met the inclusion criteria, with ICU patients older than 18 years who received RBC transfusions at hemoglobin thresholds below 7 g/dl (**Fig. 1**).

The nine included RCTs ranged in publication year from 1999 to 2017 and contained a total of 3551 patients[20-23]. The patient population sizes of the included trials were very diverse, ranging from 44 to 998. Three studies enrolled more than 800 patients, while four trials enrolled fewer than 200 eligible patients. Four studies enrolled 1480 patients with septic shock, including two studies complicated by cancer diagnoses. In addition, four trials were multicenter studies (**Table 1**)

Risk of bias

Most of the RCTs met the randomization requirements and used rational distribution methods. In some of the included trials, however, it was challenging to blind the attending physicians and nurses to the outcome assessment based on the intervention, which resulted in high risk of performance bias. Two trials that were reported in conference abstracts had high percentages of unclear risks (**Supplementary Fig. 1**).

Quality of evidence

The summary of findings for the outcomes of interest and the levels of evidence are provided (**Supplementary Table 1**). The qualities of the primary outcome data and some secondary outcome data, including myocardial infarction and ischemic events, were all ranked as moderate. However, the lengths of hospital and ICU stays displayed low and very low quality, respectively.

Table 1 Characteristics of the included studies

Author	Year of Publication	No. of sites	Population			Transfusion Triggers		Mortality Data	References
			Clinical Settings	Details	Number of Participants	Restrictive	Liberal		
Bergamin et al.	2014	Single	Critical illness	Patients with cancer with septic shock	136	Hb 7	Hb 9	28-day mortality	[20]
Hebert et al.	1999	25	Critical illness	Euvolemic critically ill patients	838	Hb 7	Hb 10	30-day mortality 60-day mortality ICU mortality Hospital mortality	[7]
Holst et al.	2014	32	Critical illness	Patients with septic shock	998	Hb 7	Hb 9	90-day mortality	[17]
Mazza et al.	2015	Single	Critical illness	Patients with septic shock	46	Hb 7	Hb 9	Hospital mortality	[18]
Robertson et al.	2014	2	Traumatic brain injury	Patients with closed head injuries	200	Hb 7	Hb 10	Six-month mortality	[21]
Villanueva et al.	2013	Single	Upper UGIB	Patients with hematemesis, melena or both	889	Hb 7	Hb 9	45-day mortality	[22]
Walsh et al.	2013	6	Critical illness	Older critically ill patients receiving mechanical ventilation	100	Hb 7	Hb 9	30-day mortality 60-day mortality 180-day mortality ICU mortality Hospital mortality	[23]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	28-day mortality 60-day mortality 90-day mortality	[27]
Gobatto et al.	2017	Single	Traumatic brain injury	Patients with moderate or severe traumatic brain injury	44	Hb 7	Hb 9	Hospital mortality	[26]

Primary outcome: short-term mortality

Within this meta-analysis, there were four RCTs that reported 28-day or 30-day mortality, and two that reported in-hospital mortality only. After generating the forest plot, we found no significant difference in short-term mortality between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal strategy (OR: 0.92; 95% CI: 0.70-1.20; *P*=0.52; I^2=47%). Meanwhile, we noticed that the RCT reported by Bergamin et al. (19) was the main resource of heterogeneity, and removing that study resulted in a marked reduction in heterogeneity (I^2=24%, *P*=0.24) (**Fig. 2**).

Secondary outcome: length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events

Four included studies documented the length of hospital stay, which revealed shorter hospital stays when the threshold of hemoglobin < 7 g/dl was used compared with the more liberal threshold (MD: -1.57, 95% CI: -2.65-0.50, *P*=0.004, I^2=29%, **Fig. 3**). The outcome of length of ICU stay was reported by three trials, and there was no significant difference between the two thresholds (MD: -0.05, 95% CI: -0.70-0.61, *P*=0.89, I^2=0%, **Fig. 4**). Likewise, no significant differences were noted between the two transfusion thresholds for critically ill patients for myocardial infarction (OR: 0.56, 95% CI: 0.30-1.04, *P*=0.07; I^2=0%, **Fig. 5**) or ischemic/thromboembolic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%, **Fig. 6**).

Publication bias

We constructed a funnel plot to assess the possible publication bias. After inspecting the funnel plot, we found no evidence of publication bias. Furthermore, we

used Begg's test (P=0.63) and Egger's test (P=0.65) to evaluate the funnel plot asymmetry, which also showed no statistically significant evidence of publication bias (**Supplementary Fig. 2**).

Subgroup analysis

The subgroup analysis of the septic shock and nonsepsis groups investigated short-term mortality. From the forest plot, there were no significant differences in short-term mortality between two thresholds in either the septic shock group or the nonsepsis group (**Fig. 7**).

Discussion

Major findings

The current study demonstrated that restricting the transfusion threshold to a hemoglobin concentration less than 7 g/dl did not result in significant differences in short-term mortality, length of ICU, myocardial infarction, or ischemic events, when compared with more liberal thresholds. The length of hospital stay was shortened in the restrictive group than in the liberal group. Within the primary outcome analysis, the heterogeneity of enrolled trials was moderate, with an I^2 of 47% according to the heterogeneity test; this finding was assumed to be due to different clinical settings, especially for patients with septic shock. We further performed a subgroup analysis after classifying the studies into a septic shock group and a non-sepsis group, as septic shock was recognized as one of the major causes of death in critical ill patients. In septic shock group, patients with a transfusion threshold < 7 g/dl showed no significant difference in short-term mortality compared to those with a more liberal transfusion threshold, while the heterogeneity was markedly decreased (I^2=20%). In

non-sepsis group, no significant difference in short-term mortality was noted between the two thresholds with only five trials included. Additionally, the highly disparate sample size of included studies could be another resource of heterogeneity. Given the fact that several studies came from conference abstracts, we were unable to evaluate their methodology and data quality in detail.

Relations to other meta-analysis

Carefully designed meta-analyses on RBC transfusions in critically ill patients have been published recently. In 2014, the first time Salpeter and colleagues reported the benefits of restrictive blood transfusion at hemoglobin trigger of <7 g/dL in critical ill patients via conducting meta-analysis, which presented with significant reductions in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR: 0.74; 95% CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute coronary syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95% CI, 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR: 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold group[11]. However, this meta-analysis did not provide a convincing conclusion with only three RCTs included, and also failed to separate adult and pediatric participants, as each population shared different transfusion protocols.

Recently, in a review by Fominskiy E et al. [12], the restrictive and liberal RBC transfusion thresholds in critically ill patients resulted in no significant difference in all-cause 90-day mortality (OR: 1.10; 95% CI: 0.99-1.23; P=0.07; I^2=34%). In fact, this study was the first comprehensive meta-analysis to address different transfusion thresholds among critically ill and perioperative patients, but it lacked a valid analysis of secondary outcomes which were noteworthy factors for the effects of RBC

transfusions. Furthermore, Chong and colleagues also conducted an updated analysis on the effects of RBC transfusion, which included two more RCTs other than the same 10 trials included in the Fominskiy's study[12, 13, 18, 24]. These results suggested that RBC transfusion with restrictive threshold significantly reduced the risk of overall 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97; *P*=0.019) when compared with that with liberal threshold, accompanied with declining rsik of stroke/transient ischemic attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99; *P*=0.04), transfusion reactions (OR: 0.48; 95% CI, 0.29-0.80; *P*=0.005), allogenic blood exposure (OR: 0.04; 95% CI: 0.01-0.14; *P*=0.001), and length of hospital stay (95% CI: 0.42-1.64; *P*=0.001), hinting the safety of using restrictive transfusion protocol. Actually, above two studies focused on different primary outcomes, 30-day and 90-day mortality for each study, and further drew different conclusions even though both included similar RCTs , indicating that the effects of RBC transfusion varied with the stage of critical settings. However, Hovaguimian F et al. [25] performed a context-specific systematic review and meta-analysis comparing the restrictive and liberal transfusion thresholds and found no significant differences in early mortality (OR: 0.94; 95% CI: 0.73-1.20; *P*=0.09; I^2=45%) between the two thresholds, indicating that the specific types and severity of critical illness might be in need of different strategies of RBC transfusion, especially for patients with major surgery.

In the present study, we specifically concentrated on the restrictive transfusion threshold of hemoglobin < 7 g/dl in ICU patients. We included data from the newly published Transfusion Requirements after Head Trauma (TRAHT) trial and the Transfusion Requirements in Critically Ill Oncological Patients (TRICOP) trial, which showed with increased mortality rate in the group with restrictive transfusion thresholds than that with liberal transfusion threshold [26, 27]. This study showed that

RBC transfusion with restrictive threshold of < 7 g/dl did not result in significant improvement in short-term mortality, myocardial infarction, as well as ischemic events, when compared with those using liberal thresholds.

Subgroup analysis

The first review with regard to the impact of blood transfusion on the prognosis of septic shock patients was conducted by Dupuis and colleagues [28]. They showed no association between RBC transfusion and mortality rate in patients with septic shock, and also failed to determine correlations between the two different transfusion thresholds or to infer the optimal transfusion threshold for septic shock patients because of a shortage of high-quality RCTs [28]. In fact, a 10 g/dl hemoglobin threshold has been universally proposed for treatment of septic shock as the crucial role of RBC transfusions in early goal-directed therapy [29]. Nonetheless, severe adverse events caused by extensive blood transfusion have been reported as a great threat for septic shock patients by several studies[30-32]. The restrictive strategy, as reported previously, was beneficial for the improvement of microcirculation, while also saving blood products [7, 33]. The landmark TRISS trial that was conducted by Holst L et al. [17] revealed no significant differences in 90-day mortality between patients in the group with the transfusion thresholds of 7 g/dl and those with the more liberal thresholds. In addition, the number of patients experiencing ischemic events and severe adverse reactions was also similar between the two groups. The TRISS trial demonstrated the safety and economic efficiency of the restrictive blood transfusion threshold, with a well-controlled risk of bias. Mazza BF et al. [18] performed a randomized physiological study of septic shock patients with the endpoint of abnormal lactate and $ScvO_2$ under distinct pretransfusion hemoglobin

concentrations. However, they failed to provide valid data on mortality with a relatively small sample size provided. Recently, Bergamin and colleagues focused on cancer patients who developed septic shock in the ICU through a single-center RCT [27]. Indeed, tumor patients that were complicated by septic shock were in urgent need of blood transfusion as high risk of anemia[17, 34]. Ideally, the more restrictive threshold for transfusion might reduce the occurrence of multiple transfusion-related complications. In this study, we conducted a comprehensive meta-analysis after enrolled all recently published RCTs that covered septic shock cases. No marked difference in mortality was observed between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal transfusion threshold (OR: 1.08; 95% CI, 0.82-1.41; P=0.54; I^2=20%). We assumed that this results might be, at least in part, due to the overwhelming weight that the TRISS trial carried and the relatively low quality of the other three studies. Moreover, the study by Mazza BF et al. [18] enrolled participants with a diagnosis of malignant tumoral, which might generate heterogeneity. Taken together, we can't determine that blood transfusion at thresholds of 7 g/dl is the optimal transfusion threshold for patients with septic shock based on current evidences, which urges more as well as large clinical trials.

Strengths and limitations

Our meta-analysis is the first report concerning the feasibility of a transfusion threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients. Unlike the previously published meta-analyses, which enrolled studies with different restrictive transfusion thresholds, we only included RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl. Simultaneously, we performed an updated and comprehensive

analysis that focused on ICU patients with septic shock. Meanwhile, this analysis revealed no evidence of significant publication bias according to visual inspection of the funnel plot, Begg's test and Egger's test.

Some limitations are also noted in the current systematic review and meta-analysis. Firstly, the number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl. Five relevant studies that discussed the two different transfusion thresholds among critically ill patients were excluded because of their different definition of restrictive RBC transfusion thresholds [24, 35-38]. Secondly, the heterogeneity in our meta-analysis was relatively high, which was caused by different outcome measurements and clinical settings. Some trials with low quality evidence and insufficient participants might be another source of heterogeneity. Correspondingly, we tried to eliminate the heterogeneity by conducting a subgroup analysis and analyzing the effects. Thirdly, there was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions. Fourthly, the sample sizes of all incorporated RCTs were varied. We applied the Mantel-Haenszel method to address this diversity in sample sizes and to avoid our results from being dominated by the larger studies. Finally, we failed to testify if hemoglobin level less than 7 g/dl is the optimal threshold for the blood transfusions in critically ill patients and in those with septic shock basing on a lack of sufficient evidence.

Conclusions

The present meta-analysis of RCTs focused on the effect of RBC transfusions at the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients. RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in

significantly different in short-term mortality when compared with transfusions administered at a more liberal threshold; there were also no differences in the length of ICU stay or the rates of myocardial infarctions and ischemic events. Within the ICU patient population with septic shock, RBC transfusions at the restrictive threshold did not improve short-term mortality compared with transfusions at the more liberal threshold.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Abbreviations

RBCs: Red blood cell; ICUs: Intensive care units; MI: Myocardial infarction; ORs: Odds ratios; RCTs: Randomized controlled trials; TRICC: Transfusion requirements in critical care; PRISMA: Preferred items for systematic reviews and meta-analyses; GRADE: Grading of recommendations, assessment, development and evaluation; CIs: Confidence intervals; M-H: Mantel-Haenszel; TIA: Transient ischemic attack; TRAHT: Transfusion requirements after head trauma; TRICOP: Transfusion requirements in critically ill oncological patients.

Author contributions

YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data. YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper. RQY undertook the statistical analyses. All authors contributed to and revised the final manuscript.

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Figure legends

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Figure 2. Forest plot of all-cause short-term mortality in ICU patients. The odds ratio and 95% CI for short-term mortality between the restrictive and liberal transfusion thresholds are presented in the forest plot. The threshold of hemoglobin < 7 g/dl showed no obvious improvement in short-term mortality when compared with the liberal threshold.

Figure 3. Forest plot of the length of hospital stay. The forest plot shows the mean difference and 95% CI for the length of hospital stay between the two groups. Blood transfusion at the restrictive threshold resulted in shorter hospital stays than blood transfusion at the more liberal threshold.

Figure 4. Forest plot of the length of ICU stay. The difference in the length of ICU stay in the groups with different transfusion thresholds is shown by the mean difference and 95% CI in the forest plot. No marked improvement was seen in the length of ICU stay with a transfusion threshold of hemoglobin < 7 g/dl.

Figure 5. Forest plot of myocardial infarction in ICU patients after RBCs transfusion. The forest plot shows the odds ratios and 95% CI for myocardial infarction in the groups of ICU patients with different transfusion thresholds. Blood transfusion at a threshold of hemoglobin < 7 g/dl displayed no significant decrease in

the rate of myocardial infarction compared with the more liberal threshold.

