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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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Manuscripts

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9 **meta-analysis and systematic review**  
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For peer review only



## 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

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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

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4 found that blood transfusions triggered at a threshold of 7 g/dl are much safer in  
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6 critically ill patients with cardiovascular diseases [7, 10]. Therefore, the thresholds for  
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8 blood transfusion should be different for patients with various diseases and need to be  
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10 carefully evaluated.  
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14       Though the benefits of blood transfusions have been discussed by many  
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16 systematic reviews and meta-analyses, the results remain controversial [6, 8, 9, 11-13].  
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18 Different clinical settings, participants, methods, and study designs all account for the  
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20 diversity of outcomes. In addition, no studies have reported the impact of the  
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22 transfusion threshold of 7 g/dl on the short-term outcomes of critically ill patients or  
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24 the financial value of a different transfusion strategy. Therefore, we performed a  
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26 systematic review and meta-analysis in which we investigated differences between the  
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28 7 g/dl transfusion threshold and a lower threshold.  
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35       Septic shock is commonly recognized as a substantial threat to ICU, and it is  
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37 related to high hospital costs and poor outcomes [14]. It presents with insufficient  
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39 tissue perfusion, like hypovolemic shock, followed by the disruption and dysfunction  
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41 of cellular metabolism, but it cannot be reversed by prompt fluid resuscitation and the  
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43 administration of vasoactive drugs. Blood transfusion is frequently administered as a  
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45 treatment for patients with septic shock, but the protocol for transfusion is different in  
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47 patients with septic shock than in patients with other critical illnesses [15-17]. In fact,  
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49 there is still a lack of conclusive data regarding the rational transfusion threshold for  
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51 patients with septic shock [17, 18]. Thus, in the present study, a subgroup analysis  
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53 was further performed with patients with or without septic shock.  
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## 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

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

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22 Two reviewers (RQY and CR) independently screened the titles and abstracts of  
23  
24 the relevant trials. If the abstract of a potentially eligible article failed to provide  
25  
26 adequate information, the full-text version was then screened to determine its  
27  
28 eligibility. Differing opinions between the two authors were settled by discussion and  
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30 consensus. If a consensus could not be reached, a consulting group including two  
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32 experts (ZFX and YMY) resolved the disagreements.  
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### 40 **Data collection**

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



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

23  
24 Most of the RCTs met the randomization requirements and used rational  
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26 distribution methods. In some of the included trials, however, it was challenging to  
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28 blind the attending physicians and nurses to the outcome assessment based on the  
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30 intervention, which resulted in high risk of performance bias. Two trials that were  
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32 reported in conference abstracts had high percentages of unclear risks  
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38 (**Supplementary Fig. 1**).  
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### 43 **Quality of evidence**

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45 The summary of findings for the outcomes of interest and the levels of evidence  
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47 are provided (**Supplementary Table 1**). The qualities of the primary outcome data  
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49 and some secondary outcome data, including myocardial infarction and ischemic  
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51 events, were all ranked as moderate. However, the lengths of hospital and ICU stays  
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53 displayed low and very low quality, respectively.  
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**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	[7]
Holst et al.	2014	32	Critical illness	Patients with septic shock	998	Hb 7	Hb 9	Hospital mortality 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	[23]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	Hospital mortality 28-day mortality 60-day mortality	[27]
Gobatto et al.	2017	Single	Traumatic brain injury	Patients with moderate or severe traumatic brain injury	44	Hb 7	Hb 9	90-day mortality 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

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3 used Begg's test ( $P=0.63$ ) and Egger's test ( $P=0.65$ ) to evaluate the funnel plot  
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5 asymmetry, which also showed no statistically significant evidence of publication bias  
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8 **(Supplementary Fig. 2).**  
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### 10 11 12 **Subgroup analysis**

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14 The subgroup analysis of the septic shock and nonsepsis groups investigated  
15 short-term mortality. From the forest plot, there were no significant differences in  
16 short-term mortality between two thresholds in either the septic shock group or the  
17 nonsepsis group (**Fig. 7**).  
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### 23 24 25 26 **Discussion**

#### 27 28 **Major findings**

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30 The current study demonstrated that restricting the transfusion threshold to a  
31 hemoglobin concentration less than 7 g/dl did not result in significant differences in  
32 short-term mortality, length of ICU, myocardial infarction, or ischemic events, when  
33 compared with more liberal thresholds. The length of hospital stay was shortened in  
34 the restrictive group than in the liberal group. Within the primary outcome analysis,  
35 the heterogeneity of enrolled trials was moderate, with an  $I^2$  of 47% according to the  
36 heterogeneity test; this finding was assumed to be due to different clinical settings,  
37 especially for patients with septic shock. We further performed a subgroup analysis  
38 after classifying the studies into a septic shock group and a non-sepsis group, as septic  
39 shock was recognized as one of the major causes of death in critical ill patients. In  
40 septic shock group, patients with a transfusion threshold  $< 7$  g/dl showed no  
41 significant difference in short-term mortality compared to those with a more liberal  
42 transfusion threshold, while the heterogeneity was markedly decreased ( $I^2=20\%$ ). In  
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3 non-sepsis group, no significant difference in short-term mortality was noted between  
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5 the two thresholds with only five trials included. Additionally, the highly disparate  
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7 sample size of included studies could be another resource of heterogeneity. Given the  
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9 fact that several studies came from conference abstracts, we were unable to evaluate  
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11 their methodology and data quality in detail.  
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### 17 **Relations to other meta-analysis**

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19 Carefully designed meta-analyses on RBC transfusions in critically ill patients  
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21 have been published recently. In 2014, the first time Salpeter and colleagues reported  
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23 the benefits of restrictive blood transfusion at hemoglobin trigger of <7 g/dL in  
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25 critical ill patients via conducting meta-analysis, which presented with significant  
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27 reductions in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR:  
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29 0.74; 95% CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute  
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31 coronary syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95%  
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33 CI, 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR:  
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35 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold  
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37 group[11]. However, this meta-analysis did not provide a convincing conclusion with  
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39 only three RCTs included, and also failed to separate adult and pediatric participants,  
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41 as each population shared different transfusion protocols.  
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47 Recently, in a review by Fominskiy E et al. [12], the restrictive and liberal RBC  
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49 transfusion thresholds in critically ill patients resulted in no significant difference in  
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51 all-cause 90-day mortality (OR: 1.10; 95% CI: 0.99-1.23;  $P=0.07$ ;  $I^2=34\%$ ). In fact,  
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53 this study was the first comprehensive meta-analysis to address different transfusion  
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55 thresholds among critically ill and perioperative patients, but it lacked a valid analysis  
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57 of secondary outcomes which were noteworthy factors for the effects of RBC  
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3 transfusions. Furthermore, Chong and colleagues also conducted an updated analysis  
4 on the effects of RBC transfusion, which included two more RCTs other than the  
5 same 10 trials included in the Fominskiy's study[12, 13, 18, 24]. These results  
6 suggested that RBC transfusion with restrictive threshold significantly reduced the  
7 risk of overall 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97;  $P=0.019$ ) when  
8 compared with that with liberal threshold, accompanied with declining risk of  
9 stroke/transient ischemic attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99;  $P=0.04$ ),  
10 transfusion reactions (OR: 0.48; 95% CI, 0.29-0.80;  $P=0.005$ ), allogenic blood  
11 exposure (OR: 0.04; 95% CI: 0.01-0.14;  $P=0.001$ ), and length of hospital stay (95%  
12 CI: 0.42-1.64;  $P=0.001$ ), hinting the safety of using restrictive transfusion protocol.  
13 Actually, above two studies focused on different primary outcomes, 30-day and  
14 90-day mortality for each study, and further drew different conclusions even though  
15 both included similar RCTs, indicating that the effects of RBC transfusion varied  
16 with the stage of critical settings. However, Hovaguimian F et al. [25] performed a  
17 context-specific systematic review and meta-analysis comparing the restrictive and  
18 liberal transfusion thresholds and found no significant differences in early mortality  
19 (OR: 0.94; 95% CI: 0.73-1.20;  $P=0.09$ ;  $I^2=45\%$ ) between the two thresholds,  
20 indicating that the specific types and severity of critical illness might be in need of  
21 different strategies of RBC transfusion, especially for patients with major surgery.  
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47 In the present study, we specifically concentrated on the restrictive transfusion  
48 threshold of hemoglobin  $< 7$  g/dl in ICU patients. We included data from the newly  
49 published Transfusion Requirements after Head Trauma (TRAHT) trial and the  
50 Transfusion Requirements in Critically Ill Oncological Patients (TRICOP) trial, which  
51 showed with increased mortality rate in the group with restrictive transfusion  
52 thresholds than that with liberal transfusion threshold [26, 27]. This study showed that  
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3 RBC transfusion with restrictive threshold of < 7 g/dl did not result in significant  
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5 improvement in short-term mortality, myocardial infarction, as well as ischemic  
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7 events, when compared with those using liberal thresholds.  
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### 10 11 12 **Subgroup analysis** 13