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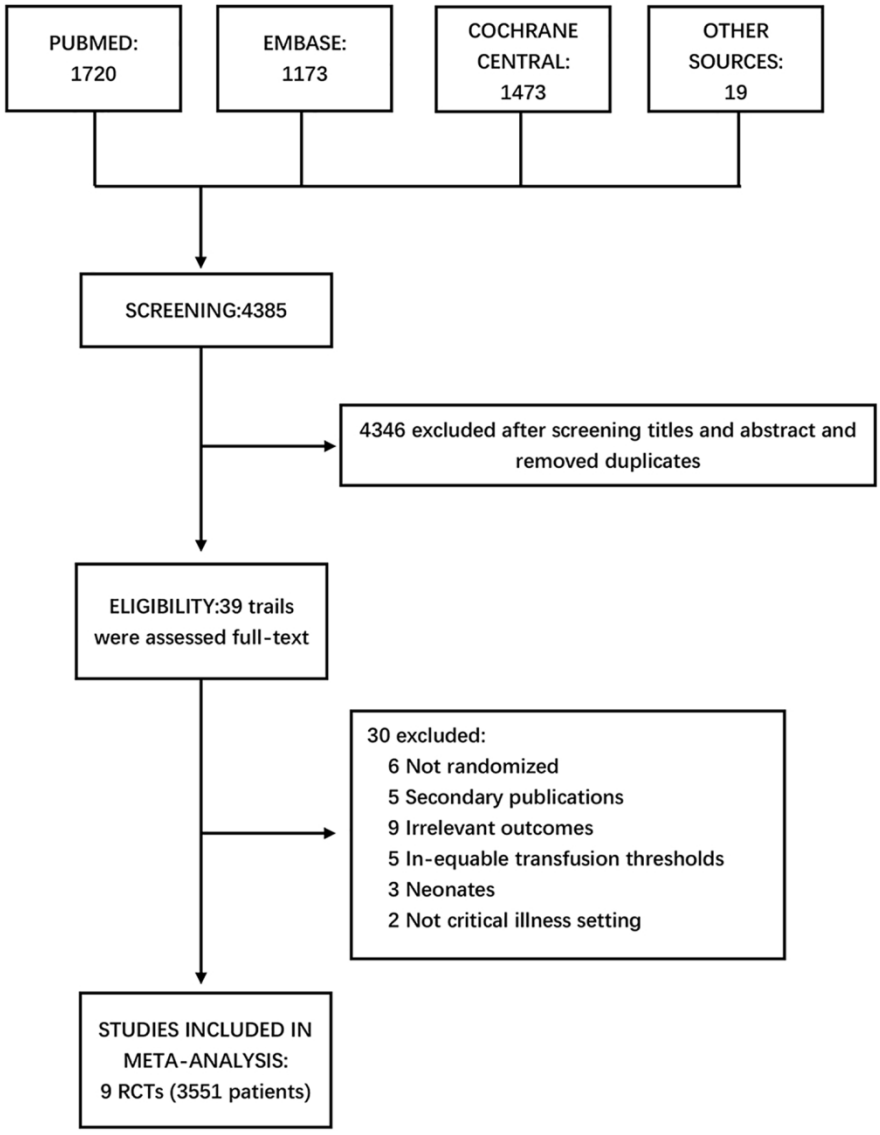
Figure 7. Forest plot for short-term mortality following subgroup analysis. The forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of patients receiving RBC transfusions at various thresholds according to the subgroup analysis of the septic shock and nonsepsis groups. Restrictive transfusion was incapable of decreasing short-term mortality in septic ICU patients.



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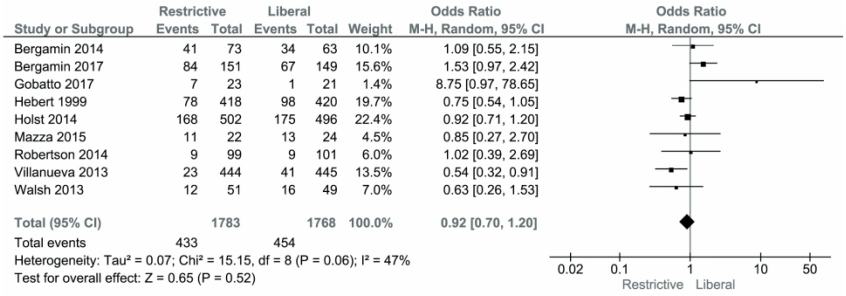

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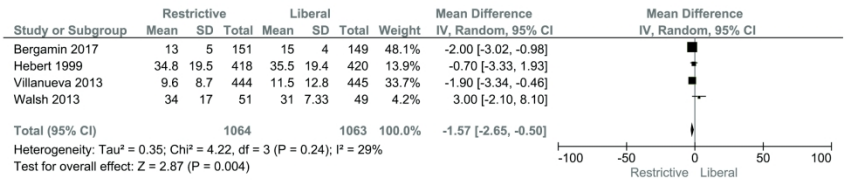

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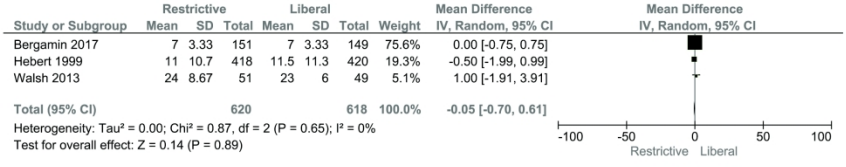

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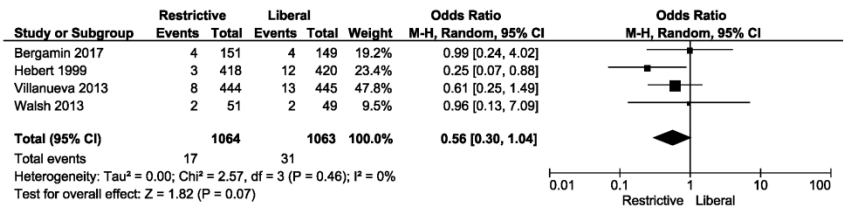

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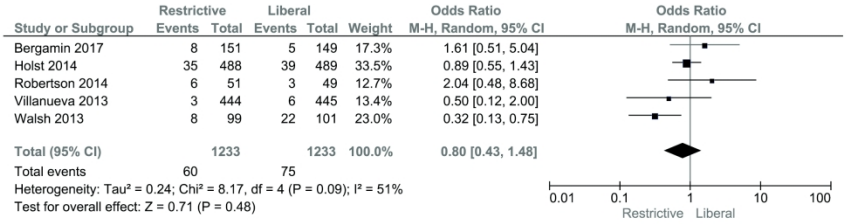

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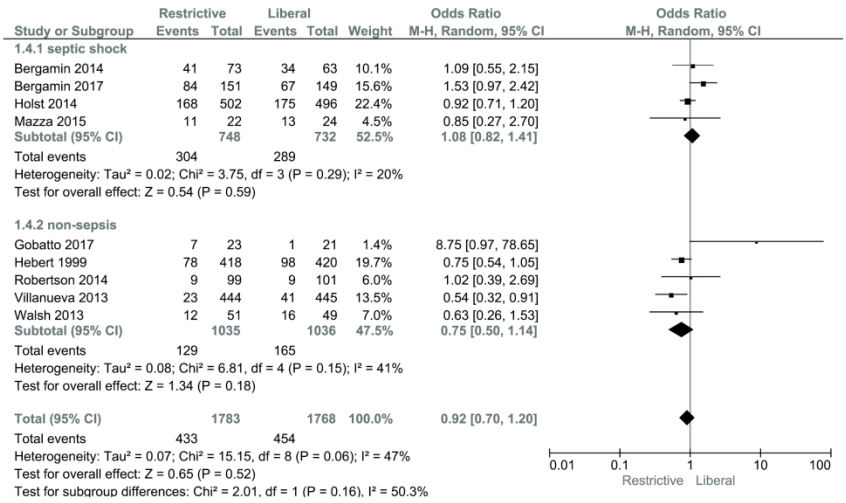

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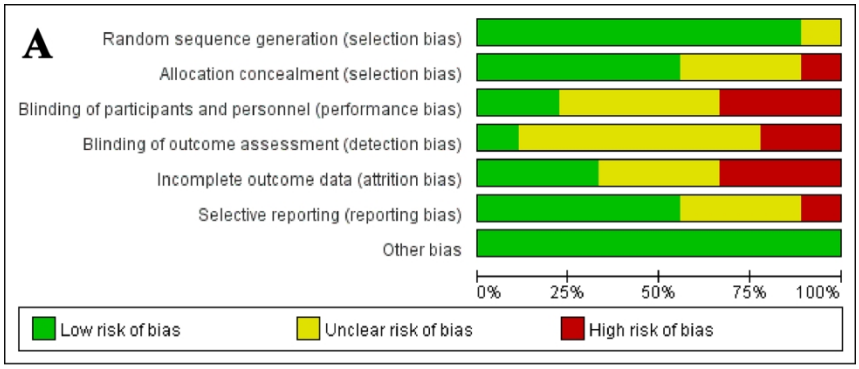
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Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
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Other bias
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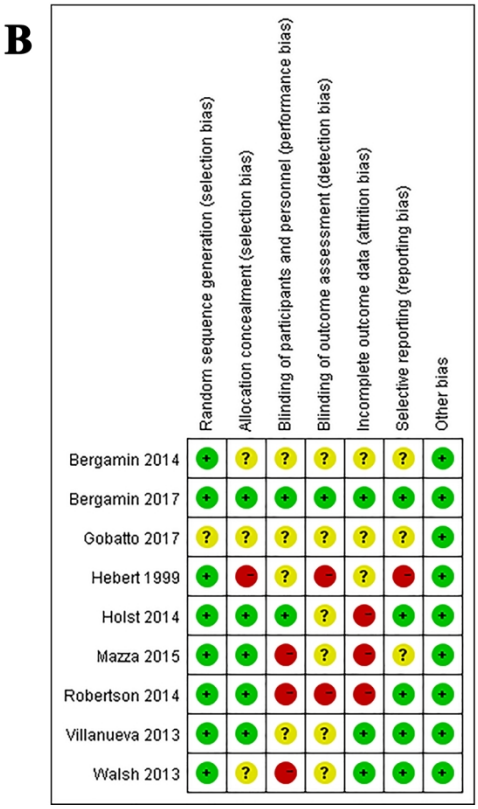
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias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Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
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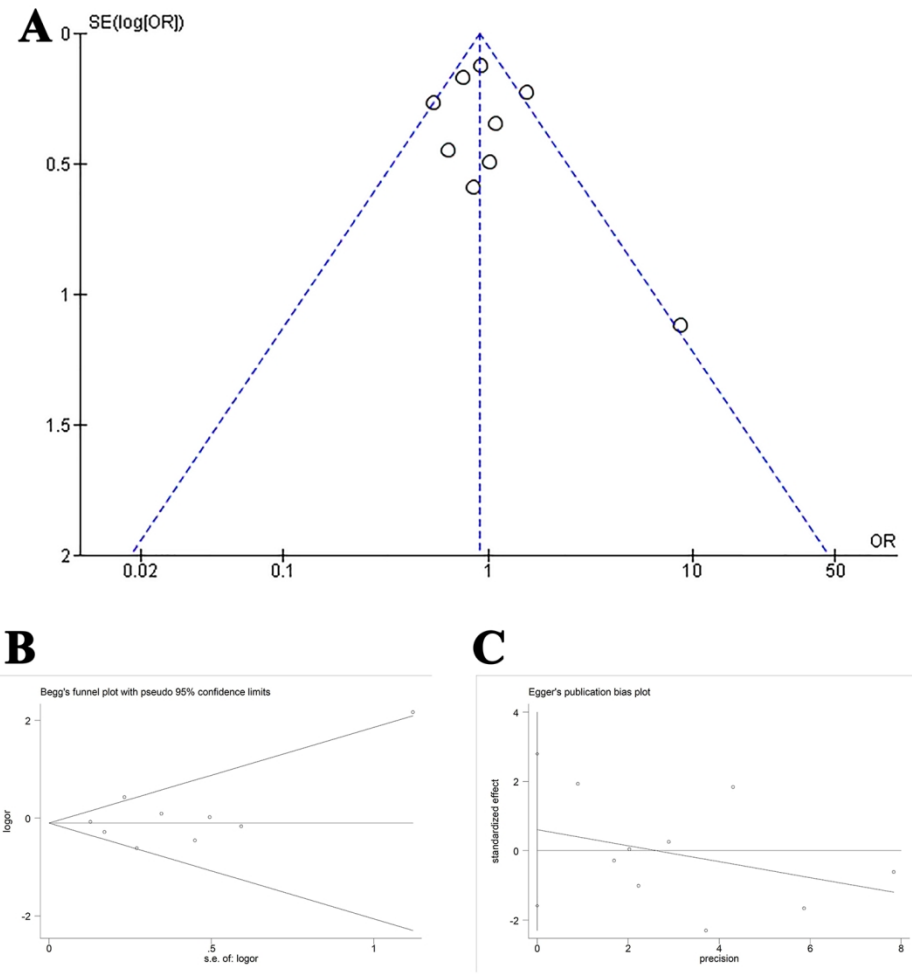
Villanueva 2013
Walsh 2013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Begg's funnel plot with pseudo 95% confidence limits
logor
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C
Egger's publication bias plot
standardized effect
precision

Supplemental Table 1 Summary of Findings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Critical illness				
short-term mortality	**Study population**		**OR 0.92** (0.7 to 1.2)	3551 (9 studies)	⊕⊕⊕⊖ **moderate**[1]	
	257 per 1000	**241 per 1000** (195 to 293)				
	Moderate					
	327 per 1000	**309 per 1000** (254 to 368)				
Myocardial Infraction	**Study population**		**OR 0.56** (0.3 to 1.04)	2127 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	29 per 1000	**17 per 1000** (9 to 30)				
	Moderate					
	29 per 1000	**16 per 1000** (9 to 30)				
Ischemic event	**Study population**		**OR 0.8** (0.43 to 1.48)	2466 (5 studies)	⊕⊕⊕⊖ **moderate**[1]	
	61 per 1000	**49 per 1000** (27 to 87)				
	Moderate					
	61 per 1000	**49 per 1000** (27 to 88)				

mortality - septic shock	**Study population**		**OR 1.08**	1480	⊕⊕⊕⊖
	395 per 1000	**413 per 1000** (349 to 479)	(0.82 to 1.41)	(4 studies)	**moderate**[1]
	Moderate				
	495 per 1000	**514 per 1000** (446 to 580)			
mortality - non-sepsis	**Study population**		**OR 0.75**	2071	⊕⊕⊕⊖
	159 per 1000	**124 per 1000** (87 to 178)	(0.5 to 1.14)	(5 studies)	**moderate**[1]
	Moderate				
	92 per 1000	**71 per 1000** (48 to 104)			
ICU length of stay		The mean icu length of stay in the intervention groups was **0.05 lower** (0.7 lower to 0.61 higher)		1238 (3 studies)	⊕⊖⊖⊖ **very low**[1]
hospital length of stay		The mean hospital length of stay in the intervention groups was **1.57 lower** (2.65 to 0.5 lower)		2127 (4 studies)	⊕⊕⊖⊖ **low**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No explanation was provided

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

www.prisma-statement.org

You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Section/Topic	Item No.	Checklist item	Reported on Page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8

Section/Topic	Item No.	Checklist item	Reported on Page No.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			

Section/Topic	Item No.	Checklist item	Reported on Page No.
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review

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Manuscript ID	bmjopen-2019-030854.R1
Article Type:	Original research
Date Submitted by the Author:	02-Oct-2019
Complete List of Authors:	Yao, Ren; Changhai Hospital Ren, Chao; Chinese PLA General Hospital, Zhang, Zi; Changhai Hospital Zhu, Yibing; Beijing Fuxing Hospital, ICU Xia, Zhao Fan; Changhai Hospital, Department of Burns YAO, Yongming; Fourth Medical Center of the Chinese PLA General Hospital
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Red blood cells, Transfusion, Intensive care units, Septic shock

Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review

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(+86) 1066867394; Fax: (+86) 1068989955; Email: c_ff@sina.com.

Ren-qi Yao and Chao Ren contributed equally to this manuscript.

Abstract

Objectives: We employed a comprehensive systematic review and meta-analysis to assess benefits and risks of a threshold of hemoglobin level below 7g/dl vs liberal transfusion strategy among critically ill patients, and even patients with septic shock.

Design: Systematic review and meta-analysis.

Data sources: We performed systematical searches for relevant randomized controlled studies (RCTs) in the Cochrane Library, EMBASE, and PubMed databases up to Sep 1, 2019.

Eligibility criteria: RCTs among adult ICU patients comparing 7 g/dl as restrictive strategy and liberal transfusion were incorporated.

Data extraction and synthesis: The clinical outcomes, including short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction (MI), and ischemic events, were screened and analyzed after data collection. We applied odds ratios (ORs) to analyze dichotomous outcomes and mean differences to analyze continuous outcomes with fixed or random effects model.

Results: Eight RCTs with 3415 patients were included. Compared with a more liberal threshold, an RBC transfusion threshold < 7 g/dl hemoglobin showed no significant difference in short-term mortality (OR: 0.90, 95% CI: 0.67-1.21; *P*=0.48; I^2=53%), length of ICU stay (MD: -0.09, 95% CI: -0.74-0.56, *P*=0.78, I^2=0%), or ischemic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%). However, the length of hospital stay (MD: -1.72, 95% CI: -2.51--0.94, *P* < 0.001, I^2=18%) was shorter, and the incidence of MI (OR: 0.54, 95% CI: 0.30-0.98, *P*=0.04; I^2=0%) was lower in the group with the threshold < 7 g/dl than that with the more liberal threshold.

Conclusions: A RBC transfusion threshold < 7 g/dl hemoglobin is incapable of decreasing short-term mortality in ICU patients according to currently published

evidence, while it might have potential role in shortening hospitalization as well as reducing MI incidence.

Keywords: Red blood cells, Transfusion, Intensive care units, Septic shock

Strengths and limitations of this study

1. This meta-analysis focused on the feasibility of a transfusion threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients through only including RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl.

2. In this meta-analysis, we performed an updated and comprehensive analysis that focused on ICU patients with septic shock.

3. The number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl.

4. There was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions.

Introduction

Allogenic red blood cell (RBC) transfusion remains a commonly used and crucial treatment among patients admitted to the intensive care unit (ICU), as anemia is commonly complicated and critically involved in poor outcomes[1]. Every year, approximately 75 million units of blood are reportedly obtained worldwide, with higher levels of consumption in the UK, Canada, and US [2] [3]. In ICU settings, 40%~50% of critically ill patients receive at least one unit of RBC transfusion, and the average consumption reaches five units during their ICU stay[4]. Undoubtedly, appropriate blood transfusion can benefit critical ill patients by increasing oxygen delivery and reducing oxygen debt, protecting against multiple organ dysfunction[5]. While these data also urge the cautious use of RBCs because of the substantial cost and supply shortage. For example, Holst LB and colleagues have reported that the units of RBCs used for liberal transfusion trigger strategies are almost twice the amount of RBCs transfusion with restrictive strategies, which puts great pressure for hospital cost and source of RBC products as no significant difference is noted between restrictive and liberal triggers in assessment of primary outcomes[6]. Additionally, the risk of complications, such as volume overload, infection, transfusion reactions, and even increased mortality, also raises concerns about the threshold for RBC transfusion in ICU patients [7-9]. However, the optimal thresholds for RBC transfusion in diverse critical care settings remain controversial. The results of the Transfusion Requirements in Critical Care (TRICC) study have confirmed the superiority of a restrictive transfusion strategy (RBC transfusions were given when

hemoglobin concentration was below 7 g/dl) in controlling the 30-day mortality of critical ill patients with younger age and lower Acute Physiology and Chronic Health Evaluation (APACHE II) score. Indeed, conservative blood transfusion could result in a marked decline in the use of RBCs, which further decreases the in-hospital cost of ICU patients [2] [10]. Recently, various studies have extensively discussed transfusion strategies to optimize the outcomes. For instance, no significance was shown between restrictive and liberal transfusion strategies in terms of adverse effects, as reported by some studies [11] [12]. In addition, other researchers found that blood transfusions triggered at a threshold of 7 g/dl are much safer in critically ill patients with cardiovascular diseases [10] [13]. However, Silva Junior JM et al have found that RBC transfusion was an independent risk factor for mortality of critical ill patients, followed with longer ICU and hospital stay, which is associated with different decisions regarding transfusion triggers[14]. Other indexes, such as oxygen delivery (DO_2) and oxygen consumption (VO_2), also show marked deviation among various studies. Study from Conrad SA et al reveals significant improvement in DO_2 but no influence in VO_2 after blood transfusion on septic patients[15]. While Steffes CP and colleagues have reported that blood transfusion is capable of elevating DO_2 and VO_2 in septic surgical patients[16]. Therefore, the thresholds for blood transfusion should be different for patients with various diseases and need to be carefully evaluated.

Actually, the benefits and harms of blood transfusions in patients admitted to intensive care units have been discussed by many systematic reviews and meta-analyses, but the results remain controversial due to the distinct inclusion

criteria and outcome measurement across studies.[9 11 12 17-19]. Salpeter and colleagues found restrictive blood transfusion trigger at 7g/dl could significantly reduce mortality of disparate phase, as well as diverse transfusion-related complications compared to the liberal transfusion trigger. However, they didn't distinguish pediatric and adult ICU settings, and enrolled merely 3 RCTs[17]. Systematic reviews conducted by Fominskiy E et al revealed no statistical difference of 90-day mortality between two transfusion thresholds[18]. Nevertheless, recently updated publication by Chong and colleagues incorporated almost same RCTs as Fominskiy E et al did, while they identified a significant reduction of 30-day mortality in ICU patients with restrictive strategy in comparison of more liberal transfusion trigger[19]. In addition, the specific thresholds of hemoglobin concentration for effective RBC transfusion is one of the most important factors for decision of transfusion regarding various clinical practice. However, no studies have reported the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or the financial value of a different transfusion strategy, even though it is considered as a common trigger for restrictive transfusion strategy. Furthermore, different types of clinical conditions also show remarkable deviation in RBCs administration. For example, septic shock is commonly recognized as a substantial threat to ICU, and it is related to high hospital costs and poor outcomes [20]. Anemia is also commonly complicated during the progression of sepsis, as it presents with insufficient tissue perfusion, like hypovolemic shock, and dysfunction of cellular metabolism, which cannot be reversed by prompt fluid resuscitation and the administration of vasoactive drugs. Indeed, blood transfusion is

frequently administered as an efficient remedy for patients with septic shock, but the protocol for transfusion is different in patients with septic shock than in patients with other critical illnesses [1 21 22]. In fact, there is still a lack of conclusive data regarding the rational transfusion threshold for patients with septic shock [22 23]. The transfusion requirements in septic shock (TRISS) trial did provide strong evidences that no significant difference was noted between RBC transfusion with lower and higher hemoglobin thresholds in long term mortality and adverse reactions[22]. However, other researchers found that RBC transfusion was related to unfavorable outcomes of septic patients, such as sequential organ failure assessment (SOFA) score and length of stay in ICU. In addition, the association between RBC transfusion and short-term outcomes of septic patients hasn't been established yet. In the present study, we aim to perform a comprehensive systematic review and meta-analysis specifically determining whether hemoglobin level below 7g/dl is an optimal trigger for blood transfusion among adult ICU patients when compared to more liberal transfusion thresholds by evaluating its impacts on short-term mortality and adverse reactions. Additionally, a subgroup analysis is further performed with patients with or without septic shock to seek the optimal transfusion strategy for this unique subset of critically ill patients.

Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

statement[24].

Patient and Public Involvement

No patient involved.

Search strategy and information sources

Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. We conceived strategy comprised of following combination of exploded Medical Subject Heading (MeSH) terms: “critical care”, “intensive care unit”, “blood transfusion”. Detailed search strategy was presented in **Supplementary File 1**. Relevant studies up to Sep 1, 2019, were searched without any language limitations. In addition, ongoing trials and conference abstracts were identified to obtain additional evidence. We also obtained references by searching the reference lists of reviews and trial registries. There was no language restriction for the search process.

Eligibility and exclusion criteria

This meta-analysis included RCTs among adult ICU patients (age>18 years) who underwent allogenic RBC transfusion. The recruited studies had to compare two distinct blood transfusion thresholds, a restrictive threshold and a liberal one. The definition of transfusion thresholds in this systematic review was based on hemoglobin or hematocrit levels. Blood transfusion initiated at hemoglobin thresholds

below 7 g/dl were termed restrictive strategies, while the liberal transfusions were conducted at hemoglobin thresholds between 8.5 and 10 g/dl. Other types of studies, including observational, cohort and case-control, were excluded. Trials with pretransfusion hemoglobin concentrations higher than 7 g/dl were eliminated as well. Only ICU patients were considered, while participants in other hospital departments with critical illnesses were not eligible.

Study selection

Two reviewers (RQY and CR) independently screened the titles and abstracts of the relevant trials. If the abstract of a potentially eligible article failed to provide adequate information, the full-text version was then screened to determine its eligibility. Differing opinions between the two authors were settled by discussion and consensus. If a consensus could not be reached, a consulting group including two experts (ZFX and YMY) resolved the disagreements.

Data collection

Two reviewers (RQY and CR) extracted the data from all eligible trials with a standardized and predesigned form. First author, year of publication, baseline characteristics, the total number of included patients and the clinical settings were recorded. The clinical outcomes (short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events) and study design were also obtained.

Risk of bias assessment

The Cochrane Collaboration tool was used to evaluate the risk of bias of the RCTs. The randomization sequence, allocation concealment, blinding of personnel and participants, risk of incomplete outcome data, selective reporting bias and other sources of bias were assessed independently by two authors. Each clause was rated as 'low', 'high' or 'unclear' bias. The summarized risk of bias of each RCT was ranked as low, moderate or high.

Grading quality of evidence

The quality of evidence of each outcome was evaluated in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods. This procedure was conducted with GRADE Pro software 3.6 (McMaster University 2014, Hamilton, Canada).

Outcomes

The primary endpoint was all-cause short-term mortality, which was preferentially analyzed by 28-day or 30-day mortality. In the case of unreported short-term mortality, we contacted the authors for the original data or considered the closest available mortality data. Secondary outcomes included the following indicators: length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events.

Data synthesis and analysis

The statistical analysis was conducted with ReviewManager (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We applied odds ratios (ORs) to analyze dichotomous outcomes and mean differences for continuous outcomes. The pooled results were calculated with 95% confidence intervals (CIs). Heterogeneity among studies for each outcome was assessed by applying both χ^2 test and I^2 statistics. Either I^2 greater than 50% or p value of χ^2 test less than 0.10 was deemed as statistically significant heterogeneity. If remarkable heterogeneity existed in pooled results, random effects model combined with the Mantel-Haenszel (M-H) method was used, or else, fixed effects model was applied accordingly. For the small study bias, the funnel plot of the pooled short-term mortality data was scanned visually by reviewers. Besides, by using Stata software, version 12, we performed Begg's and Egger's tests to further assess the possible small study bias. A sensitivity analysis was also performed by means of excluding each study one at a time from the pooled effect. Additionally, we performed a subgroup analysis based on the M-H model to determine the difference between septic shock and non-sepsis groups.

Results

Search results and the characteristics of the included studies

This systematic review and meta-analysis identified 4641 relevant citations; we

removed duplicates and then scanned the titles and abstracts of 4600 studies. Eventually, the full-text articles for 41 trials were reviewed, and 8 RCTs met the inclusion criteria and were presented with full paper, with ICU patients older than 18 years who received RBC transfusions at hemoglobin thresholds below 7 g/dl (**Fig. 1**).

The eight included RCTs ranged in publication year from 1999 to 2019 and contained a total of 3415 patients[10 22 23 25-29]. The patient population sizes of the included trials were very diverse, ranging from 44 to 998. Three studies enrolled more than 800 patients, while three trials enrolled fewer than 200 eligible patients. Four studies enrolled 1480 patients with septic shock, including one studies complicated by cancer diagnoses. In addition, four trials were multicenter studies (**Table 1**)

Risk of bias

Most of the RCTs met the randomization requirements and used rational distribution methods. In some of the included trials, however, it was challenging to blind the attending physicians and nurses to the outcome assessment based on the intervention, which resulted in high risk of performance bias. (**Supplementary Fig. 1**).

Quality of evidence

The summary of findings for the outcomes of interest and the levels of evidence are provided (**Supplementary Table 1**). The qualities of the primary outcome data and some secondary outcome data, including myocardial infarction and ischemic

events, were all ranked as moderate. However, both of the lengths of hospital and ICU stays displayed low quality.

Table 1 Characteristics of the included studies

Author	Year of Publication	No. of sites	Population			Transfusion Triggers		Mortality Data	References
			Clinical Settings	Details	Number of Participants	Restrictive	Liberal		
Hebert et al.	1999	25	Critical illness	Euvolemic critically ill patients	838	Hb 7	Hb 10	30-day mortality 60-day mortality ICU mortality	[10]
Holst et al.	2014	32	Critical illness	Patients with septic shock	998	Hb 7	Hb 9	Hospital mortality 90-day mortality	[22]
Mazza et al.	2015	Single	Critical illness	Patients with septic shock	46	Hb 7	Hb 9	Hospital mortality	[23]
Robertson et al.	2014	2	Traumatic brain injury	Patients with closed head injuries	200	Hb 7	Hb 10	Six-month mortality	[25]
Villanueva et al.	2013	Single	Upper UGIB	Patients with hematemesis, melena or both	889	Hb 7	Hb 9	45-day mortality	[26]
Walsh et al.	2013	6	Critical illness	Older critically ill patients receiving mechanical ventilation	100	Hb 7	Hb 9	30-day mortality 60-day mortality 180-day mortality ICU mortality Hospital mortality	[27]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	28-day mortality 60-day mortality 90-day mortality	[29]
Gobatto et al.	2019	Single	Traumatic brain injury	Patients with moderate or severe traumatic brain injury	44	Hb 7	Hb 9	Hospital mortality ICU mortality	[28]

Primary outcome: short-term mortality

Within this meta-analysis, there were three RCTs that reported 28-day or 30-day mortality, and four that reported in-hospital mortality only. The published study from Holst LB et al did provide solid conclusions about the impacts of blood transfusion with liberal and restrictive hemoglobin thresholds on long-term mortality and rates of ischemic events, which presented with similar effects, while the information about short-term outcomes was missing[22]. Therefore, we wrote a letter asking for the important evidence of short-term mortality rates, as its analysis was based on a large sample size and was essential for our conclusion. After generating the forest plot, we found no significant difference in short-term mortality between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal strategy (OR: 0.90, 95% CI: 0.67-1.21; *P*=0.48; I^2=53%). Meanwhile, we noticed that the RCT reported by Bergamin et al. (19) was the main resource of heterogeneity, and removing that study resulted in a marked reduction in heterogeneity (I^2=29%, *P*=0.21) (**Fig. 2**).

Secondary outcome: length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events

Five included studies documented the length of hospital stay, which revealed shorter hospital stays when the threshold of hemoglobin < 7 g/dl was used compared with the more liberal threshold (MD: -1.72, 95% CI: -2.51--0.94, *P* < 0.001, I^2=18%, **Fig. 3**). The outcome of length of ICU stay was reported by four trials, and there was no significant difference between the two thresholds (MD: -0.09, 95% CI: -0.74-0.56, *P*=0.78, I^2=0%, **Fig. 4**). In addition, we identified that MI events was decreased among patients with transfusion trigger of hemoglobin < 7 g/dl compared to those with the liberal transfusion strategy, which was of statistical significance (OR: 0.54,

95% CI: 0.30-0.98, *P*=0.04; I^2=0%, **Fig. 5**). However, no significant differences was noted between the two transfusion thresholds for critically ill patients for ischemic/thromboembolic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%, **Fig. 6**). After removing study conducted by Walsh et al, the heterogeneity of this outcome decreased significantly (I^2=0%, *P*=0.21), which indicated the main source of heterogeneity.

Small study bias

We constructed a funnel plot to assess the possible small study bias. After inspecting the funnel plot, we found no evidence of small study bias. Furthermore, we used Begg's test (*P*=0.71) and Egger's test (*P*=0.62) to evaluate the funnel plot asymmetry, which also showed no statistically significant evidence of small study bias (**Supplementary Fig. 2**).

Subgroup analysis

The subgroup analysis of the septic shock and non-sepsis groups investigated short-term mortality. From the forest plot, there were no significant differences in short-term mortality between two thresholds in either the septic shock group (OR: 1.10, 95% CI: 0.75-1.62; *P*=0.63; I^2=46%) or the non-sepsis group (OR: 0.75, 95% CI: 0.50-1.14; *P*=0.15; I^2=41%) (**Fig. 7**).

Discussion

Major findings

The current study demonstrated that restricting the transfusion threshold to a hemoglobin concentration less than 7 g/dl did not result in significant differences in

short-term mortality, length of ICU, or ischemic events, when compared with more liberal thresholds. The length of hospital stay was shortened in the restrictive group than in the liberal group. However, as the uncertain status of censored data (discharge or death), as well as the high proportion of patients who died during hospitalization, we could not simply regard statistically shortened hospital length of stay as a beneficial effect of transfusion trigger at 7g/dl, which might be affected by mortality rate. Of note, the low quality of evidence of hospital/ICU length of stay should be aware of. Additionally, polled data also revealed that the incidence of MI was decreased among patients applied 7 g/dl as transfusion threshold. Nevertheless, we should be cautious when interpreting this finding. After removing the study conducted by Villanueva and his colleagues, as well as changing effects model from random to fixed effects model could alter the consequence, indicating the instability of this outcome.