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15 The first review with regard to the impact of blood transfusion on the prognosis  
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17 of septic shock patients was conducted by Dupuis and colleagues [28]. They showed  
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19 no association between RBC transfusion and mortality rate in patients with septic  
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21 shock, and also failed to determine correlations between the two different transfusion  
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23 thresholds or to infer the optimal transfusion threshold for septic shock patients  
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25 because of a shortage of high-quality RCTs [28]. In fact, a 10 g/dl hemoglobin  
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27 threshold has been universally proposed for treatment of septic shock as the crucial  
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29 role of RBC transfusions in early goal-directed therapy [29]. Nonetheless, severe  
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31 adverse events caused by extensive blood transfusion have been reported as a great  
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33 threat for septic shock patients by several studies[30-32]. The restrictive strategy, as  
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35 reported previously, was beneficial for the improvement of microcirculation, while  
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37 also saving blood products [7, 33]. The landmark TRISS trial that was conducted by  
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39 Holst L et al. [17] revealed no significant differences in 90-day mortality between  
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41 patients in the group with the transfusion thresholds of 7 g/dl and those with the more  
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43 liberal thresholds. In addition, the number of patients experiencing ischemic events  
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45 and severe adverse reactions was also similar between the two groups. The TRISS  
46  
47 trial demonstrated the safety and economic efficiency of the restrictive blood  
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49 transfusion threshold, with a well-controlled risk of bias. Mazza BF et al. [18]  
50  
51 performed a randomized physiological study of septic shock patients with the  
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53 endpoint of abnormal lactate and ScvO<sub>2</sub> under distinct pretransfusion hemoglobin  
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3 concentrations. However, they failed to provide valid data on mortality with a  
4 relatively small sample size provided. Recently, Bergamin and colleagues focused on  
5 cancer patients who developed septic shock in the ICU through a single-center RCT  
6 [27]. Indeed, tumor patients that were complicated by septic shock were in urgent  
7 need of blood transfusion as high risk of anemia[17, 34]. Ideally, the more restrictive  
8 threshold for transfusion might reduce the occurrence of multiple transfusion-related  
9 complications. In this study, we conducted a comprehensive meta-analysis after  
10 enrolled all recently published RCTs that covered septic shock cases. No marked  
11 difference in mortality was observed between the transfusion threshold of hemoglobin  
12 < 7 g/dl and the more liberal transfusion threshold (OR: 1.08; 95% CI, 0.82-1.41;  
13  $P=0.54$ ;  $I^2=20\%$ ). We assumed that this results might be, at least in part, due to the  
14 overwhelming weight that the TRISS trial carried and the relatively low quality of the  
15 other three studies. Moreover, the study by Mazza BF et al. [18] enrolled participants  
16 with a diagnosis of malignant tumoral, which might generate heterogeneity. Taken  
17 together, we can't determine that blood transfusion at thresholds of 7 g/dl is the  
18 optimal transfusion threshold for patients with septic shock based on current  
19 evidences, which urges more as well as large clinical trials.

### 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 **Strengths and limitations**

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47 Our meta-analysis is the first report concerning the feasibility of a transfusion  
48 threshold of hemoglobin < 7 g/dl with regard to short-term mortality in critically ill  
49 patients. Unlike the previously published meta-analyses, which enrolled studies with  
50 different restrictive transfusion thresholds, we only included RCTs that specified the  
51 restrictive RBC transfusion threshold as a pretransfusion hemoglobin concentration  
52 less than 7 g/dl. Simultaneously, we performed an updated and comprehensive  
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3 analysis that focused on ICU patients with septic shock. Meanwhile, this analysis  
4 revealed no evidence of significant publication bias according to visual inspection of  
5 the funnel plot, Begg's test and Egger's test.  
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10 Some limitations are also noted in the current systematic review and  
11 meta-analysis. Firstly, the number of studies we enrolled was not large enough due to  
12 the strict inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7  
13 g/dl. Five relevant studies that discussed the two different transfusion thresholds  
14 among critically ill patients were excluded because of their different definition of  
15 restrictive RBC transfusion thresholds [24, 35-38]. Secondly, the heterogeneity in our  
16 meta-analysis was relatively high, which was caused by different outcome  
17 measurements and clinical settings. Some trials with low quality evidence and  
18 insufficient participants might be another source of heterogeneity. Correspondingly,  
19 we tried to eliminate the heterogeneity by conducting a subgroup analysis and  
20 analyzing the effects. Thirdly, there was imperfect blinding of the study participants  
21 in the trials mainly owing to the nature of the interventions. Fourthly, the sample sizes  
22 of all incorporated RCTs were varied. We applied the Mantel-Haenszel method to  
23 address this diversity in sample sizes and to avoid our results from being dominated  
24 by the larger studies. Finally, we failed to testify if hemoglobin level less than 7 g/dl  
25 is the optimal threshold for the blood transfusions in critically ill patients and in those  
26 with septic shock basing on a lack of sufficient evidence.  
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## 51 **Conclusions**

52 The present meta-analysis of RCTs focused on the effect of RBC transfusions at  
53 the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients.  
54 RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in  
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3 significantly different in short-term mortality when compared with transfusions  
4 administered at a more liberal threshold; there were also no differences in the length  
5 of ICU stay or the rates of myocardial infarctions and ischemic events. Within the  
6 ICU patient population with septic shock, RBC transfusions at the restrictive  
7 threshold did not improve short-term mortality compared with transfusions at the  
8 more liberal threshold.  
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### 19 **Acknowledgements**

20  
21 This work was supported by grants from the National Natural Science  
22 Foundation (No. 81730057) and the National Key Research and Development  
23 Program of China (No. 2017YFC1103302).  
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### 30 **Conflicts of Interest**

31  
32 The authors have no conflicts of interest to declare.  
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### 38 **Abbreviations**

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

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3 YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data.  
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5 YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper.  
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8 RQY undertook the statistical analyses. All authors contributed to and revised the  
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10 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 3551 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 displayed no significant decrease in

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3 the rate of myocardial infarction compared with the more liberal threshold.  
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8 **Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients**

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

21 **Figure 7. Forest plot for short-term mortality following subgroup analysis.** The

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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.



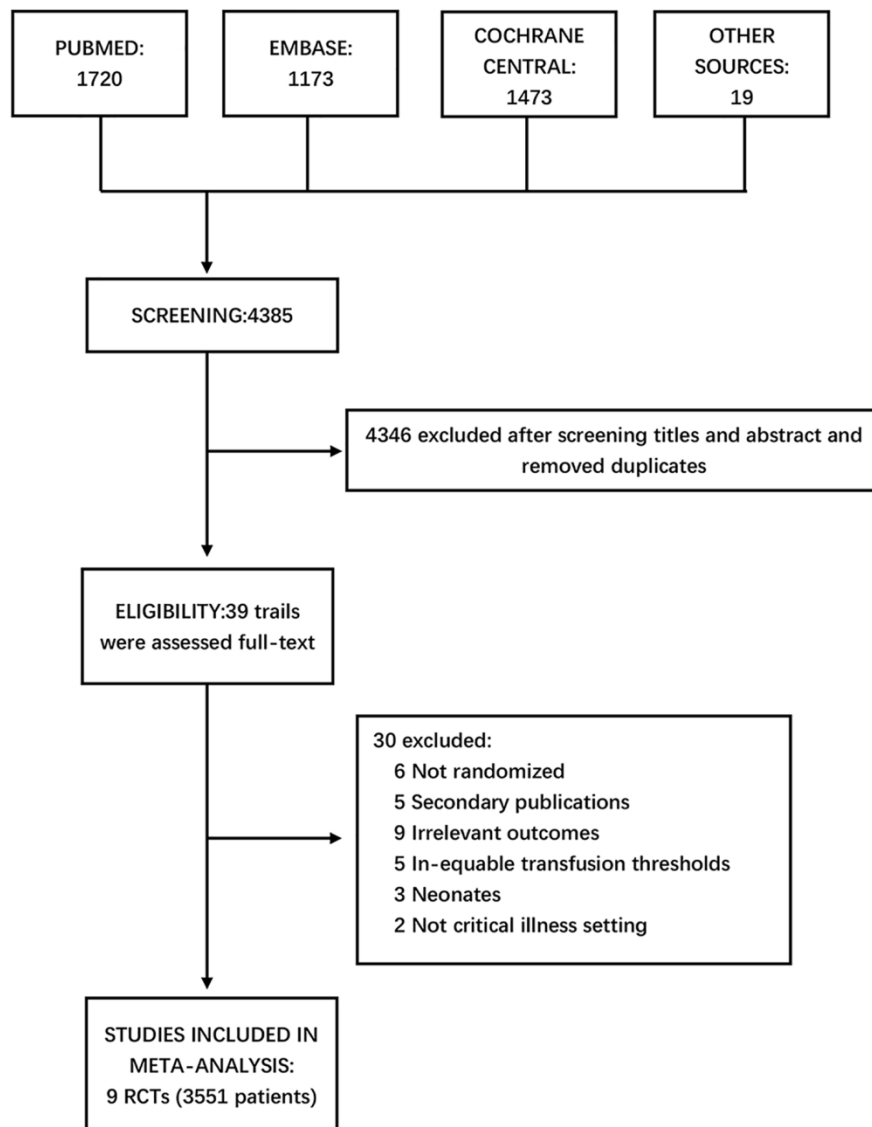


Figure 1. Flow chart for study selection. Online databases, including Cochrane Library, EMBASE, and PubMed, were systematically searched. Finally, nine RCTs with 3551 patients were included in the meta-analysis.