Within the primary outcome analysis, the heterogeneity of enrolled trials was moderate, with an I^2 of 53% according to the heterogeneity test, while sensitivity analysis revealed that remove of the Transfusion Requirements in Critically Ill Oncological Patients (TRICOP) trial resulted in dramatically decreased heterogeneity (I^2=29%, P=0.21). As this study enrolled patients diagnosed with both solid cancer and septic shock, the baseline characteristic of this unique subset might differ from other ordinary ICU patients, which could partially explain the source of heterogeneity. Also, this finding was assumed to be due to different clinical settings, especially for patients with septic shock. We further performed a subgroup analysis after classifying the studies into a septic shock group and a non-sepsis group, as septic shock was recognized as one of the major causes of death in critical ill patients. In septic shock group, patients with a transfusion threshold < 7 g/dl showed no significant difference

in short-term mortality compared to those with a more liberal transfusion threshold, while the heterogeneity was markedly decreased (I^2=46%, *P*=0.15). In non-sepsis group, no significant difference in short-term mortality was noted between the two thresholds with only five trials included. Additionally, the highly disparate sample size of included studies could be another resource of heterogeneity. Given the fact that several studies came from conference abstracts, we were unable to evaluate their methodology and data quality in detail.

Relations to other meta-analysis

Carefully designed meta-analyses on RBC transfusions in critically ill patients have been published recently. In 2014, the first time Salpeter and colleagues reported the benefits of restrictive blood transfusion at hemoglobin trigger of <7 g/dL in critical ill patients via conducting meta-analysis, which presented with significant reductions in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR: 0.74; 95% CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute coronary syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95% CI, 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR: 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold group[17]. However, this meta-analysis did not provide a convincing conclusion with only three RCTs included, and also failed to separate adult and pediatric participants, as each population shared different transfusion protocols.

Recently, in a review by Fominskiy E et al. [18], the restrictive and liberal RBC transfusion thresholds in critically ill patients resulted in no significant difference in all-cause 90-day mortality (OR: 1.10; 95% CI: 0.99-1.23; *P*=0.07; I^2=34%). In fact, this study was the first comprehensive meta-analysis to address different transfusion

thresholds among critically ill and perioperative patients, but it lacked a valid analysis of secondary outcomes which were noteworthy factors for the effects of RBC transfusions. Furthermore, Chong and colleagues also conducted an updated analysis on the effects of RBC transfusion, which included two more RCTs other than the same 10 trials included in the Fominskiy's study[18 19 23 30]. These results suggested that RBC transfusion with restrictive threshold significantly reduced the risk of overall 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97; *P*=0.019) when compared with that with liberal threshold, accompanied with declining risk of stroke/transient ischemic attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99; *P*=0.04), transfusion reactions (OR: 0.48; 95% CI, 0.29-0.80; *P*=0.005), allogenic blood exposure (OR: 0.04; 95% CI: 0.01-0.14; *P*=0.001), and length of hospital stay (95% CI: 0.42-1.64; *P*=0.001), hinting the safety of using restrictive transfusion protocol. Actually, above two studies focused on different primary outcomes, 30-day and 90-day mortality for each study, and further drew different conclusions even though both included similar RCTs, indicating that the effects of RBC transfusion varied with the stage of critical settings. However, Hovaguimian F et al.[31] performed a context-specific systematic review and meta-analysis comparing the restrictive and liberal transfusion thresholds and found no significant differences in early mortality (OR: 0.94; 95% CI: 0.73-1.20; *P*=0.09; I^2=45%) between the two thresholds, indicating that the specific types and severity of critical illness might be in need of different strategies of RBC transfusion, especially for patients with major surgery.

In the present study, we specifically concentrated on the restrictive transfusion threshold of hemoglobin < 7 g/dl in ICU patients. We included data from the newly published Transfusion Requirements after Head Trauma (TRAHT) trial and the TRICOP trial, which showed with increased mortality rate in the group with

restrictive transfusion thresholds than that with liberal transfusion threshold [28 29]. This study showed that RBC transfusion with restrictive threshold of < 7 g/dl did not result in significant improvement in short-term mortality when compared with those using liberal thresholds.

Subgroup analysis

The first review with regard to the impact of blood transfusion on the prognosis of septic shock patients was conducted by Dupuis and colleagues [32]. They showed no association between RBC transfusion and mortality rate in patients with septic shock, and also failed to determine correlations between the two different transfusion thresholds or to infer the optimal transfusion threshold for septic shock patients because of a shortage of high-quality RCTs [32]. In fact, a 10 g/dl hemoglobin threshold has been universally proposed for treatment of septic shock as the crucial role of RBC transfusions in early goal-directed therapy [33]. Nonetheless, severe adverse events caused by extensive blood transfusion have been reported as a great threat for septic shock patients by several studies[34-36]. The restrictive strategy, as reported previously, was beneficial for the improvement of microcirculation, while also saving blood products [10 37]. The landmark TRISS trial that was conducted by Holst L et al. [22] revealed no significant differences in 90-day mortality between patients in the group with the transfusion thresholds of 7 g/dl and those with the more liberal thresholds. In addition, the number of patients experiencing ischemic events and severe adverse reactions was also similar between the two groups. The TRISS trial demonstrated the safety and economic efficiency of the restrictive blood transfusion threshold, with a well-controlled risk of bias. Mazza BF et al. [23] performed a randomized physiological study of septic shock patients with the endpoint of abnormal lactate and $ScvO_2$ under

distinct pretransfusion hemoglobin concentrations. However, they failed to provide valid data on mortality with a relatively small sample size provided. Recently, Bergamin and colleagues focused on cancer patients who developed septic shock in the ICU through a single-center RCT [29]. Indeed, tumor patients that were complicated by septic shock were in urgent need of blood transfusion as high risk of anemia[22 38]. Ideally, the more restrictive threshold for transfusion might reduce the occurrence of multiple transfusion-related complications. In this study, we conducted a comprehensive meta-analysis after enrolled all recently published RCTs that covered septic shock cases. No marked difference in mortality was observed between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal transfusion threshold (OR: 1.08; 95% CI, 0.82-1.41; P=0.54; I^2=20%). We assumed that these results might be, at least in part, due to the overwhelming weight that the TRISS trial carried and the relatively low quality of the other three studies. Moreover, the study by Mazza BF et al. [23] enrolled participants with a diagnosis of malignant tumoral, which might generate heterogeneity. Taken together, we can't determine that blood transfusion at thresholds of 7 g/dl is the optimal transfusion threshold for patients with septic shock based on current evidences, which urges more as well as large clinical trials.

Strengths and limitations

This study mainly focused on analyzing the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients, which remains an essential clinical practice but with controversy. Indeed, the blood transfusion is given with different triggers by different organizations, such as surviving Sepsis Campaign (SCC), the American college of critical care medicine (ACCM) and the world health

organization (WHO)[39-41]. Further analysis shows that these guidelines are provided mainly based on long-term effects of blood transfusion on ICU patients. Our meta-analysis is the first report concerning the feasibility of a transfusion threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients, which is an essential issue for survival of ICU patients based on specific clinical characters. In addition, unlike the previously published meta-analyses, which enrolled studies with different restrictive transfusion thresholds, we only included RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl to get relative solid conclusions. Simultaneously, we performed an updated and comprehensive analysis that focused on ICU patients with septic shock. Meanwhile, this analysis revealed no evidence of significant small study bias according to visual inspection of the funnel plot, Begg's test and Egger's test.

Some limitations are also noted in the current systematic review and meta-analysis. Firstly, the number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl. Five relevant studies that discussed the two different transfusion thresholds among critically ill patients were excluded because of their different definition of restrictive RBC transfusion thresholds [30 42-45]. Secondly, the heterogeneity in our meta-analysis was relatively high, which was caused by different outcome measurements and clinical settings. Some trials with low quality evidence and insufficient participants might be another source of heterogeneity. Correspondingly, we tried to eliminate the heterogeneity by conducting a subgroup analysis and analyzing the effects. Thirdly, there was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions. Fourthly, the sample sizes of all incorporated RCTs were varied. We applied the Mantel-Haenszel method to

address this diversity in sample sizes and to avoid our results from being dominated by the larger studies. Finally, we failed to testify if hemoglobin level less than 7 g/dl is the optimal threshold for the blood transfusions in critically ill patients and in those with septic shock basing on a lack of sufficient evidence.

Conclusions and clinical implications

The present meta-analysis of RCTs focused on the effect of RBC transfusions at the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients. RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in significantly different in short-term mortality when compared with transfusions administered at a more liberal threshold. However, it might associate with decreased hospital length of stay and MI events, suggesting its potentially protecting role for critically ill patients. Besides, within the ICU patient population with septic shock, RBC transfusions at the restrictive threshold did not improve short-term mortality compared with transfusions at the more liberal threshold. Therefore, we recommended a hemoglobin trigger of 7 g/dL for critically ill patients with or without septic shock due to the cost and resource saving effect, as well as its latent value in reducing severe adverse effect. Still, further studies are required to testify our findings. This study indeed provides novel conclusions on the impact of blood transfusion on short-term outcomes of critically ill patients as well as patients with septic shock. Even though we can't determine that the hemoglobin trigger of 7 g/dL is the optimal strategy for RBC transfusion, but it does show advantages in managing the use of RBC units and urge prudent decision making in blood transfusion for critically ill patients.

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Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Abbreviations

RBCs: Red blood cell; ICUs: Intensive care units; MI: Myocardial infarction; ORs: Odds ratios; RCTs: Randomized controlled trials; TRICC: Transfusion requirements in critical care; PRISMA: Preferred items for systematic reviews and meta-analyses; GRADE: Grading of recommendations, assessment, development and evaluation; CIs: Confidence intervals; M-H: Mantel-Haenszel; TIA: Transient ischemic attack; TRAHT: Transfusion requirements after head trauma; TRICOP: Transfusion requirements in critically ill oncological patients.

Author contributions

YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data. YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper. RQY undertook the statistical analyses. All authors contributed to and revised the final manuscript.

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Figure legends

Figure 1. Flow chart for study selection. Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. Finally, nine RCTs with 3415 patients were included in the meta-analysis.

Figure 2. Forest plot of all-cause short-term mortality in ICU patients. The odds ratio and 95% CI for short-term mortality between the restrictive and liberal transfusion thresholds are presented in the forest plot. The threshold of hemoglobin < 7 g/dl showed no obvious improvement in short-term mortality when compared with the liberal threshold.

Figure 3. Forest plot of the length of hospital stay. The forest plot shows the mean difference and 95% CI for the length of hospital stay between the two groups. Blood transfusion at the restrictive threshold resulted in shorter hospital stays than blood transfusion at the more liberal threshold.

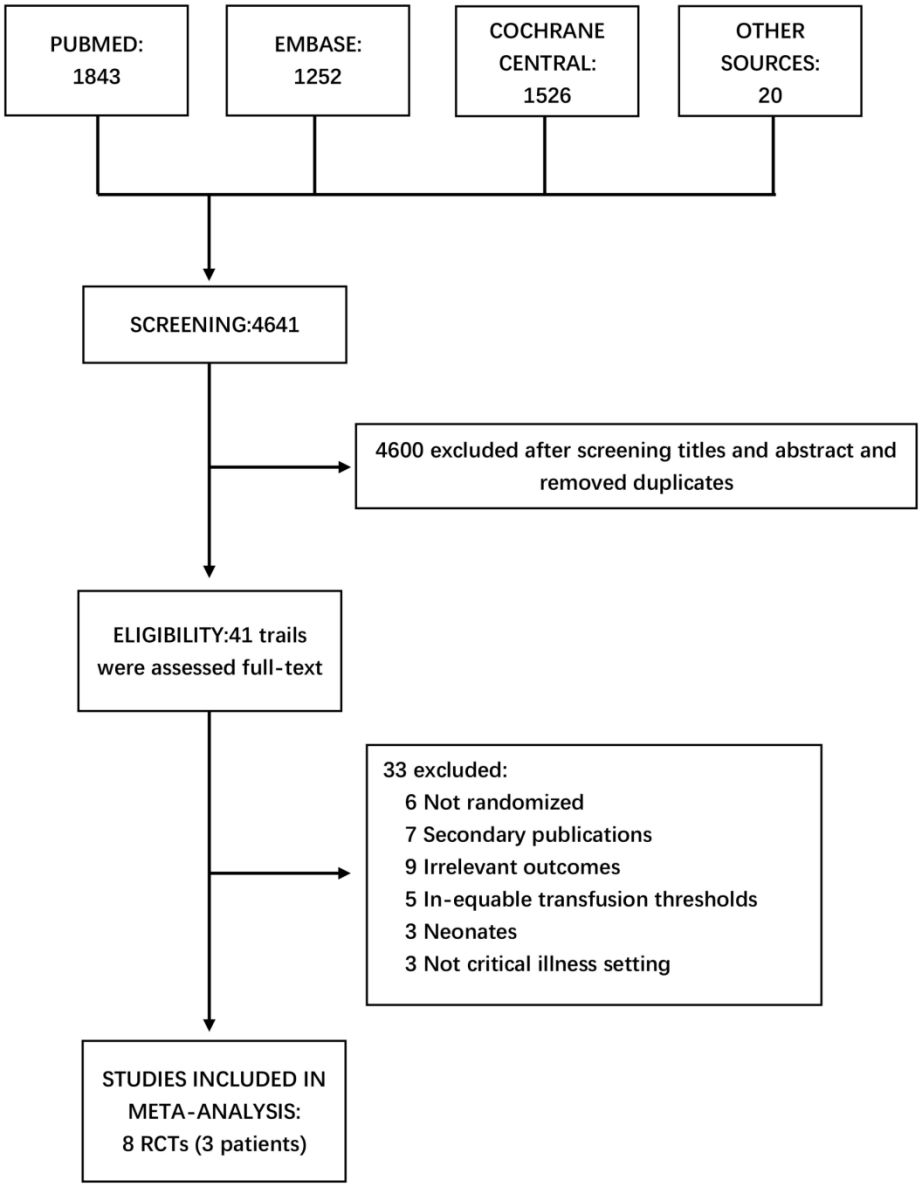
Figure 4. Forest plot of the length of ICU stay. The difference in the length of ICU stay in the groups with different transfusion thresholds is shown by the mean difference and 95% CI in the forest plot. No marked improvement was seen in the length of ICU stay with a transfusion threshold of hemoglobin < 7 g/dl.

Figure 5. Forest plot of myocardial infarction in ICU patients after RBCs transfusion. The forest plot shows the odds ratios and 95% CI for myocardial infarction in the groups of ICU patients with different transfusion thresholds. Blood transfusion at a threshold of hemoglobin < 7 g/dl significantly decrease in the rate of

myocardial infarction compared with the more liberal threshold.

Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients after RBC transfusions. The odds ratios and 95% CI for ischemic/thromboembolic events are presented in the forest plot. No significant difference was noted in ischemic/thromboembolic events between the group with the threshold of 7 g/dl hemoglobin compared with the group with the more liberal threshold.

Figure 7. Forest plot for short-term mortality following subgroup analysis. The forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of patients receiving RBC transfusions at various thresholds according to the subgroup analysis of the septic shock and non-sepsis groups. Restrictive transfusion was incapable of decreasing short-term mortality in septic ICU patients.



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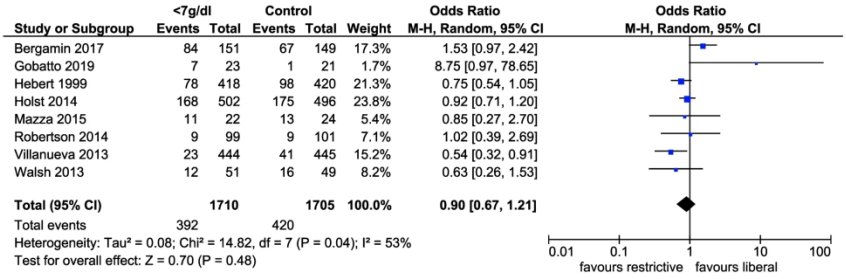

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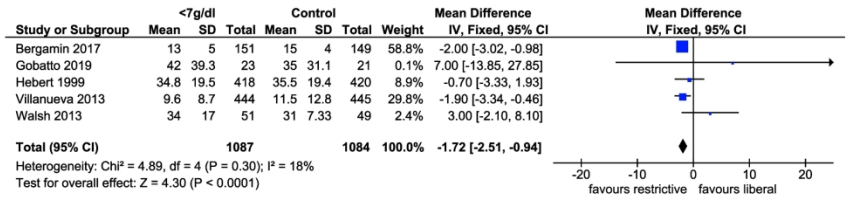

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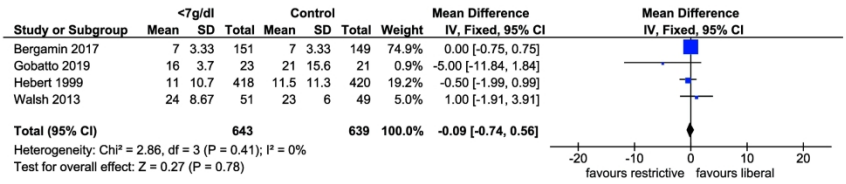

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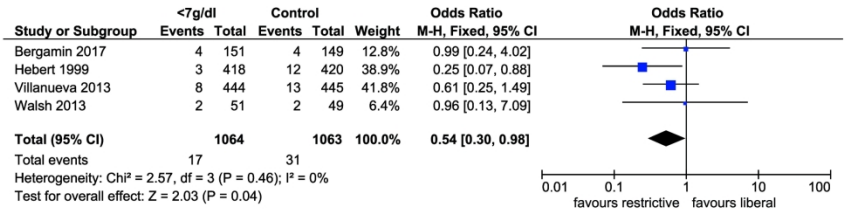

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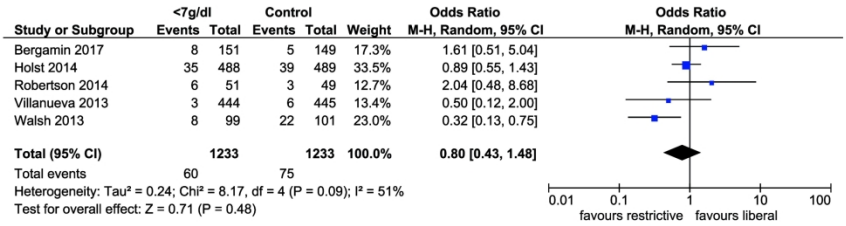

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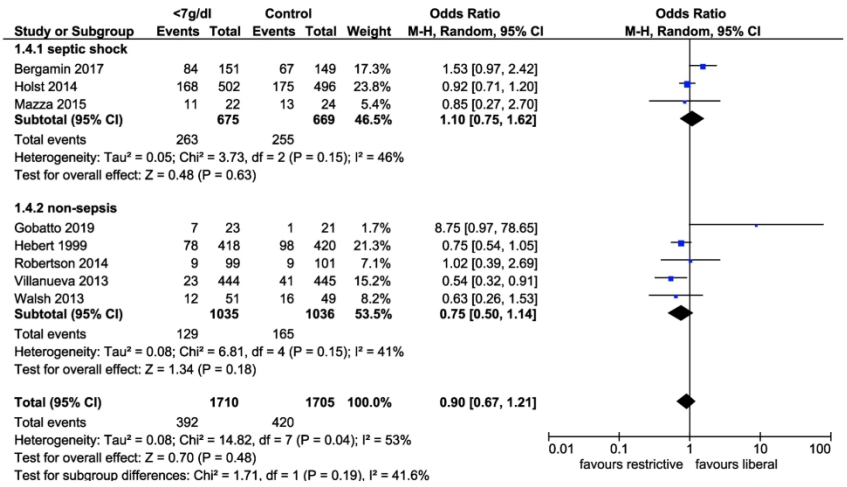

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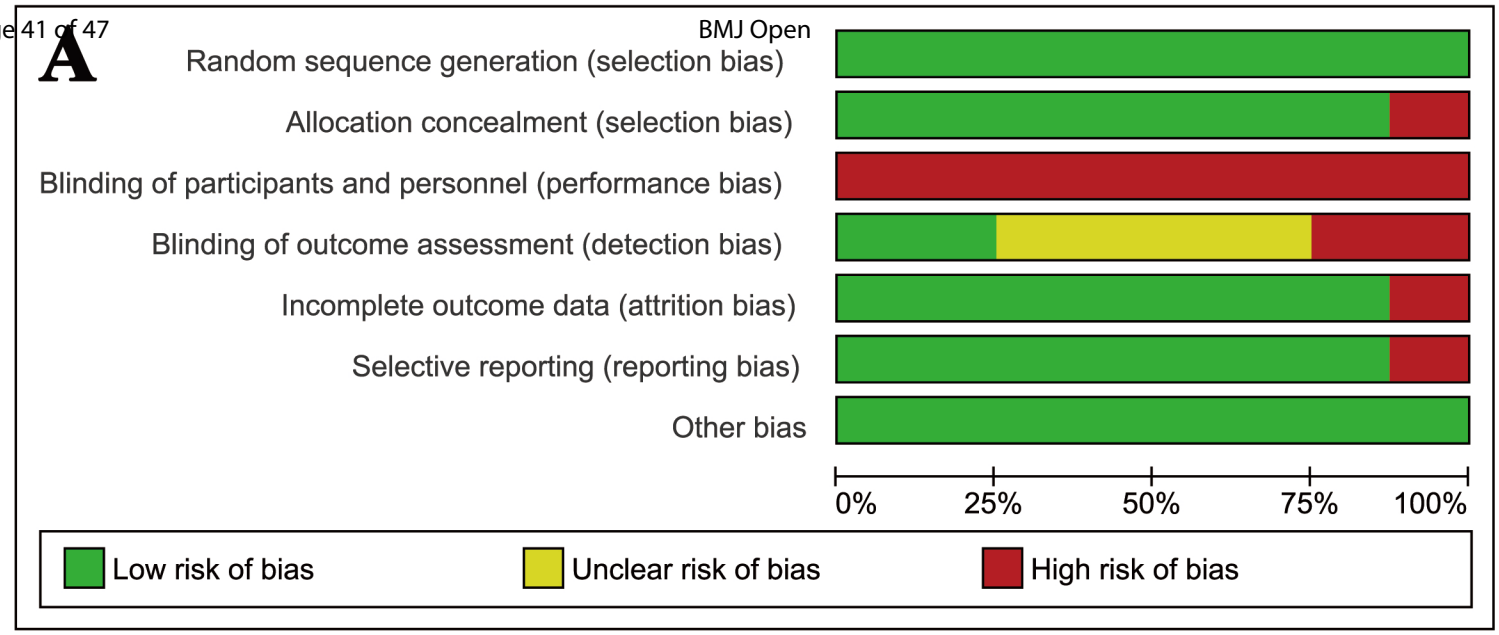
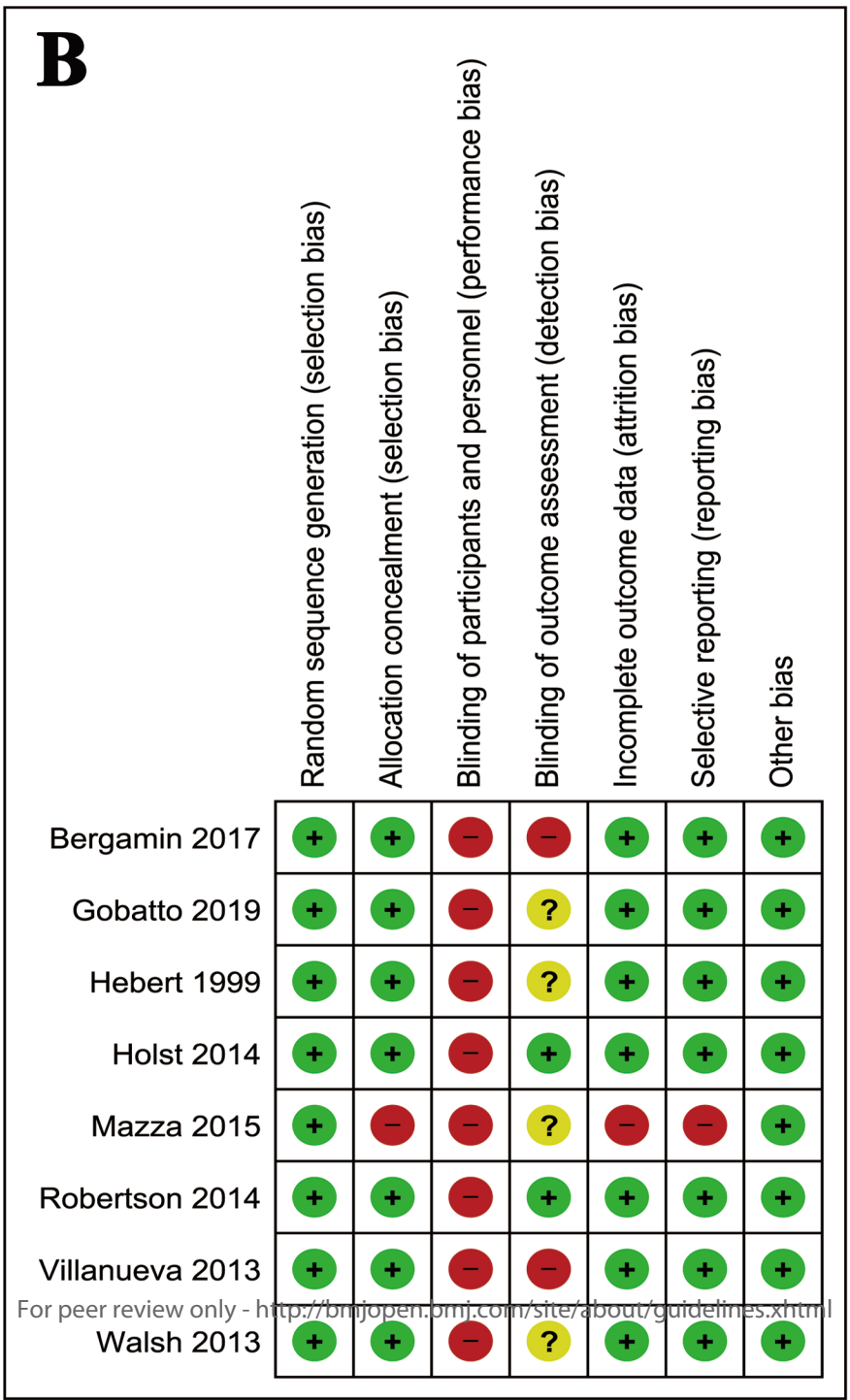
Search strategy

(((((((((critical care) OR intensive care) OR ICU) OR SICU) OR critical care[MeSH Terms]) OR intensive care unit[MeSH Terms])) AND ((((((red blood cell*[Title/Abstract]) OR blood transfusion[MeSH Terms])) AND ((((therap*[Title/Abstract]) OR transfus*[Title/Abstract]) OR restrict*[Title/Abstract]) OR liberal*[Title/Abstract] OR trigger*[Title/Abstract] OR threshold*[Title/Abstract] OR conservative*[Title/Abstract] OR aggress*[Title/Abstract]))) OR blood transfusion*[Title/Abstract]))) AND ((((((((((((random*[Title/Abstract]) OR "randomized controlled trial"[Publication Type]) OR systematic*[Title/Abstract]) OR metaanalys*[Title/Abstract]) OR meta analys*[Title/Abstract]) OR guideline*[Title/Abstract]) OR "guideline"[Publication Type]) OR consensus[Title/Abstract]) OR "appropriateness criteria"[Title/Abstract]) OR "choosing wisely"[Title/Abstract]) OR "appropriate use criteria"[Title/Abstract]) OR ((GRADE[Title/Abstract]) AND recommendation*[Title/Abstract])))





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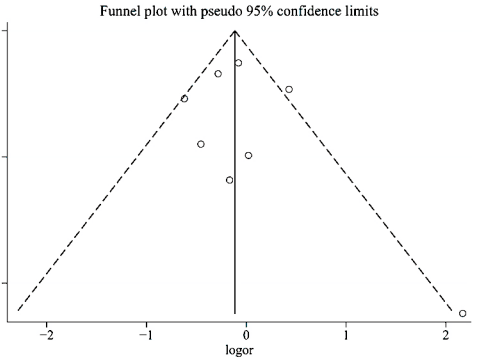

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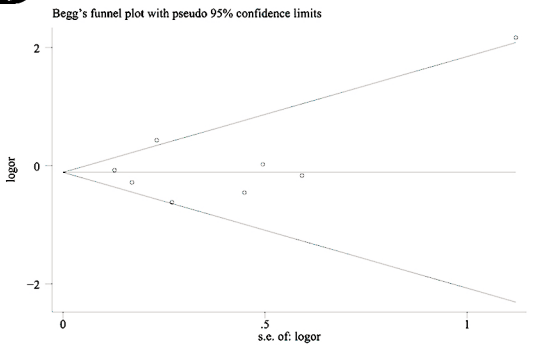

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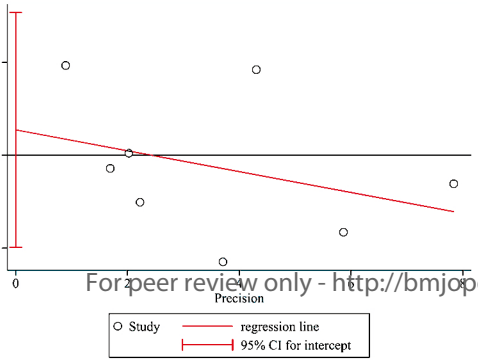

Supplementary Table 1 Summary of Findings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Critical illness				
Short-term mortality	**Study population**		**OR 0.9** (0.67 to 1.21)	3415 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
	246 per 1000	**227 per 1000** (180 to 283)				
	Moderate					
	280 per 1000	**259 per 1000** (207 to 320)				
Hospital length of stay		The mean hospital length of stay in the intervention groups was **1.72 lower** (2.51 to 0.94 lower)		2171 (5 studies)	⊕⊕⊖⊖ **low**[1]	
ICU length of stay		The mean icu length of stay in the intervention groups was **0.09 lower** (0.74 lower to 0.56 higher)		1282 (4 studies)	⊕⊕⊖⊖ **low**[1]	
Myocardial Infraction	**Study population**		**OR 0.54** (0.3 to 0.98)	2127 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	29 per 1000	**16 per 1000** (9 to 29)				
	Moderate					
	29 per 1000	**16 per 1000** (9 to 28)				
Ischemic event	**Study population**					

	61 per 1000	**49 per 1000** (27 to 87)			
	Moderate		**OR 0.8** (0.43 to 1.48)	2466 (5 studies)	⊕⊕⊕⊖ **moderate**[1]
	61 per 1000	**49 per 1000** (27 to 88)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No explanation was provided

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

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You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Section/Topic	Item No.	Checklist item	Reported on Page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11

Section/Topic	Item No.	Checklist item	Reported on Page No.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12-13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			

Section/Topic	Item No.	Checklist item	Reported on Page No.
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23-24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review

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Article Type:	Original research
Date Submitted by the Author:	25-Nov-2019
Complete List of Authors:	Yao, Ren; Changhai Hospital Ren, Chao; Chinese PLA General Hospital, Zhang, Zi; Changhai Hospital Zhu, Yibing; Beijing Fuxing Hospital, ICU Xia, Zhao Fan; Changhai Hospital, Department of Burns YAO, Yongming; Fourth Medical Center of the Chinese PLA General Hospital
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Red blood cells, Transfusion, Intensive care units, Septic shock

Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review

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Ren-qi Yao and Chao Ren contributed equally to this manuscript.

Abstract

Objectives: We employed a comprehensive systematic review and meta-analysis to assess benefits and risks of a threshold of hemoglobin level below 7g/dl vs liberal transfusion strategy among critically ill patients, and even patients with septic shock.

Design: Systematic review and meta-analysis.

Data sources: We performed systematical searches for relevant randomized controlled trials (RCTs) in the Cochrane Library, EMBASE, and PubMed databases up to Sep 1, 2019.

Eligibility criteria: RCTs among adult intensive care unit (ICU) patients comparing 7 g/dl as restrictive strategy with liberal transfusion were incorporated.

Data extraction and synthesis: The clinical outcomes, including short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction (MI), and ischemic events, were screened and analyzed after data collection. We applied odds ratios (ORs) to analyze dichotomous outcomes and standardized mean differences (SMDs) to analyze continuous outcomes with fixed or random effects models based on heterogeneity evaluation for each outcome.