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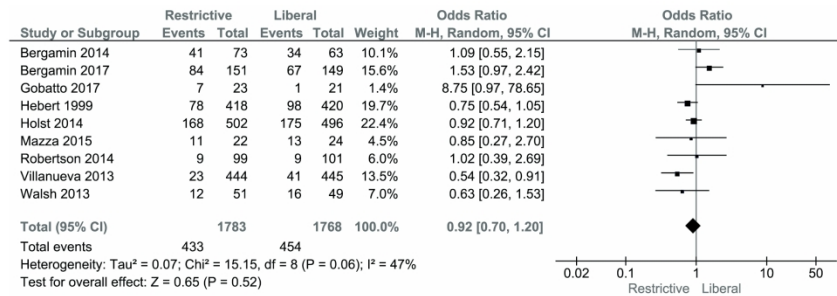


Figure 2. Forest plot of all-cause short-term mortality in ICU patients. The odds ratio and 95% CI for short-term mortality between the restrictive and liberal transfusion thresholds are presented in the forest plot. The threshold of hemoglobin < 7 g/dl showed no obvious improvement in short-term mortality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

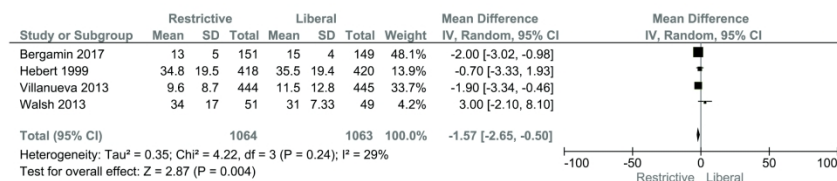


Figure 3. Forest plot of the length of hospital stay. The forest plot shows the mean difference and 95% CI for the length of hospital stay between the two groups. Blood transfusion at the restrictive threshold resulted in shorter hospital stays than blood transfusion at the more liberal threshold.

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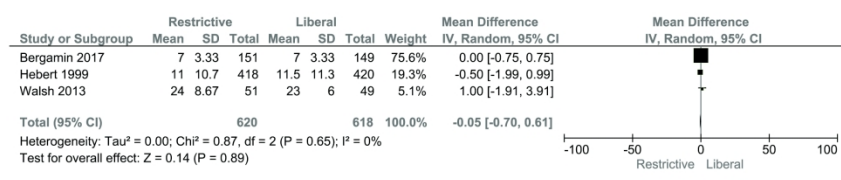


Figure 4. Forest plot of the length of ICU stay. The difference in the length of ICU stay in the groups with different transfusion thresholds is shown by the mean difference and 95% CI in the forest plot. No marked improvement was seen in the length of ICU stay with a transfusion threshold of hemoglobin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

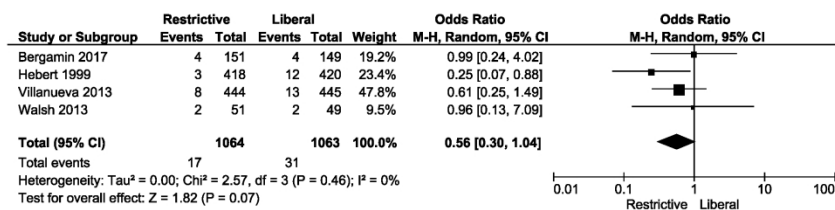


Figure 5. Forest plot of myocardial infarction in ICU patients after RBCs transfusion. The forest plot shows the odds ratios and 95% CI for myocardial infarction in the groups of ICU patients with different transfusion thresholds. Blood transfusion at a threshold of hemoglobin < 7 g/dl displayed no significant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

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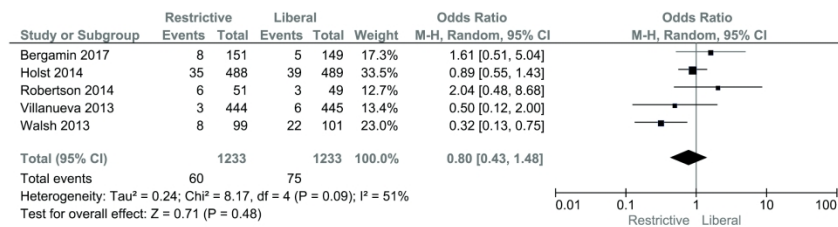


Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients after RBC transfusions. The odds ratios and 95% CI for ischemic/thromboembolic events are presented in the forest plot. No significant difference was noted in ischemic/thromboembolic events between the group with the threshold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

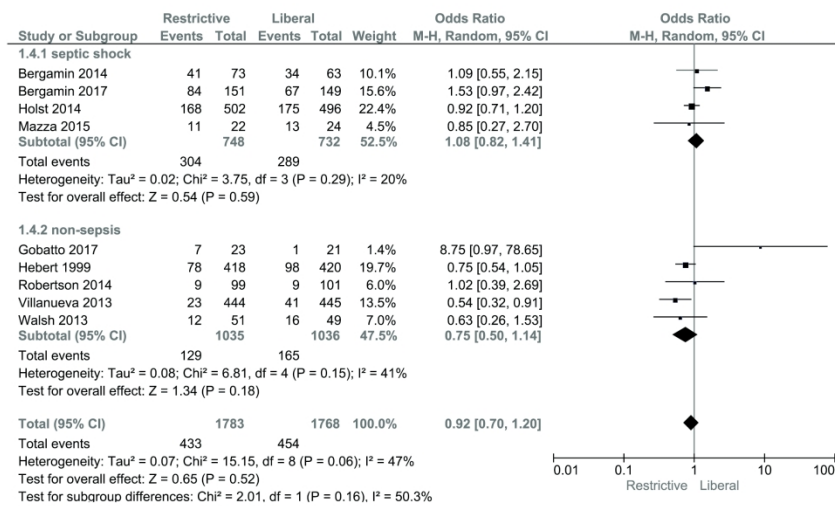
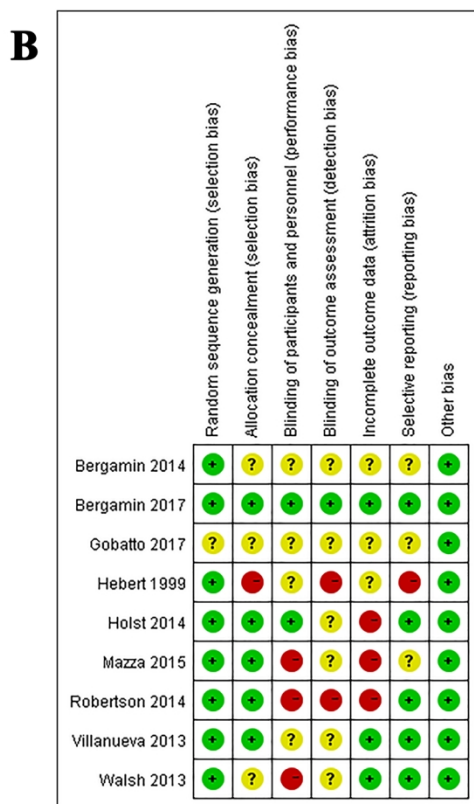
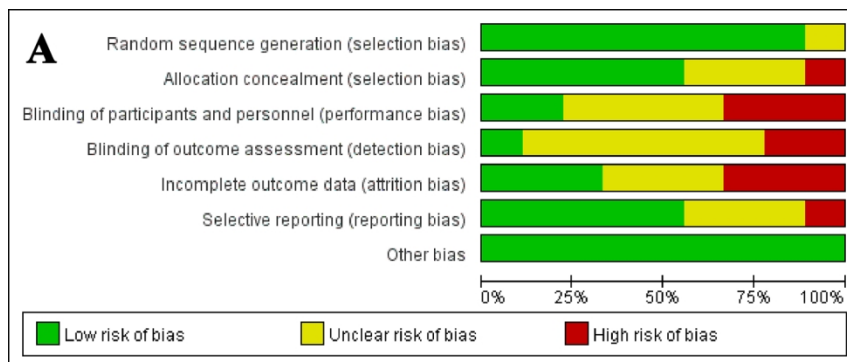
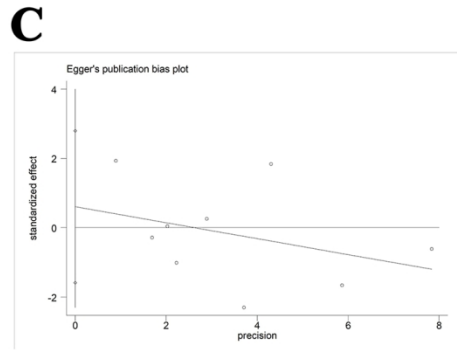
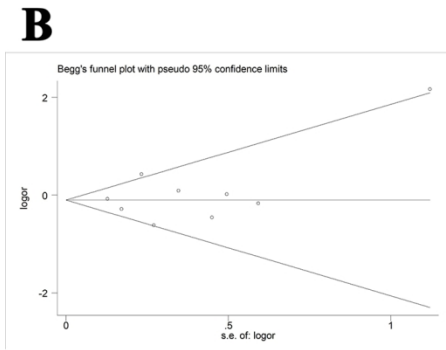
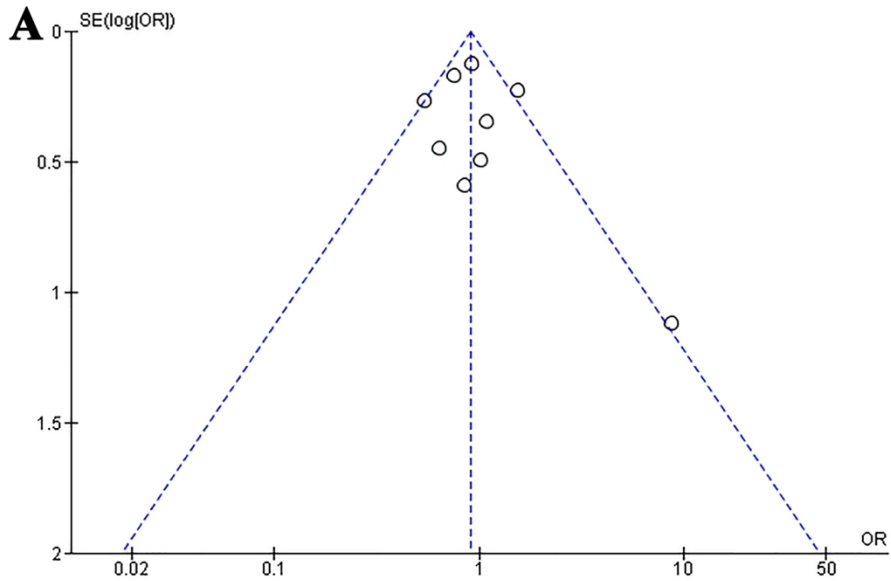