Results: Eight RCTs with 3415 patients were included. Compared with a more liberal threshold, an red blood cell (RBC) transfusion threshold < 7 g/dl hemoglobin showed no significant difference in short-term mortality (OR: 0.90, 95% CI: 0.67-1.21; *P*=0.48; I^2=53%), length of hospital stay (SMD: -0.11, 95% CI: -0.30-0.07, *P*=0.24, I^2=71%), length of ICU stay (SMD: -0.03, 95% CI: -0.14-0.08, *P*=0.54, I^2=0%), or ischemic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%). However, we found that the incidence of MI (OR: 0.54, 95% CI: 0.30-0.98, *P*=0.04; I^2=0%) was lower in the group with the threshold < 7 g/dl than that with the more liberal threshold.

Conclusions: An RBC transfusion threshold < 7 g/dl hemoglobin is incapable of decreasing short-term mortality in ICU patients according to currently published evidences, while it might have potential role in reducing MI incidence.

Keywords: Red blood cells, Transfusion, Intensive care units, Septic shock

Strengths and limitations of this study

1. This meta-analysis focused on the feasibility of a transfusion threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients through only including RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl.

2. In this meta-analysis, we performed an updated and comprehensive analysis that focused on ICU patients with septic shock.

3. The number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl.

4. There was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions.

Introduction

Allogenic red blood cell (RBC) transfusion remains a commonly used and crucial treatment among patients admitted to the intensive care unit (ICU), as anemia is commonly complicated and critically involved in poor outcomes[1]. Every year, approximately 75 million units of blood are reportedly obtained worldwide, with higher levels of consumption in the UK, Canada, and US [2] [3]. In ICU settings, 40%~50% of critically ill patients receive at least one unit of RBC transfusion, and the average consumption reaches five units during their ICU stay[4]. Undoubtedly, appropriate blood transfusion can benefit critical ill patients by increasing oxygen delivery and reducing oxygen debt, protecting against multiple organ dysfunction[5]. While these data also urge the cautious use of RBCs because of the substantial cost and supply shortage. For example, Holst LB and colleagues have reported that the units of RBCs used for liberal transfusion trigger strategies are almost twice the amount of RBCs transfusion with restrictive strategies, but no significant difference is noted between restrictive and liberal triggers in assessment of primary outcomes[6]. Additionally, the risk of complications, such as volume overload, infection, transfusion reactions, and even increased mortality, also raises concerns about the threshold for RBC transfusion in ICU patients [7-9]. However, the optimal thresholds for RBC transfusion in diverse critical care settings remain controversial. The results of the Transfusion Requirements in Critical Care (TRICC) study have confirmed the superiority of a restrictive transfusion strategy (RBC transfusions were given when hemoglobin concentration was below 7 g/dl) in controlling the 30-day mortality of

critical ill patients with younger age and lower acute physiology and chronic health evaluation (APACHE) II score. Indeed, conservative blood transfusion could result in a marked decline in the use of RBCs, which further decreases the in-hospital cost of ICU patients [2] [10]. Recently, various studies have extensively discussed transfusion strategies to optimize the outcomes. For instance, no significant difference was shown between restrictive and liberal transfusion strategies in terms of adverse effects, as reported by some studies [11] [12]. In addition, other researchers found that blood transfusions triggered at a threshold of 7 g/dl were much safer in critically ill patients with cardiovascular diseases [10] [13]. However, Silva Junior JM et al have found that RBC transfusion was an independent risk factor for mortality of critical ill patients, followed with longer ICU and hospital stay, which was associated with different decisions regarding transfusion triggers[14]. Other indexes, such as oxygen delivery (DO_2) and oxygen consumption (VO_2), also show marked deviation among various studies. Study by Conrad SA and colleagues revealed significant improvement in DO_2 but no influence in VO_2 after blood transfusion on septic patients[15]. While Steffes CP and colleagues have reported that blood transfusion is capable of elevating DO_2 and VO_2 in septic surgical patients[16]. Therefore, the thresholds for blood transfusion should be different for patients with various diseases and need to be carefully evaluated.

Actually, the benefits and harms of blood transfusions in patients admitted to intensive care units have been discussed by many systematic reviews and meta-analyses, but the results remain controversial due to the distinct inclusion

criteria and outcome measurement across studies.[9 11 12 17-19]. Salpeter and colleagues found restrictive blood transfusion trigger at 7g/dl could significantly reduce mortality of disparate phase, as well as diverse transfusion-related complications compared to the liberal transfusion trigger. However, they didn't distinguish pediatric and adult ICU settings, and merely enrolled 3 randomized controlled trials (RCTs)[17]. Systematic reviews conducted by Fominskiy E et al revealed no statistical difference in 90-day mortality between two transfusion thresholds[18]. Nevertheless, recently updated publication by Chong and colleagues incorporated almost same RCTs as Fominskiy E et al did, while they identified a significant reduction of 30-day mortality in ICU patients with restrictive strategy in comparison with those with more liberal transfusion trigger[19]. In addition, the specific thresholds of hemoglobin concentration are essential for decision of RBC transfusion regarding various clinical practice. However, no studies have reported the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or the financial value of a different transfusion strategy, even though it is considered as a common trigger to implement restrictive transfusion strategy. Furthermore, different types of clinical conditions also show remarkable deviation in RBCs administration. For example, septic shock is commonly recognized as a substantial threat to ICU, and it is related to high hospital costs and poor outcomes [20]. Anemia is also commonly complicated during the progression of sepsis, as it presents with insufficient tissue perfusion, like hypovolemic shock, and dysfunction of cellular metabolism, which cannot be reversed by prompt fluid resuscitation and administration of vasoactive drugs. Indeed,

blood transfusion is frequently administered as an efficient remedy for patients with septic shock, but the protocol for transfusion is different in patients with septic shock from patients with other critical illnesses [1 21 22]. In fact, there is still a lack of conclusive data regarding the rational transfusion threshold for patients with septic shock [22 23]. The transfusion requirements in septic shock (TRISS) trial did provide strong evidences that no significant difference was noted between RBC transfusion with lower and higher hemoglobin thresholds in long term mortality and adverse reactions[22]. However, other researchers found that RBC transfusion was related to unfavorable outcomes of septic patients, such as sequential organ failure assessment (SOFA) score and length of stay in ICU. In addition, the association between RBC transfusion and short-term outcomes of septic patients hasn't been established yet. In the present study, we aim to perform a comprehensive systematic review and meta-analysis specifically determining whether hemoglobin level below 7g/dl is an optimal trigger for blood transfusion among adult ICU patients when compared to more liberal transfusion thresholds by evaluating its impacts on short-term mortality and adverse reactions. Additionally, a subgroup analysis is further performed with patients with or without septic shock to seek the optimal transfusion strategy for this unique subset of critically ill patients.

Materials and methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

statement[24].

Patient and public involvement

There were no patients' involvement in the development of the research question, outcome measurement, design of this study, or the recruitment to and conduct of the study. The results will not be disseminated to study participants.

Search strategy and information sources

Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. We conceived strategy comprised of following combination of exploded Medical Subject Heading (MeSH) terms: "critical care", "intensive care unit", "blood transfusion". Detailed search strategy was presented in **Supplementary File 1**. Relevant studies up to Sep 1, 2019, were searched without any language limitations. In addition, ongoing trials and conference abstracts were identified to obtain additional evidences. We also obtained references by searching the reference lists of reviews and trial registries.

Eligibility and exclusion criteria

This meta-analysis included RCTs among adult ICU patients (age>18 years) who underwent allogenic RBC transfusion. The recruited studies had to compare two distinct blood transfusion thresholds, a restrictive threshold and a liberal one. The definition of transfusion thresholds in this systematic review was based on

hemoglobin or hematocrit levels. Blood transfusion initiated at hemoglobin thresholds below 7 g/dl were termed restrictive strategies, while the liberal transfusions were conducted at hemoglobin thresholds between 8.5 and 10 g/dl. Other types of studies, including observational, cohort and case-control, were excluded. Trials with pretransfusion hemoglobin concentrations higher than 7 g/dl were eliminated as well. Only ICU patients were considered, while participants in other hospital departments were not eligible.

Study selection

Two reviewers (RQY and CR) independently screened the titles and abstracts of the relevant trials. If the abstract of a potentially eligible article failed to provide adequate information, the full-text version was then screened to determine its eligibility. Differing opinions between the two authors were settled by discussion and consensus. If a consensus could not be reached, a consulting group including two experts (ZFX and YMY) resolved the disagreements.

Data collection

Two reviewers (RQY and CR) extracted the data from all eligible trials with a standardized and predesigned form. First author, year of publication, baseline characteristics, the total number of included patients and the clinical settings were recorded. The clinical outcomes (short-term mortality, length of hospital stay, length of ICU stay, myocardial infarction (MI), and ischemic events) and study design were

also obtained.

Risk of bias assessment

The Cochrane Collaboration tool was used to evaluate the risk of bias of the RCTs. The randomization sequence, allocation concealment, blinding of personnel and participants, risk of incomplete outcome data, selective reporting bias and other sources of bias were assessed independently by two authors. Each clause was rated as 'low', 'high' or 'unclear' bias. The summarized risk of bias of each RCT was ranked as low, moderate or high.

Grading quality of evidence

The quality of evidence of each outcome was evaluated in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods. This procedure was conducted with GRADE Pro software 3.6 (McMaster University 2014, Hamilton, Canada).

Outcomes

The primary endpoint was all-cause short-term mortality, which was preferentially analyzed by 28-day or 30-day mortality. In the case of unreported short-term mortality, we contacted the authors for the original data or considered the closest available mortality data. Secondary outcomes included the following indicators: length of hospital stay, length of ICU stay, myocardial infarction, and

ischemic events.

Data synthesis and analysis

The statistical analysis was conducted with ReviewManager (RevMan 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We applied odds ratios (ORs) to analyze dichotomous outcomes and standardized mean differences (SMDs) for continuous outcomes. The pooled results were calculated with 95% confidence intervals (CIs). Heterogeneity among studies for each outcome was assessed by applying both χ^2 test and I^2 statistics. Either I^2 greater than 50% or p value of χ^2 test less than 0.10 was deemed as statistically significant heterogeneity. If remarkable heterogeneity existed in pooled results, random effects models combined with the Mantel-Haenszel (M-H) method were used, or else, fixed effects models was applied accordingly. For the small study bias, the funnel plot of the pooled short-term mortality data was scanned visually by reviewers. Besides, by using Stata software, version 12, we performed Begg's and Egger's tests to further assess the possible small study bias. A sensitivity analysis was also performed by means of excluding each study one at a time from the pooled effect. Additionally, we performed a subgroup analysis based on the M-H model to determine the difference between septic shock and non-sepsis groups.

Results

Search results and the characteristics of the included studies

This systematic review and meta-analysis identified 4641 relevant citations; we removed duplicates and then scanned the titles and abstracts of 4600 studies. Eventually, the full-text articles for 41 trials were reviewed, and 8 RCTs met the inclusion criteria and were presented with full paper, with ICU patients older than 18 years who received RBC transfusions at hemoglobin thresholds below 7 g/dl (**Fig. 1**).

The eight included RCTs ranged in publication year from 1999 to 2019 and contained a total of 3415 patients[10 22 23 25-29]. The patient population sizes of the included trials were very diverse, ranging from 44 to 998. Three studies enrolled more than 800 patients, while three trials enrolled fewer than 200 eligible patients. Four studies enrolled 1480 patients with septic shock, including one studies complicated by cancer diagnoses. In addition, four trials were multicenter studies (**Table 1**)

Risk of bias

Most of the RCTs met the randomization requirements and used rational distribution methods. In some of the included trials, however, it was challenging to blind the attending physicians and nurses to the outcome assessment based on the intervention, which resulted in high risk of performance bias (**Supplementary Fig. 1**).

Quality of evidence

The summary of findings for the outcomes of interest and the levels of evidence were provided (**Supplementary Table 1**). The qualities of the primary outcome data and some secondary outcome data, including myocardial infarction and ischemic

events, were all ranked as moderate. However, the length of stay both in hospital and ICU displayed low quality.

Table 1 Characteristics of the included studies

Author	Year of Publication	No. of sites	Population			Transfusion Triggers		Mortality Data	References
			Clinical Settings	Details	Number of Participants	Restrictive	Liberal		
Hebert et al.	1999	25	Critical illness	Euvolemic critically ill patients	838	Hb 7	Hb 10	30-day mortality 60-day mortality ICU mortality	[10]
Holst et al.	2014	32	Critical illness	Patients with septic shock	998	Hb 7	Hb 9	Hospital mortality 90-day mortality	[22]
Mazza et al.	2015	Single	Critical illness	Patients with septic shock	46	Hb 7	Hb 9	Hospital mortality	[23]
Robertson et al.	2014	2	Traumatic brain injury	Patients with closed head injuries	200	Hb 7	Hb 10	Six-month mortality	[25]
Villanueva et al.	2013	Single	Upper UGIB	Patients with hematemesis, melena or both	889	Hb 7	Hb 9	45-day mortality	[26]
Walsh et al.	2013	6	Critical illness	Older critically ill patients receiving mechanical ventilation	100	Hb 7	Hb 9	30-day mortality 60-day mortality 180-day mortality ICU mortality Hospital mortality	[27]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	28-day mortality 60-day mortality 90-day mortality	[29]
Gobatto et al.	2019	Single	Traumatic brain injury	Patients with moderate or severe traumatic brain injury	44	Hb 7	Hb 9	Hospital mortality ICU mortality	[28]

Primary outcome: short-term mortality

Within this meta-analysis, there were three RCTs that reported 28-day or 30-day mortality, and four reported in-hospital mortality only. The published study from Holst LB et al did provide solid conclusions about the impacts of blood transfusion with liberal and restrictive hemoglobin thresholds on long-term mortality and rates of ischemic events, which presented with similar effects, while the information about short-term outcomes was missing[22]. Therefore, we wrote a letter asking for the important evidence of short-term mortality rates, as its analysis was based on a large sample size and was essential for our conclusions. After generating the forest plot, we found no significant difference in short-term mortality between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal strategy (OR: 0.90, 95% CI: 0.67-1.21; *P*=0.48; I^2=53%). Meanwhile, we noticed that the RCT reported by Bergamin et al. (19) was the main resource of heterogeneity, and removing that study resulted in a marked reduction in heterogeneity (I^2=29%, *P*=0.21) (**Fig. 2**).

Secondary outcome: length of hospital stay, length of ICU stay, myocardial infarction, and ischemic events

Five included studies documented the length of hospital stay, which revealed no significant difference in hospital stays when the threshold of hemoglobin < 7 g/dl was used, comparing with the more liberal threshold (SMD: -0.11, 95% CI: -0.30-0.07, P=0.24, I^2=71%, **Fig. 3**). Sensitivity analysis indicated that study by Bergamin et al was the main source of heterogeneity, exclusion of which could significantly reduce heterogeneity (I^2=45%, P=0.51). The outcome of length of ICU stay was reported by four trials, and there was no significant difference between the two thresholds (SMD: -0.03, 95% CI: -0.14-0.08, P=0.54, I^2=0%, **Fig. 4**). In addition, we identified that MI

events was decreased among patients with transfusion trigger of hemoglobin < 7 g/dl when compared to those with the liberal transfusion strategy (OR: 0.54, 95% CI: 0.30-0.98, *P*=0.04; I^2=0%, **Fig. 5**). However, no significant differences were noted between the two transfusion thresholds for critically ill patients in ischemic/thromboembolic events (OR, 0.80; 95% CI, 0.43-1.48; *P*=0.48; I^2=51%, **Fig. 6**). After removing study conducted by Walsh et al, the heterogeneity of this outcome decreased significantly (I^2=0%, *P*=0.21), which indicated the main source of heterogeneity.

Small study bias

We constructed a funnel plot to assess the possible small study bias. After inspecting the funnel plot, we found no evidence of small study bias. Furthermore, we used Begg's test (*P*=0.71) and Egger's test (*P*=0.62) to evaluate the funnel plot asymmetry, which also showed no significant statistical evidence of small study bias (**Supplementary Fig. 2**).

Subgroup analysis

The subgroup analysis of the septic shock and non-sepsis groups investigated short-term mortality. From the forest plot, there were no significant differences in short-term mortality between two thresholds in either the septic shock group (OR: 1.10, 95% CI: 0.75-1.62; *P*=0.63; I^2=46%) or the non-sepsis group (OR: 0.75, 95% CI: 0.50-1.14; *P*=0.15; I^2=41%) (**Fig. 7**).

Discussion

Major findings

The current study demonstrated that restricting the transfusion threshold to a hemoglobin concentration less than 7 g/dl did not result in significant differences in short-term mortality, ICU/hospital length of stay, or ischemic events, when compared with more liberal thresholds. Of note, the length of stay of both ICU and hospital displayed low quality of evidence. Additionally, pooled data also revealed that the incidence of MI was decreased among patients applied 7 g/dl as transfusion threshold. Nevertheless, we should be cautious when interpreting this finding. After removing the study conducted by Villanueva and his colleagues, as well as changing effects model from random effects models to fixed effects models could alter the consequence, indicating the instability of this outcome.

Within the primary outcome analysis, the heterogeneity of enrolled trials was moderate, with an I^2 of 53% according to the heterogeneity test, while sensitivity analysis revealed that remove of the Transfusion Requirements in Critically Ill Oncological Patients (TRICOP) trial resulted in dramatically decreased heterogeneity (I^2=29%, P=0.21). As this study enrolled patients diagnosed with both solid cancer and septic shock, the baseline characteristic of this unique subset might differ from other ordinary ICU patients, which could partially explain the source of heterogeneity. Also, this finding was assumed to be due to different clinical settings, especially for patients with septic shock. We further performed a subgroup analysis after classifying the studies into a septic shock group and a non-sepsis group, as septic shock was recognized as one of the major causes of death in critical ill patients. In septic shock group, patients with a transfusion threshold < 7 g/dl showed no significant difference in short-term mortality compared to those with a more liberal transfusion threshold, while the heterogeneity was markedly decreased (I^2=46%, P=0.15). In non-sepsis group, no significant difference in short-term mortality was noted between the two

thresholds with only five trials included. Additionally, the highly disparate sample sizes of included studies could be another resource of heterogeneity. Given the fact that several studies came from conference abstracts, we were unable to evaluate their methodology and data quality in detail.

Relations to other meta-analysis

Carefully designed meta-analyses on RBC transfusions in critically ill patients have been published recently. In 2014, the first time Salpeter and colleagues reported the benefits of restrictive blood transfusion at hemoglobin trigger <7 g/dL in critical ill patients via conducting meta-analysis, which presented with significant reductions in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR: 0.74; 95% CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute coronary syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95% CI, 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR: 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold group[17]. However, this meta-analysis did not provide a convincing conclusion with only three RCTs included, and also failed to separate adult and pediatric participants, as each population shared different transfusion protocols.

Recently, in a review by Fominskiy E et al. [18], the restrictive and liberal RBC transfusion thresholds in critically ill patients showed no significant difference in all-cause 90-day mortality (OR: 1.10; 95% CI: 0.99-1.23; P=0.07; I^2=34%). In fact, this study was the first comprehensive meta-analysis to address different transfusion thresholds among critically ill and perioperative patients, but it lacked a valid analysis of secondary outcomes which were noteworthy factors for the effects of RBC transfusions. Furthermore, Chong and colleagues also conducted an updated analysis

on the effects of RBC transfusion, which included two more RCTs other than the same 10 trials included in the Fominskiy's study[18 19 23 30]. These results suggested that RBC transfusion with restrictive threshold significantly reduced the risk of overall 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97; *P*=0.019) when compared with that with liberal threshold, accompanied with declining risk of stroke/transient ischemic attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99; *P*=0.04), transfusion reactions (OR: 0.48; 95% CI, 0.29-0.80; *P*=0.005), allogenic blood exposure (OR: 0.04; 95% CI: 0.01-0.14; *P*=0.001), and length of hospital stay (95% CI: 0.42-1.64; *P*=0.001), hinting the safety of using restrictive transfusion protocol. Actually, above two studies focused on different primary outcomes, 30-day and 90-day mortality respectively, and further drew different conclusions even though both included similar RCTs, indicating that the effects of RBC transfusion varied with the stage of critical settings. However, Hovaguimian F et al.[31] performed a context-specific systematic review and meta-analysis comparing the restrictive and liberal transfusion thresholds and found no significant differences in early mortality (OR: 0.94; 95% CI: 0.73-1.20; *P*=0.09; I^2=45%) between the two thresholds, indicating that the specific types and severity of critical illness might be in need of different strategies of RBC transfusion, especially for patients with major surgery.

In the present study, we specifically concentrated on the restrictive transfusion threshold of hemoglobin < 7 g/dl in ICU patients. We included data from the newly published Transfusion Requirements after Head Trauma (TRAHT) trial and the TRICOP trial, which presented with increased mortality rate in the group with restrictive transfusion thresholds in comparison with liberal transfusion threshold group[28 29]. This study showed that RBC transfusion with restrictive threshold < 7 g/dl did not result in significant improvement in short-term mortality when compared with

those using liberal thresholds.

Subgroup analysis

The first review with regard to the impact of blood transfusion on the prognosis of septic shock patients was conducted by Dupuis and colleagues [32]. They showed no association between RBC transfusion and mortality rate in patients with septic shock, and also failed to determine correlations between the two different transfusion thresholds or to infer the optimal transfusion threshold for septic shock patients because of a shortage of high-quality RCTs [32]. In fact, a 10 g/dl hemoglobin threshold has been universally proposed for treatment of septic shock as the crucial role of RBC transfusions in early goal-directed therapy [33]. Nonetheless, severe adverse events caused by extensive blood transfusion have been reported as a great threat for septic shock patients by several studies[34-36]. The restrictive strategy, as reported previously, was beneficial for the improvement of microcirculation, while also saving blood products [10 37]. The landmark TRISS trial that was conducted by Holst L et al. [22] revealed no significant differences in 90-day mortality between patients in the group with the transfusion thresholds of 7 g/dl and those with the more liberal thresholds. In addition, the number of patients experiencing ischemic events and severe adverse reactions was also similar between the two groups. The TRISS trial demonstrated the safety and economic efficiency of the restrictive blood transfusion threshold, with a well-controlled risk of bias. Mazza BF et al. [23] performed a randomized physiological study of septic shock patients with the endpoint of abnormal lactate and $ScvO_2$ under distinct pretransfusion hemoglobin concentrations. However, they failed to provide valid data on mortality with a relatively small sample size provided. Recently, Bergamin and colleagues focused on cancer patients who developed septic shock in

the ICU through a single-center RCT [29]. Indeed, tumor patients that were complicated by septic shock were in urgent need of blood transfusion as high risk of anemia[22 38]. Ideally, the more restrictive threshold for transfusion might reduce the occurrence of multiple transfusion-related complications. In this study, we conducted a comprehensive meta-analysis after enrolled all recently published RCTs that covered septic shock cases. No marked difference in mortality was observed between the transfusion threshold of hemoglobin < 7 g/dl and the more liberal transfusion threshold (OR: 1.08; 95% CI, 0.82-1.41; P=0.54; I^2=20%). We assumed that these results might be, at least in part, due to the overwhelming weight that the TRISS trial carried and the relatively low quality of the other three studies. Moreover, the study by Mazza BF et al. [23] enrolled participants with a diagnosis of malignant tumoral, which might generate heterogeneity. Taken together, we can't determine that blood transfusion at thresholds of 7 g/dl is the optimal transfusion threshold for patients with septic shock based on current evidences, which urges more as well as large clinical trials.

Strengths and limitations

This study mainly focused on analyzing the impact of the transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients, which remains an essential clinical practice but with controversy. Indeed, the blood transfusion is given with different triggers by different organizations, such as surviving Sepsis Campaign (SCC), the American college of critical care medicine (ACCM) and the world health organization (WHO)[39-41]. Further analysis shows that these guidelines are provided mainly based on long-term effects of blood transfusion on ICU patients. Our meta-analysis is the first report concerning the feasibility of a transfusion threshold of

hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients, which is an essential issue for survival of ICU patients based on specific clinical characters. In addition, unlike the previously published meta-analyses, which enrolled studies with different restrictive transfusion thresholds, we only included RCTs that specified the restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration less than 7 g/dl to get relative solid conclusions. Simultaneously, we performed an updated and comprehensive analysis that focused on ICU patients with septic shock. Meanwhile, this analysis revealed no evidence of significant small study bias according to visual inspection of the funnel plot, Begg's test and Egger's test.

Some limitations are also noted in the current systematic review and meta-analysis. Firstly, the number of studies we enrolled was not large enough due to the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl. Five relevant studies that discussed the two different transfusion thresholds among critically ill patients were excluded because of their different definition of restrictive RBC transfusion thresholds [30 42-45]. Secondly, the heterogeneity in our meta-analysis was relatively high, which was caused by different outcome measurements and clinical settings. Some trials with low quality evidence and insufficient participants might be another source of heterogeneity. Correspondingly, we tried to eliminate the heterogeneity by conducting a subgroup analysis and analyzing the effects. Thirdly, there was imperfect blinding of the study participants in the trials mainly owing to the nature of the interventions. Fourthly, the sample sizes of all incorporated RCTs were varied. We applied the Mantel-Haenszel method to address this diversity in sample sizes and to avoid our results from being dominated by the larger studies. Finally, we failed to testify if hemoglobin level less than 7 g/dl was the optimal threshold for the blood transfusions in critically ill patients and in

those with septic shock basing on a lack of sufficient evidence.

Conclusions and clinical implications

The present meta-analysis of RCTs focused on the effect of RBC transfusions at the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients. RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in significant difference in short-term mortality when compared with transfusions administered at a more liberal threshold. However, it might associate with decreased MI events, suggesting its potentially protecting role for critically ill patients. Besides, regarding ICU patient with septic shock, RBC transfusions at the restrictive threshold did not improve short-term mortality compared with transfusions at the more liberal threshold. Therefore, we recommend a hemoglobin trigger of 7 g/dL for critically ill patients with or without septic shock due to the cost and resource saving effect, as well as its latent value in reducing severe adverse effect. Still, further studies are required to validate our findings. This study indeed provides novel conclusions on the impact of blood transfusion on short-term outcomes of critically ill patients as well as patients with septic shock. Even though it was hard to determine that the hemoglobin trigger of 7 g/dL was the optimal strategy for RBC transfusion, but it did show advantages in managing the use of RBC units and urged prudent decision-making in blood transfusion for critically ill patients.

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Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Abbreviations

RBC: Red blood cell; ICU: Intensive care unit; TRICC: Transfusion requirements in critical care; APACHE: Acute physiology and chronic health evaluation; DO_2: oxygen delivery; VO_2: oxygen consumption; RCT: Randomized controlled trial; TRISS: The transfusion requirements in septic shock; SOFA: sequential organ failure assessment; PRISMA: Preferred items for systematic reviews and meta-analyses; MeSH: Medical Subject Heading; MI: Myocardial infarction; GRADE: Grading of recommendations, assessment, development and evaluation; ORs: Odds ratios; SMDs: standardized mean differences; CIs: Confidence intervals; M-H: Mantel-Haenszel; TRICOP: Transfusion requirements in critically ill oncological patients; TIA: Transient ischemic attack; TRAHT: Transfusion requirements after head trauma; SCC: Surviving sepsis campaign; ACCM: American

college of critical care medicine; WHO: World health organization.

Author contributions

YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data. YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper. RQY undertook the statistical analyses. All authors contributed to and revised the final manuscript.

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Figure legends

Figure 1. Flow chart for study selection. Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. Finally, nine RCTs with 3415 patients were included in the meta-analysis.

Figure 2. Forest plot of all-cause short-term mortality in ICU patients. The odds ratio and 95% CI for short-term mortality between the restrictive and liberal transfusion thresholds are presented in the forest plot. The threshold of hemoglobin < 7 g/dl showed no obvious improvement in short-term mortality when compared with the liberal threshold.

Figure 3. Forest plot of the length of hospital stay. The forest plot shows the mean difference and 95% CI for the length of hospital stay between the two groups. Blood transfusion at the restrictive threshold resulted in no significant difference of hospital stays compared to blood transfusion at the more liberal threshold.

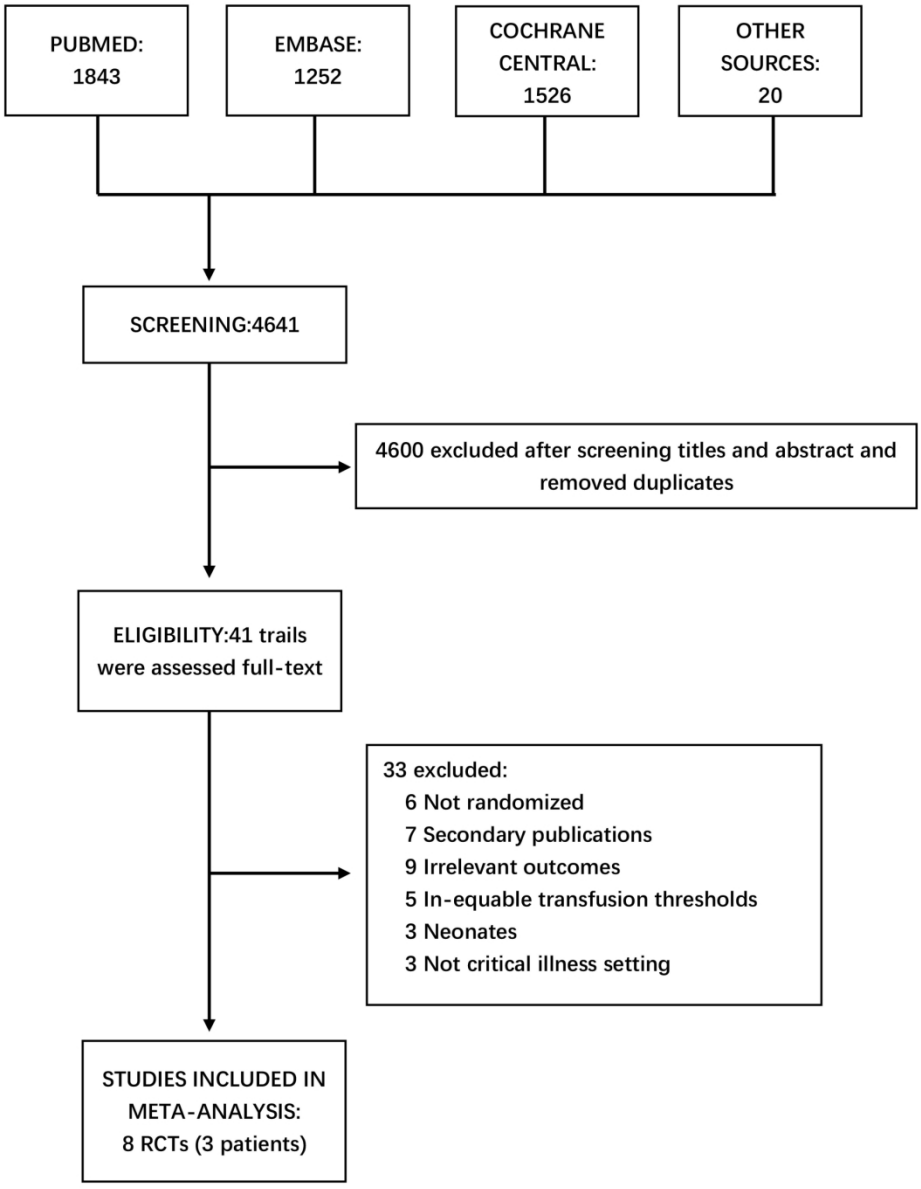
Figure 4. Forest plot of the length of ICU stay. The difference in the length of ICU stay in the groups with different transfusion thresholds is shown by the mean difference and 95% CI in the forest plot. No marked improvement was seen in the length of ICU stay with a transfusion threshold of hemoglobin < 7 g/dl.

Figure 5. Forest plot of myocardial infarction in ICU patients after RBCs transfusion. The forest plot shows the odds ratios and 95% CI for myocardial infarction in the groups of ICU patients with different transfusion thresholds. Blood transfusion at a threshold of hemoglobin < 7 g/dl significantly decrease in the rate of

myocardial infarction compared with the more liberal threshold.

Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients after RBC transfusions. The odds ratios and 95% CI for ischemic/thromboembolic events are presented in the forest plot. No significant difference was noted in ischemic/thromboembolic events between the group with the threshold of 7 g/dl hemoglobin compared with the group with the more liberal threshold.