Figure 7. Forest plot for short-term mortality following subgroup analysis. The forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of patients receiving RBC transfusions at various thresholds according to the subgroup analysis of the septic shock and nonsepsis groups.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





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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	Corresponding risk				
	Control	Critical illness				
short-term mortality	Study population		OR 0.92 (0.7 to 1.2)	3551 (9 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
	257 per 1000	241 per 1000 (195 to 293)				
	Moderate					
Myocardial Infraction	Study population		OR 0.56 (0.3 to 1.04)	2127 (4 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
	29 per 1000	17 per 1000 (9 to 30)				
	Moderate					
Ischemic event	Study population		OR 0.8 (0.43 to 1.48)	2466 (5 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
	61 per 1000	49 per 1000 (27 to 87)				
	Moderate					
	Study population					
	61 per 1000	49 per 1000 (27 to 88)				
	Moderate					

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<b>mortality - septic shock</b>	<b>Study population</b>		<b>OR 1.08</b> (0.82 to 1.41)	1480 (4 studies)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>
	<b>395 per 1000</b>	<b>413 per 1000</b> (349 to 479)			
	<b>Moderate</b>				
<b>mortality - non-sepsis</b>	<b>Study population</b>		<b>OR 0.75</b> (0.5 to 1.14)	2071 (5 studies)	⊕⊕⊕⊖ <b>moderate</b> <sup>1</sup>
	<b>159 per 1000</b>	<b>124 per 1000</b> (87 to 178)			
	<b>Moderate</b>				
<b>ICU length of stay</b>	The mean icu length of stay in the intervention groups was <b>0.05 lower</b> (0.7 lower to 0.61 higher)		1238 (3 studies)	⊕⊖⊖⊖ <b>very low</b> <sup>1</sup>	
<b>hospital length of stay</b>	The mean hospital length of stay in the intervention groups was <b>1.57 lower</b> (2.65 to 0.5 lower)		2127 (4 studies)	⊕⊕⊖⊖ <b>low</b> <sup>1</sup>	

\*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

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**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.

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<sup>1</sup> No explanation was provided

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

[www.prisma-statement.org](http://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.
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
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.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
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.	
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.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
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.	

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).	
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.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
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.	
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.	
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).	
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.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
<b>DISCUSSION</b>			
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).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			

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.	

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

Journal:	<i>BMJ Open</i>
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
<b>Primary Subject Heading</b>:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Red blood cells, Transfusion, Intensive care units, Septic shock

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Manuscripts



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4 1 **Is hemoglobin below 7.0 g/dl an optimal trigger for allogenic red**  
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6 2 **blood cell transfusion in patients admitted to intensive care units? A**  
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9 3 **meta-analysis and systematic review**  
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14 5 Ren-qi Yao<sup>1</sup>, Chao Ren<sup>2</sup>, Zi-cheng Zhang<sup>3</sup>, Yi-bing Zhu<sup>4</sup>, Zhao-fan Xia<sup>1</sup>,  
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3 Ren-qi Yao and Chao Ren contributed equally to this manuscript.

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## 1 Abstract

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

5 **Design:** Systematic review and meta-analysis.

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

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

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

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

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

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3 1 evidence, while it might have potential role in shortening hospitalization as well as  
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5 2 reducing MI incidence.  
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8 3 **Keywords:** Red blood cells, Transfusion, Intensive care units, Septic shock  
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3           **Strengths and limitations of this study**  
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5           2           1. This meta-analysis focused on the feasibility of a transfusion threshold of  
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7 hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients  
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10          4           through only including RCTs that specified the restrictive RBC transfusion threshold  
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12 as a pretransfusion hemoglobin concentration less than 7 g/dl.  
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14          6           2. In this meta-analysis, we performed an updated and comprehensive analysis  
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16 that focused on ICU patients with septic shock.  
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18          8           3. The number of studies we enrolled was not large enough due to the strict  
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20 inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl.  
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23          10          4. There was imperfect blinding of the study participants in the trials mainly  
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25 owing to the nature of the interventions.  
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## 1 Introduction

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

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

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

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



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

19

## 20 **Materials and methods**

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

1 statement<sup>24</sup>.

2

### 3 **Patient and Public Involvement**

4 No patient involved.

5

### 6 **Search strategy and information sources**

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

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### 17 **Eligibility and exclusion criteria**

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

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

7

## 8 **Study selection**

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

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## 16 **Data collection**

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

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56 2 **Risk of bias assessment**

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9 3 The Cochrane Collaboration tool was used to evaluate the risk of bias of the  
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11 4 RCTs. The randomization sequence, allocation concealment, blinding of personnel  
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14 5 and participants, risk of incomplete outcome data, selective reporting bias and other  
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17 6 sources of bias were assessed independently by two authors. Each clause was rated as  
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19 7 'low', 'high' or 'unclear' bias. The summarized risk of bias of each RCT was ranked  
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22 8 as low, moderate or high.  
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27 10 **Grading quality of evidence**

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30 11 The quality of evidence of each outcome was evaluated in accordance with the  
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32 12 Grading of Recommendations, Assessment, Development and Evaluation (GRADE)  
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35 13 methods. This procedure was conducted with GRADE Pro software 3.6 (McMaster  
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38 14 University 2014, Hamilton, Canada).  
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43 16 **Outcomes**

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45 17 The primary endpoint was all-cause short-term mortality, which was  
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48 18 preferentially analyzed by 28-day or 30-day mortality. In the case of unreported  
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51 19 short-term mortality, we contacted the authors for the original data or considered the  
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54 20 closest available mortality data. Secondary outcomes included the following  
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56 21 indicators: length of hospital stay, length of ICU stay, myocardial infarction, and  
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59 22 ischemic events.  
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6 2 **Data synthesis and analysis**

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9 3 The statistical analysis was conducted with ReviewManager (RevMan 5.3,  
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11 4 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We  
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13 5 applied odds ratios (ORs) to analyze dichotomous outcomes and mean differences for  
14  
15 6 continuous outcomes. The pooled results were calculated with 95% confidence  
16  
17 7 intervals (CIs). Heterogeneity among studies for each outcome was assessed by  
18  
19 8 applying both  $\chi^2$  test and  $I^2$  statistics. Either  $I^2$  greater than 50% or p value of  $\chi^2$  test  
20  
21 9 less than 0.10 was deemed as statistically significant heterogeneity. If remarkable  
22  
23 10 heterogeneity existed in pooled results, random effects model combined with the  
24  
25 11 Mantel-Haenszel (M-H) method was used, or else, fixed effects model was applied  
26  
27 12 accordingly. For the small study bias, the funnel plot of the pooled short-term  
28  
29 13 mortality data was scanned visually by reviewers. Besides, by using Stata software,  
30  
31 14 version 12, we performed Begg's and Egger's tests to further assess the possible small  
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33 15 study bias. A sensitivity analysis was also performed by means of excluding each  
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35 16 study one at a time from the pooled effect. Additionally, we performed a subgroup  
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37 17 analysis based on the M-H model to determine the difference between septic shock  
38  
39 18 and non-sepsis groups.

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53 20 **Results**54  
55 21 **Search results and the characteristics of the included studies**56  
57 22 This systematic review and meta-analysis identified 4641 relevant citations; we  
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1 removed duplicates and then scanned the titles and abstracts of 4600 studies.  
2 Eventually, the full-text articles for 41 trials were reviewed, and 8 RCTs met the  
3 inclusion criteria and were presented with full paper, with ICU patients older than 18  
4 years who received RBC transfusions at hemoglobin thresholds below 7 g/dl (**Fig. 1**).

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

## 12 **Risk of bias**

13 Most of the RCTs met the randomization requirements and used rational  
14 distribution methods. In some of the included trials, however, it was challenging to  
15 blind the attending physicians and nurses to the outcome assessment based on the  
16 intervention, which resulted in high risk of performance bias. (**Supplementary Fig.**  
17 **1**).

## 19 **Quality of evidence**

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

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

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**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	[27]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	Hospital mortality 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]



### 1 **Primary outcome: short-term mortality**

2 Within this meta-analysis, there were three RCTs that reported 28-day or 30-day  
3 mortality, and four that reported in-hospital mortality only. The published study from  
4 Holst LB et al did provide solid conclusions about the impacts of blood transfusion  
5 with liberal and restrictive hemoglobin thresholds on long-term mortality and rates of  
6 ischemic events, which presented with similar effects, while the information about  
7 short-term outcomes was missing<sup>22</sup>. Therefore, we wrote a letter asking for the  
8 important evidence of short-term mortality rates, as its analysis was based on a large  
9 sample size and was essential for our conclusion. After generating the forest plot, we  
10 found no significant difference in short-term mortality between the transfusion  
11 threshold of hemoglobin < 7 g/dl and the more liberal strategy (OR: 0.90, 95% CI:  
12 0.67-1.21;  $P=0.48$ ;  $I^2=53\%$ ). Meanwhile, we noticed that the RCT reported by  
13 Bergamin et al. (19) was the main resource of heterogeneity, and removing that study  
14 resulted in a marked reduction in heterogeneity ( $I^2=29\%$ ,  $P=0.21$ ) (**Fig. 2**).

### 16 **Secondary outcome: length of hospital stay, length of ICU stay, myocardial 17 infarction, and ischemic events**

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

1 95% CI: 0.30-0.98,  $P=0.04$ ;  $I^2=0\%$ , **Fig. 5**). However, no significant differences was  
2 noted between the two transfusion thresholds for critically ill patients for  
3 ischemic/thromboembolic events (OR, 0.80; 95% CI, 0.43-1.48;  $P=0.48$ ;  $I^2=51\%$ , **Fig.**  
4 **6**). After removing study conducted by Walsh et al, the heterogeneity of this outcome  
5 decreased significantly ( $I^2=0\%$ ,  $P=0.21$ ), which indicated the main source of  
6 heterogeneity.