Figure 7. Forest plot for short-term mortality following subgroup analysis. The forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of patients receiving RBC transfusions at various thresholds according to the subgroup analysis of the septic shock and non-sepsis groups. Restrictive transfusion was incapable of decreasing short-term mortality in septic ICU patients.



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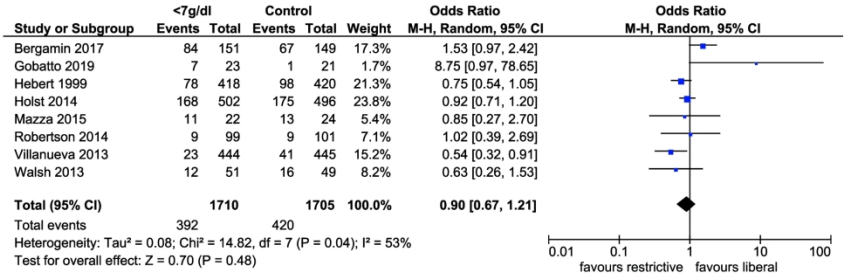

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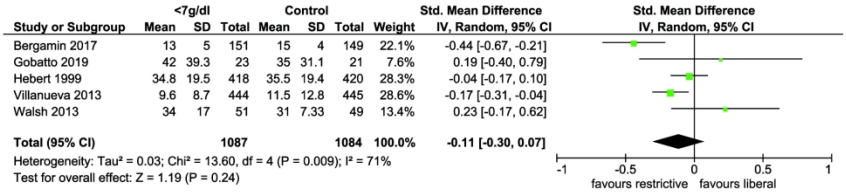

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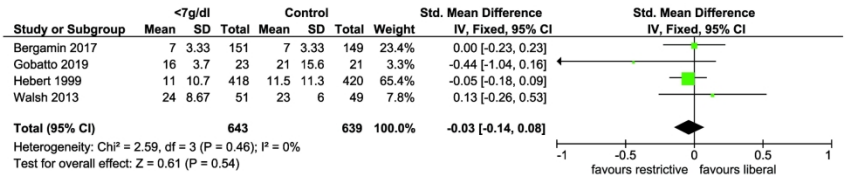

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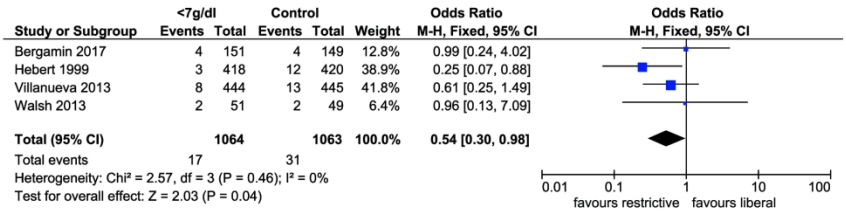

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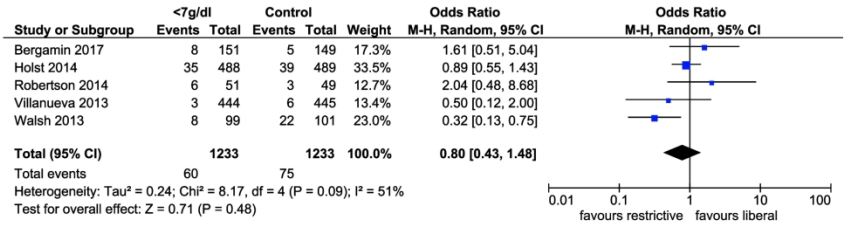

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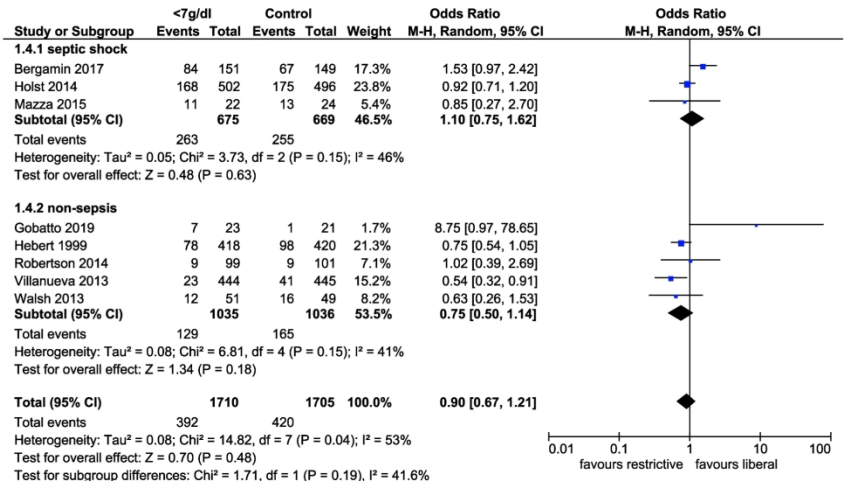

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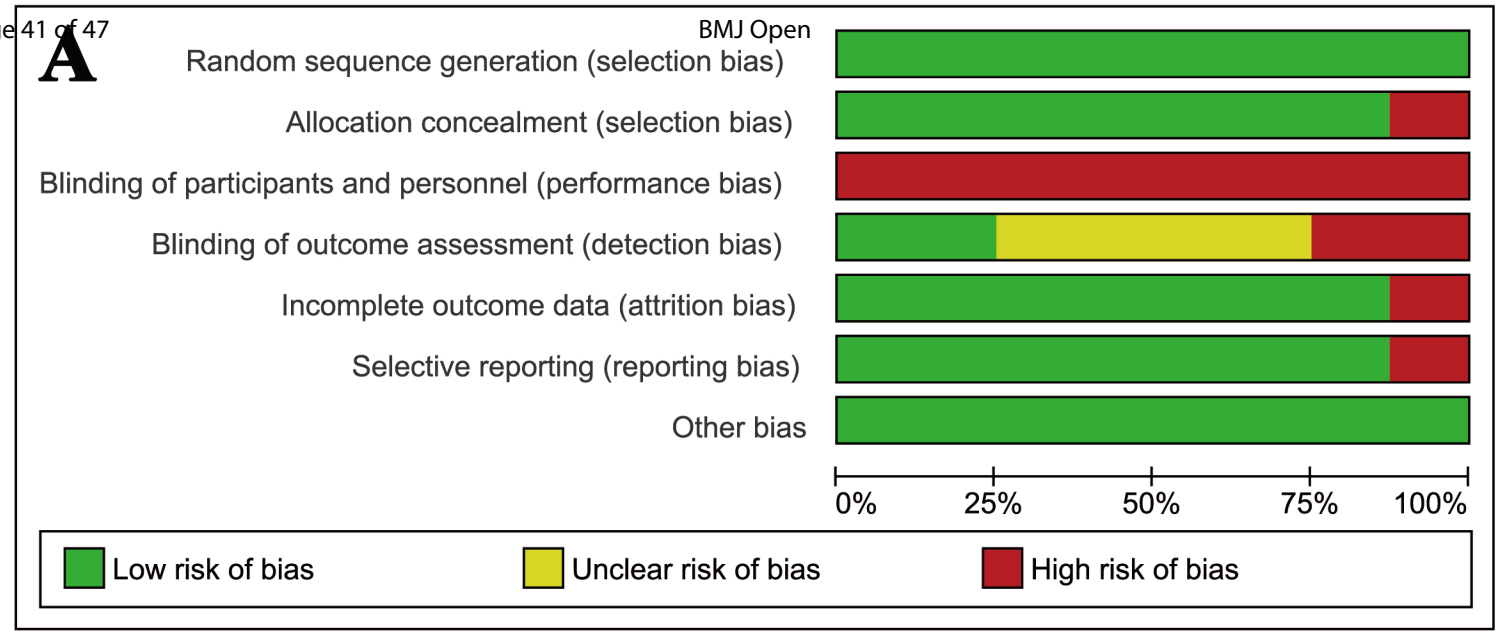
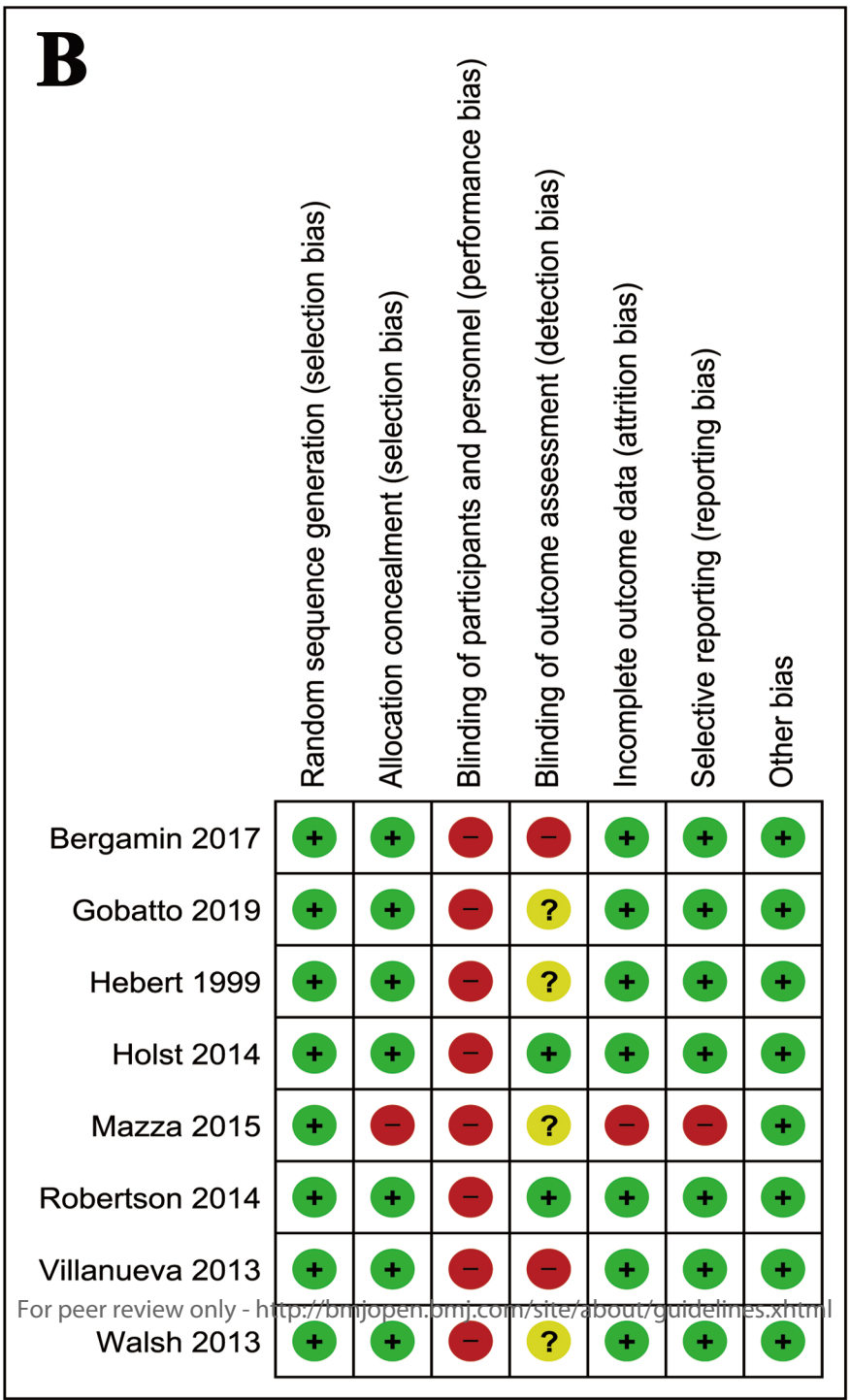
Search strategy

(((((((((critical care) OR intensive care) OR ICU) OR SICU) OR critical care[MeSH Terms]) OR intensive care unit[MeSH Terms])) AND ((((((red blood cell*[Title/Abstract]) OR blood transfusion[MeSH Terms])) AND ((((therap*[Title/Abstract]) OR transfus*[Title/Abstract]) OR restrict*[Title/Abstract]) OR liberal*[Title/Abstract] OR trigger*[Title/Abstract] OR threshold*[Title/Abstract] OR conservative*[Title/Abstract] OR aggress*[Title/Abstract]))) OR blood transfusion*[Title/Abstract]))) AND ((((((((((((random*[Title/Abstract]) OR "randomized controlled trial"[Publication Type]) OR systematic*[Title/Abstract]) OR metaanalys*[Title/Abstract]) OR meta analys*[Title/Abstract]) OR guideline*[Title/Abstract]) OR "guideline"[Publication Type]) OR consensus[Title/Abstract]) OR "appropriateness criteria"[Title/Abstract]) OR "choosing wisely"[Title/Abstract]) OR "appropriate use criteria"[Title/Abstract]) OR ((GRADE[Title/Abstract]) AND recommendation*[Title/Abstract])))





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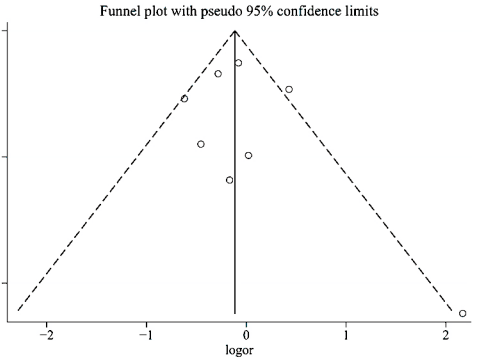

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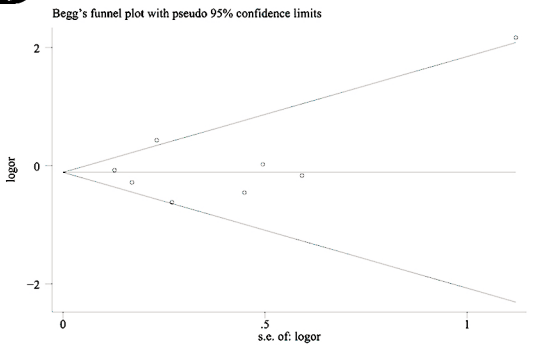

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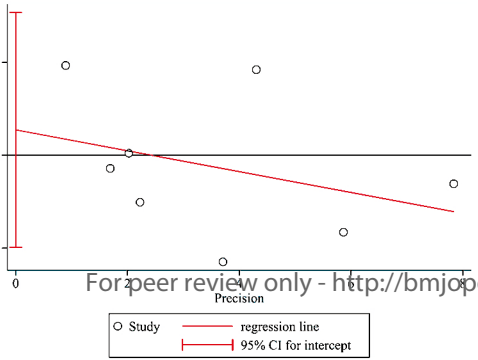

Supplementary Table 1 Summary of Findings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Critical illness				
Short-term mortality	**Study population**		**OR 0.9** (0.67 to 1.21)	3415 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
	246 per 1000	**227 per 1000** (180 to 283)				
	Moderate					
	280 per 1000	**259 per 1000** (207 to 320)				
Hospital length of stay		The mean hospital length of stay in the intervention groups was **0.11 standard deviations lower** (0.30 lower to 0.07 higher)	**SMD -0.11** (-0.30 to 0.07)	2171 (5 studies)	⊕⊕⊖⊖ **low**[1]	
ICU length of stay		The mean icu length of stay in the intervention groups was **0.03 standard deviations lower** (0.14 lower to 0.08 higher)	**SMD -0.03** (-0.14 to 0.08)	1282 (4 studies)	⊕⊕⊖⊖ **low**[1]	
Myocardial Infraction	**Study population**		**OR 0.54** (0.3 to 0.98)	2127 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	29 per 1000	**16 per 1000** (9 to 29)				
	Moderate					
	29 per 1000	**16 per 1000** (9 to 28)				
Ischemic event	**Study population**					

	61 per 1000	**49 per 1000** (27 to 87)			
	Moderate		**OR 0.8** (0.43 to 1.48)	2466 (5 studies)	⊕⊕⊕⊖ **moderate**[1]
	61 per 1000	**49 per 1000** (27 to 88)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No explanation was provided

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

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You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Section/Topic	Item No.	Checklist item	Reported on Page No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11-12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	11-12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12

Section/Topic	Item No.	Checklist item	Reported on Page No.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	17-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	17-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25
FUNDING			

Section/Topic	Item No.	Checklist item	Reported on Page No.
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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