7

### 8 **Small study bias**

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

14

### 15 **Subgroup analysis**

16 The subgroup analysis of the septic shock and non-sepsis groups investigated  
17 short-term mortality. From the forest plot, there were no significant differences in  
18 short-term mortality between two thresholds in either the septic shock group (OR:  
19 1.10, 95% CI: 0.75-1.62;  $P=0.63$ ;  $I^2=46\%$ ) or the non-sepsis group (OR: 0.75, 95% CI:  
20 0.50-1.14;  $P=0.15$ ;  $I^2=41\%$ ) (**Fig. 7**).

21

## 22 **Discussion**

### 23 **Major findings**

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

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

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

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

8

### 9 **Relations to other meta-analysis**

10 Carefully designed meta-analyses on RBC transfusions in critically ill patients  
11 have been published recently. In 2014, the first time Salpeter and colleagues reported  
12 the benefits of restrictive blood transfusion at hemoglobin trigger of  $<7$  g/dL in  
13 critical ill patients via conducting meta-analysis, which presented with significant  
14 reductions in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR:  
15 0.74; 95% CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute  
16 coronary syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95%  
17 CI, 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR:  
18 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold  
19 group<sup>17</sup>. However, this meta-analysis did not provide a convincing conclusion with  
20 only three RCTs included, and also failed to separate adult and pediatric participants,  
21 as each population shared different transfusion protocols.

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

1 thresholds among critically ill and perioperative patients, but it lacked a valid analysis  
2 of secondary outcomes which were noteworthy factors for the effects of RBC  
3 transfusions. Furthermore, Chong and colleagues also conducted an updated analysis  
4 on the effects of RBC transfusion, which included two more RCTs other than the  
5 same 10 trials included in the Fominskiy's study<sup>18 19 23 30</sup>. These results suggested that  
6 RBC transfusion with restrictive threshold significantly reduced the risk of overall  
7 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97;  $P=0.019$ ) when compared with that  
8 with liberal threshold, accompanied with declining risk of stroke/transient ischemic  
9 attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99;  $P=0.04$ ), transfusion reactions (OR: 0.48;  
10 95% CI, 0.29-0.80;  $P=0.005$ ), allogenic blood exposure (OR: 0.04; 95% CI: 0.01-0.14;  
11  $P=0.001$ ), and length of hospital stay (95% CI: 0.42-1.64;  $P=0.001$ ), hinting the safety  
12 of using restrictive transfusion protocol. Actually, above two studies focused on  
13 different primary outcomes, 30-day and 90-day mortality for each study, and further  
14 drew different conclusions even though both included similar RCTs, indicating that  
15 the effects of RBC transfusion varied with the stage of critical settings. However,  
16 Hovaguimian F et al.<sup>31</sup> performed a context-specific systematic review and  
17 meta-analysis comparing the restrictive and liberal transfusion thresholds and found  
18 no significant differences in early mortality (OR: 0.94; 95% CI: 0.73-1.20;  $P=0.09$ ;  
19  $I^2=45\%$ ) between the two thresholds, indicating that the specific types and severity of  
20 critical illness might be in need of different strategies of RBC transfusion, especially  
21 for patients with major surgery.

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

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

### 6 **Subgroup analysis**

7 The first review with regard to the impact of blood transfusion on the prognosis  
8 of septic shock patients was conducted by Dupuis and colleagues <sup>32</sup>. They showed no  
9 association between RBC transfusion and mortality rate in patients with septic shock,  
10 and also failed to determine correlations between the two different transfusion  
11 thresholds or to infer the optimal transfusion threshold for septic shock patients  
12 because of a shortage of high-quality RCTs <sup>32</sup>. In fact, a 10 g/dl hemoglobin threshold  
13 has been universally proposed for treatment of septic shock as the crucial role of RBC  
14 transfusions in early goal-directed therapy <sup>33</sup>. Nonetheless, severe adverse events  
15 caused by extensive blood transfusion have been reported as a great threat for septic  
16 shock patients by several studies<sup>34-36</sup>. The restrictive strategy, as reported previously,  
17 was beneficial for the improvement of microcirculation, while also saving blood  
18 products <sup>10 37</sup>. The landmark TRISS trial that was conducted by Holst L et al. <sup>22</sup>  
19 revealed no significant differences in 90-day mortality between patients in the group  
20 with the transfusion thresholds of 7 g/dl and those with the more liberal thresholds. In  
21 addition, the number of patients experiencing ischemic events and severe adverse  
22 reactions was also similar between the two groups. The TRISS trial demonstrated the  
23 safety and economic efficiency of the restrictive blood transfusion threshold, with a  
24 well-controlled risk of bias. Mazza BF et al. <sup>23</sup> performed a randomized physiological  
25 study of septic shock patients with the endpoint of abnormal lactate and ScvO<sub>2</sub> under

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

## 19 20 **Strengths and limitations**

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



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

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



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3 1 address this diversity in sample sizes and to avoid our results from being dominated  
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5 2 by the larger studies. Finally, we failed to testify if hemoglobin level less than 7 g/dl  
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7 3 is the optimal threshold for the blood transfusions in critically ill patients and in those  
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9 4 with septic shock basing on a lack of sufficient evidence.  
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## 15 6 **Conclusions and clinical implications**

17 7 The present meta-analysis of RCTs focused on the effect of RBC transfusions at  
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19 8 the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients.  
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21 9 RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in  
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23 10 significantly different in short-term mortality when compared with transfusions  
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25 11 administered at a more liberal threshold. However, it might associate with decreased  
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27 12 hospital length of stay and MI events, suggesting its potentially protecting role for  
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29 13 critically ill patients. Besides, within the ICU patient population with septic shock,  
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31 14 RBC transfusions at the restrictive threshold did not improve short-term mortality  
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33 15 compared with transfusions at the more liberal threshold. Therefore, we recommended  
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35 16 a hemoglobin trigger of 7 g/dL for critically ill patients with or without septic shock  
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37 17 due to the cost and resource saving effect, as well as its latent value in reducing severe  
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39 18 adverse effect. Still, further studies are required to testify our findings. This study  
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41 19 indeed provides novel conclusions on the impact of blood transfusion on short-term  
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43 20 outcomes of critically ill patients as well as patients with septic shock. Even though  
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45 21 we can't determine that the hemoglobin trigger of 7 g/dL is the optimal strategy for  
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47 22 RBC transfusion, but it does show advantages in managing the use of RBC units and  
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49 23 urge prudent decision making in blood transfusion for critically ill patients.  
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#### 4 5 **Data Availability Statement**

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

#### 8 9 **Conflicts of Interest**

10 The authors have no conflicts of interest to declare.

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13 We greatly appreciated the excellent job and kind share of professor Holst in  
14 providing important evidence on the impact of blood transfusion with liberal and  
15 restrictive hemoglobin thresholds on short-term mortality.

#### 16 17 **Abbreviations**

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

25

## 1 **Author contributions**

2 YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data.  
3 YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper.  
4 RQY undertook the statistical analyses. All authors contributed to and revised the  
5 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

1 myocardial infarction compared with the more liberal threshold.

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3 **Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients**

4 **after RBC transfusions.** The odds ratios and 95% CI for ischemic/thromboembolic

5 events are presented in the forest plot. No significant difference was noted in

6 ischemic/thromboembolic events between the group with the threshold of 7 g/dl

7 hemoglobin compared with the group with the more liberal threshold.

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9 **Figure 7. Forest plot for short-term mortality following subgroup analysis.** The

10 forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of

11 patients receiving RBC transfusions at various thresholds according to the subgroup

12 analysis of the septic shock and non-sepsis groups. Restrictive transfusion was

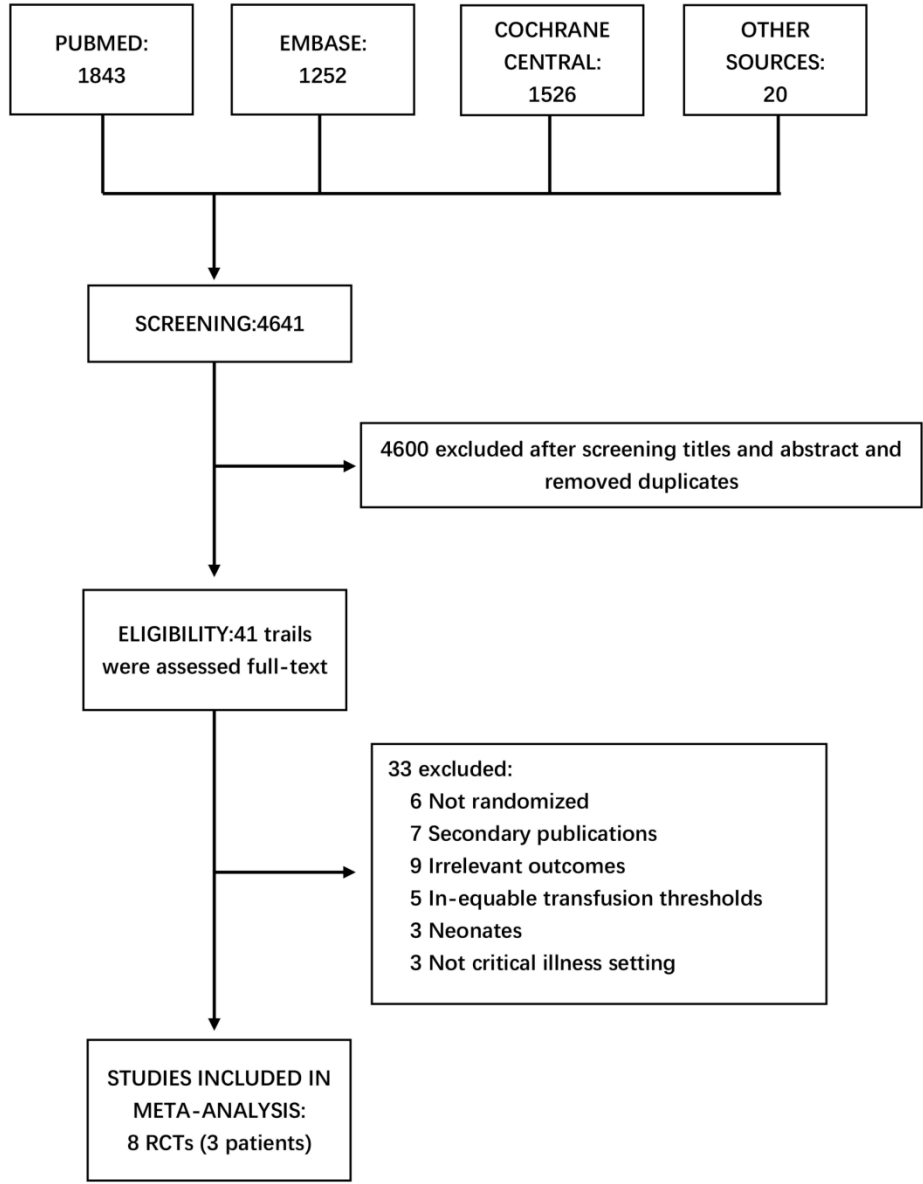
13 incapable of decreasing short-term mortality in septic ICU patients.

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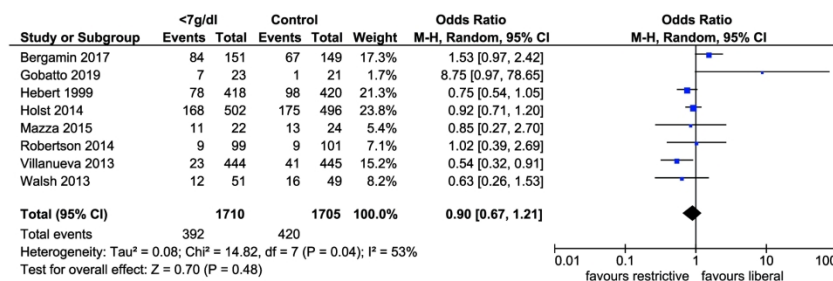


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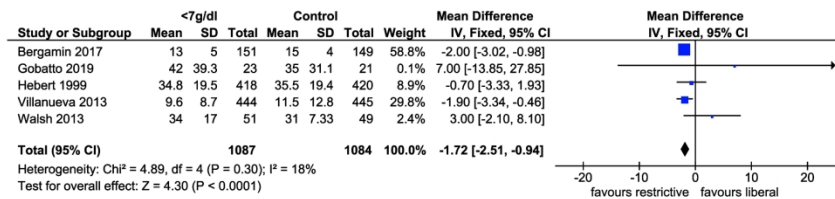


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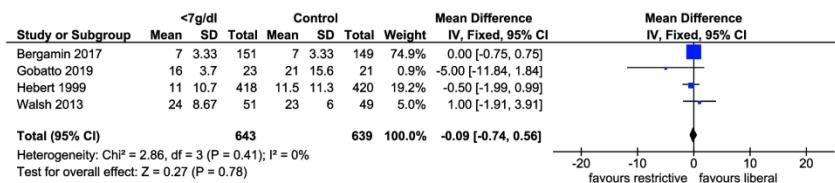


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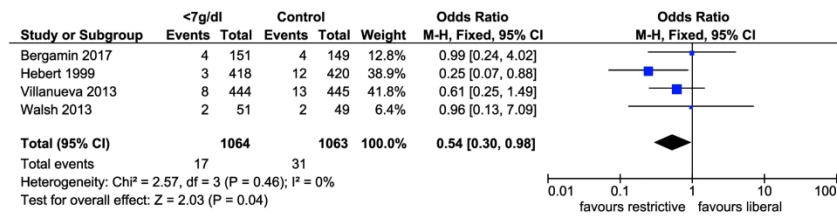
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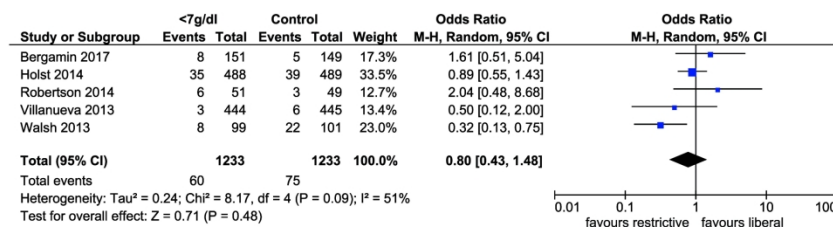
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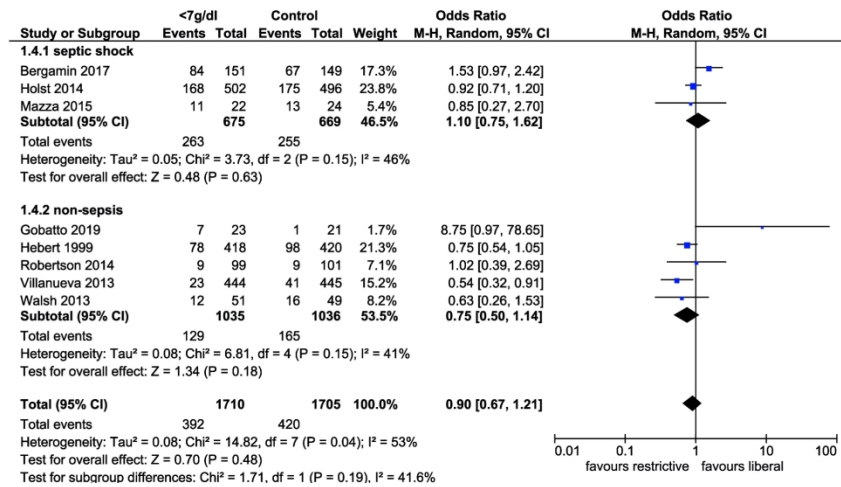
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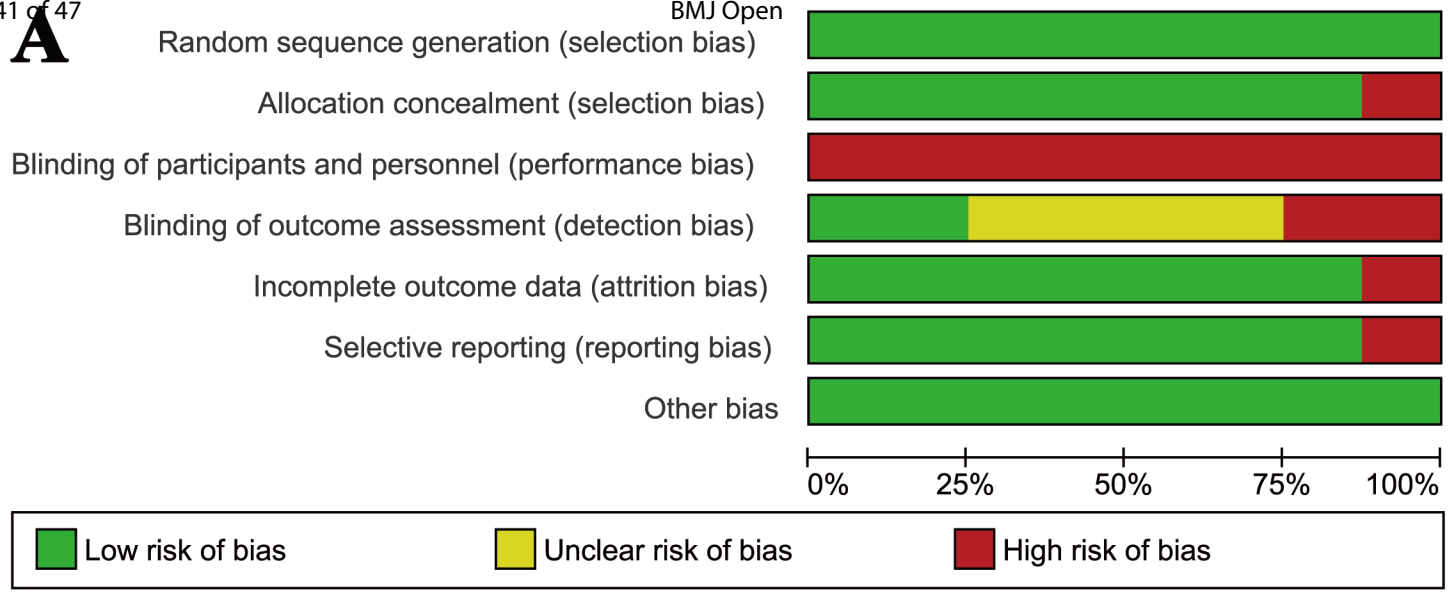
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### Search strategy

((((((((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]))



**A**

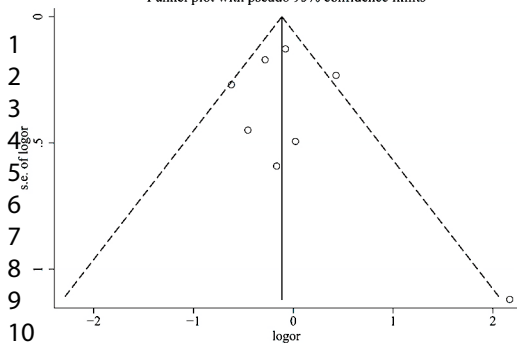


**B**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bergamin 2017	+	+	-	-	+	+	+
Gobatto 2019	+	+	-	?	+	+	+
Hebert 1999	+	+	-	?	+	+	+
Holst 2014	+	+	-	+	+	+	+
Mazza 2015	+	-	-	?	-	-	+
Robertson 2014	+	+	-	+	+	+	+
Villanueva 2013	+	+	-	-	+	+	+
Walsh 2013	+	+	-	?	+	+	+

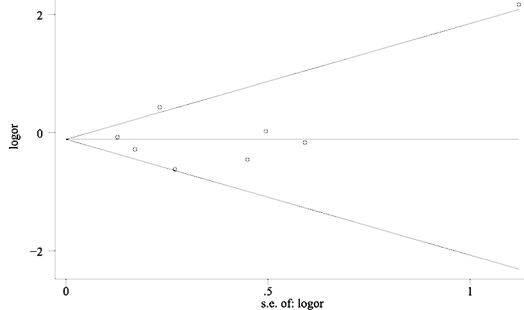
**A**

Funnel plot with pseudo 95% confidence limits

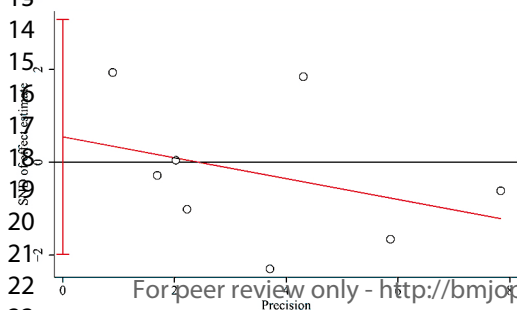


**B**

Begg's funnel plot with pseudo 95% confidence limits



**C**



○ Study — regression line  
 ┆ 95% CI for intercept

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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 <sup>1</sup>	
	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 <sup>1</sup>	
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 <sup>1</sup>	
Myocardial Infraction	Study population		OR 0.54 (0.3 to 0.98)	2127 (4 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
	29 per 1000	16 per 1000 (9 to 29)				
	Moderate					
	29 per 1000	16 per 1000 (9 to 28)				
Ischemic event	Study population					

	<b>61 per 1000</b>	<b>49 per 1000</b>			
		(27 to 87)			
	<b>Moderate</b>		<b>OR 0.8</b>	2466	⊕⊕⊕⊖
			(0.43 to 1.48)	(5 studies)	<b>moderate</b> <sup>1</sup>
	<b>61 per 1000</b>	<b>49 per 1000</b>			
		(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.

<sup>1</sup> No explanation was provided



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

[www.prisma-statement.org](http://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.
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
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.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
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.	
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.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
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.	

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).	
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.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
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.	
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.	
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).	
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.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
<b>DISCUSSION</b>			
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).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			

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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.	

*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

**Once you have completed this checklist, please save a copy and upload it as part of your submission. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

For peer review only

# 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030854.R2
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
<b>Primary Subject Heading</b>:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	Red blood cells, Transfusion, Intensive care units, Septic shock

SCHOLARONE™  
Manuscripts



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14 5 Ren-qi Yao<sup>1</sup>, Chao Ren<sup>2</sup>, Zi-cheng Zhang<sup>3</sup>, Yi-bing Zhu<sup>4</sup>, Zhao-fan Xia<sup>1</sup>,  
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## 1 Abstract

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

5 **Design:** Systematic review and meta-analysis.

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

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

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

17 **Results:** Eight RCTs with 3415 patients were included. Compared with a more  
18 liberal threshold, an red blood cell (RBC) transfusion threshold < 7 g/dl hemoglobin  
19 showed no significant difference in short-term mortality (OR: 0.90, 95% CI:  
20 0.67-1.21;  $P=0.48$ ;  $I^2=53\%$ ), length of hospital stay (SMD: -0.11, 95% CI: -0.30-0.07,  
21  $P=0.24$ ,  $I^2=71\%$ ), length of ICU stay (SMD: -0.03, 95% CI: -0.14-0.08,  $P=0.54$ ,  
22  $I^2=0\%$ ), or ischemic events (OR, 0.80; 95% CI, 0.43-1.48;  $P=0.48$ ;  $I^2=51\%$ ). However,  
23 we found that the incidence of MI (OR: 0.54, 95% CI: 0.30-0.98,  $P=0.04$ ;  $I^2=0\%$ ) was  
24 lower in the group with the threshold < 7 g/dl than that with the more liberal  
25 threshold.

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

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

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3 **1 Strengths and limitations of this study**  
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5 2 1. This meta-analysis focused on the feasibility of a transfusion threshold of  
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7 hemoglobin < 7 g/dl with regard to short-term mortality in critically ill patients  
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10 4 through only including RCTs that specified the restrictive RBC transfusion threshold  
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12 5 as a pretransfusion hemoglobin concentration less than 7 g/dl.  
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14 6 2. In this meta-analysis, we performed an updated and comprehensive analysis  
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17 7 that focused on ICU patients with septic shock.  
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19 8 3. The number of studies we enrolled was not large enough due to the strict  
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22 9 inclusion criteria of a restrictive transfusion threshold of hemoglobin < 7 g/dl.  
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24 10 4. There was imperfect blinding of the study participants in the trials mainly  
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26 11 owing to the nature of the interventions.  
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## 1 Introduction

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

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4 1 critical ill patients with younger age and lower acute physiology and chronic health  
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6 2 evaluation (APACHE) II score. Indeed, conservative blood transfusion could result in  
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9 3 a marked decline in the use of RBCs, which further decreases the in-hospital cost of  
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11 4 ICU patients <sup>2 10</sup>. Recently, various studies have extensively discussed transfusion  
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14 5 strategies to optimize the outcomes. For instance, no significant difference was shown  
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17 6 between restrictive and liberal transfusion strategies in terms of adverse effects, as  
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19 7 reported by some studies <sup>11 12</sup>. In addition, other researchers found that blood  
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22 8 transfusions triggered at a threshold of 7 g/dl were much safer in critically ill patients  
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25 9 with cardiovascular diseases <sup>10 13</sup>. However, Silva Junior JM et al have found that  
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28 10 RBC transfusion was an independent risk factor for mortality of critical ill patients,  
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31 11 followed with longer ICU and hospital stay, which was associated with different  
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33 12 decisions regarding transfusion triggers<sup>14</sup>. Other indexes, such as oxygen delivery  
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35 13 ( $DO_2$ ) and oxygen consumption ( $VO_2$ ), also show marked deviation among various  
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38 14 studies. Study by Conrad SA and colleagues revealed significant improvement in  $DO_2$   
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41 15 but no influence in  $VO_2$  after blood transfusion on septic patients<sup>15</sup>. While Steffes CP  
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43 16 and colleagues have reported that blood transfusion is capable of elevating  $DO_2$  and  
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45 17  $VO_2$  in septic surgical patients<sup>16</sup>. Therefore, the thresholds for blood transfusion  
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48 18 should be different for patients with various diseases and need to be carefully  
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51 19 evaluated.

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53 20 Actually, the benefits and harms of blood transfusions in patients admitted to  
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56 21 intensive care units have been discussed by many systematic reviews and  
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59 22 meta-analyses, but the results remain controversial due to the distinct inclusion  
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1 criteria and outcome measurement across studies.<sup>9 11 12 17-19</sup>. Salpeter and colleagues  
2 found restrictive blood transfusion trigger at 7g/dl could significantly reduce mortality  
3 of disparate phase, as well as diverse transfusion-related complications compared to  
4 the liberal transfusion trigger. However, they didn't distinguish pediatric and adult  
5 ICU settings, and merely enrolled 3 randomized controlled trials (RCTs)<sup>17</sup>. Systematic  
6 reviews conducted by Fominskiy E et al revealed no statistical difference in 90-day  
7 mortality between two transfusion thresholds<sup>18</sup>. Nevertheless, recently updated  
8 publication by Chong and colleagues incorporated almost same RCTs as Fominskiy E  
9 et al did, while they identified a significant reduction of 30-day mortality in ICU  
10 patients with restrictive strategy in comparison with those with more liberal  
11 transfusion trigger<sup>19</sup>. In addition, the specific thresholds of hemoglobin concentration  
12 are essential for decision of RBC transfusion regarding various clinical practice.  
13 However, no studies have reported the impact of the transfusion threshold of 7 g/dl on  
14 the short-term outcomes of critically ill patients or the financial value of a different  
15 transfusion strategy, even though it is considered as a common trigger to implement  
16 restrictive transfusion strategy. Furthermore, different types of clinical conditions also  
17 show remarkable deviation in RBCs administration. For example, septic shock is  
18 commonly recognized as a substantial threat to ICU, and it is related to high hospital  
19 costs and poor outcomes<sup>20</sup>. Anemia is also commonly complicated during the  
20 progression of sepsis, as it presents with insufficient tissue perfusion, like  
21 hypovolemic shock, and dysfunction of cellular metabolism, which cannot be  
22 reversed by prompt fluid resuscitation and administration of vasoactive drugs. Indeed,



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

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## 20 **Materials and methods**

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

1 statement<sup>24</sup>.

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### 3 **Patient and public involvement**

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

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### 8 **Search strategy and information sources**

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

17

### 18 **Eligibility and exclusion criteria**

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

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

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### 9 **Study selection**

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

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### 17 **Data collection**

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

1 also obtained.

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### 3 **Risk of bias assessment**

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

10

### 11 **Grading quality of evidence**

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

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### 17 **Outcomes**

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

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4 1 ischemic events.  
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### 9 3 **Data synthesis and analysis**

10 4 The statistical analysis was conducted with ReviewManager (RevMan 5.3,  
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12 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We  
13  
14 applied odds ratios (ORs) to analyze dichotomous outcomes and standardized mean  
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16 differences (SMDs) for continuous outcomes. The pooled results were calculated with  
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18 95% confidence intervals (CIs). Heterogeneity among studies for each outcome was  
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20 assessed by applying both  $\chi^2$  test and  $I^2$  statistics. Either  $I^2$  greater than 50% or p value  
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22 of  $\chi^2$  test less than 0.10 was deemed as statistically significant heterogeneity. If  
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24 remarkable heterogeneity existed in pooled results, random effects models combined  
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26 with the Mantel-Haenszel (M-H) method were used, or else, fixed effects models was  
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28 applied accordingly. For the small study bias, the funnel plot of the pooled short-term  
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30 mortality data was scanned visually by reviewers. Besides, by using Stata software,  
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32 version 12, we performed Begg's and Egger's tests to further assess the possible small  
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34 study bias. A sensitivity analysis was also performed by means of excluding each  
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36 study one at a time from the pooled effect. Additionally, we performed a subgroup  
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38 analysis based on the M-H model to determine the difference between septic shock  
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40 and non-sepsis groups.  
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## 55 21 **Results**

### 56 22 **Search results and the characteristics of the included studies**

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

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

### 12 13 **Risk of bias**

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

### 18 19 **Quality of evidence**

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

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

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**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	[27]
Bergamin et al.	2017	Single	Critical illness	Patients with cancer with septic shock	300	Hb 7	Hb 9	Hospital mortality 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]



### 1 **Primary outcome: short-term mortality**

2        Within this meta-analysis, there were three RCTs that reported 28-day or 30-day  
3 mortality, and four reported in-hospital mortality only. The published study from  
4 Holst LB et al did provide solid conclusions about the impacts of blood transfusion  
5 with liberal and restrictive hemoglobin thresholds on long-term mortality and rates of  
6 ischemic events, which presented with similar effects, while the information about  
7 short-term outcomes was missing<sup>22</sup>. Therefore, we wrote a letter asking for the  
8 important evidence of short-term mortality rates, as its analysis was based on a large  
9 sample size and was essential for our conclusions. After generating the forest plot, we  
10 found no significant difference in short-term mortality between the transfusion  
11 threshold of hemoglobin < 7 g/dl and the more liberal strategy (OR: 0.90, 95% CI:  
12 0.67-1.21;  $P=0.48$ ;  $I^2=53\%$ ). Meanwhile, we noticed that the RCT reported by  
13 Bergamin et al. (19) was the main resource of heterogeneity, and removing that study  
14 resulted in a marked reduction in heterogeneity ( $I^2=29\%$ ,  $P=0.21$ ) (**Fig. 2**).

### 16 **Secondary outcome: length of hospital stay, length of ICU stay, myocardial** 17 **infarction, and ischemic events**

18        Five included studies documented the length of hospital stay, which revealed no  
19 significant difference in hospital stays when the threshold of hemoglobin < 7 g/dl was  
20 used, comparing with the more liberal threshold (SMD: -0.11, 95% CI: -0.30-0.07,  
21  $P=0.24$ ,  $I^2=71\%$ , **Fig. 3**). Sensitivity analysis indicated that study by Bergamin et al  
22 was the main source of heterogeneity, exclusion of which could significantly reduce  
23 heterogeneity ( $I^2=45\%$ ,  $P=0.51$ ). The outcome of length of ICU stay was reported by  
24 four trials, and there was no significant difference between the two thresholds (SMD:  
25 -0.03, 95% CI: -0.14-0.08,  $P=0.54$ ,  $I^2=0\%$ , **Fig. 4**). In addition, we identified that MI

1 events was decreased among patients with transfusion trigger of hemoglobin < 7 g/dl  
2 when compared to those with the liberal transfusion strategy (OR: 0.54, 95% CI:  
3 0.30-0.98,  $P=0.04$ ;  $I^2=0\%$ , **Fig. 5**). However, no significant differences were noted  
4 between the two transfusion thresholds for critically ill patients in  
5 ischemic/thromboembolic events (OR, 0.80; 95% CI, 0.43-1.48;  $P=0.48$ ;  $I^2=51\%$ , **Fig.**  
6 **6**). After removing study conducted by Walsh et al, the heterogeneity of this outcome  
7 decreased significantly ( $I^2=0\%$ ,  $P=0.21$ ), which indicated the main source of  
8 heterogeneity.

### 10 **Small study bias**

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

### 17 **Subgroup analysis**

18 The subgroup analysis of the septic shock and non-sepsis groups investigated  
19 short-term mortality. From the forest plot, there were no significant differences in  
20 short-term mortality between two thresholds in either the septic shock group (OR:  
21 1.10, 95% CI: 0.75-1.62;  $P=0.63$ ;  $I^2=46\%$ ) or the non-sepsis group (OR: 0.75, 95% CI:  
22 0.50-1.14;  $P=0.15$ ;  $I^2=41\%$ ) (**Fig. 7**).

## 24 **Discussion**

### 25 **Major findings**

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

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

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

## 6 **Relations to other meta-analysis**

7 Carefully designed meta-analyses on RBC transfusions in critically ill patients  
8 have been published recently. In 2014, the first time Salpeter and colleagues reported  
9 the benefits of restrictive blood transfusion at hemoglobin trigger  $<7$  g/dL in critical  
10 ill patients via conducting meta-analysis, which presented with significant reductions  
11 in total mortality (RR: 0.80; 95% CI, 0.65-0.98), in-hospital mortality (RR: 0.74; 95%  
12 CI, 0.60-0.92), 30-day mortality (RR: 0.77; 95% CI, 0.61-0.96), acute coronary  
13 syndrome (RR: 0.44; 95% CI, 0.22-0.89), pulmonary edema (RR: 0.48; 95% CI,  
14 0.33-0.72), rebleeding (RR: 0.64; 95% CI, 0.45-0.90) and bacterial infections (RR:  
15 0.86; 95% CI, 0.73-1.00) when compared with the liberal transfusion threshold  
16 group<sup>17</sup>. However, this meta-analysis did not provide a convincing conclusion with  
17 only three RCTs included, and also failed to separate adult and pediatric participants,  
18 as each population shared different transfusion protocols.

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

1 on the effects of RBC transfusion, which included two more RCTs other than the  
2 same 10 trials included in the Fominskiy's study<sup>18 19 23 30</sup>. These results suggested that  
3 RBC transfusion with restrictive threshold significantly reduced the risk of overall  
4 30-day mortality (OR: 0.82; 95% CI: 0.70-0.97;  $P=0.019$ ) when compared with that  
5 with liberal threshold, accompanied with declining risk of stroke/transient ischemic  
6 attack (TIA) (OR: 0.63; 95% CI, 0.40-0.99;  $P=0.04$ ), transfusion reactions (OR: 0.48;  
7 95% CI, 0.29-0.80;  $P=0.005$ ), allogenic blood exposure (OR: 0.04; 95% CI: 0.01-0.14;  
8  $P=0.001$ ), and length of hospital stay (95% CI: 0.42-1.64;  $P=0.001$ ), hinting the safety  
9 of using restrictive transfusion protocol. Actually, above two studies focused on  
10 different primary outcomes, 30-day and 90-day mortality respectively, and further  
11 drew different conclusions even though both included similar RCTs, indicating that  
12 the effects of RBC transfusion varied with the stage of critical settings. However,  
13 Hovaguimian F et al.<sup>31</sup> performed a context-specific systematic review and  
14 meta-analysis comparing the restrictive and liberal transfusion thresholds and found  
15 no significant differences in early mortality (OR: 0.94; 95% CI: 0.73-1.20;  $P=0.09$ ;  
16  $I^2=45\%$ ) between the two thresholds, indicating that the specific types and severity of  
17 critical illness might be in need of different strategies of RBC transfusion, especially  
18 for patients with major surgery.

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

1 those using liberal thresholds.

2

### 3 **Subgroup analysis**

4       The first review with regard to the impact of blood transfusion on the prognosis  
5 of septic shock patients was conducted by Dupuis and colleagues<sup>32</sup>. They showed no  
6 association between RBC transfusion and mortality rate in patients with septic shock,  
7 and also failed to determine correlations between the two different transfusion  
8 thresholds or to infer the optimal transfusion threshold for septic shock patients  
9 because of a shortage of high-quality RCTs<sup>32</sup>. In fact, a 10 g/dl hemoglobin threshold  
10 has been universally proposed for treatment of septic shock as the crucial role of RBC  
11 transfusions in early goal-directed therapy<sup>33</sup>. Nonetheless, severe adverse events  
12 caused by extensive blood transfusion have been reported as a great threat for septic  
13 shock patients by several studies<sup>34-36</sup>. The restrictive strategy, as reported previously,  
14 was beneficial for the improvement of microcirculation, while also saving blood  
15 products<sup>10 37</sup>. The landmark TRISS trial that was conducted by Holst L et al.<sup>22</sup>  
16 revealed no significant differences in 90-day mortality between patients in the group  
17 with the transfusion thresholds of 7 g/dl and those with the more liberal thresholds. In  
18 addition, the number of patients experiencing ischemic events and severe adverse  
19 reactions was also similar between the two groups. The TRISS trial demonstrated the  
20 safety and economic efficiency of the restrictive blood transfusion threshold, with a  
21 well-controlled risk of bias. Mazza BF et al.<sup>23</sup> performed a randomized physiological  
22 study of septic shock patients with the endpoint of abnormal lactate and ScvO<sub>2</sub> under  
23 distinct pretransfusion hemoglobin concentrations. However, they failed to provide  
24 valid data on mortality with a relatively small sample size provided. Recently,  
25 Bergamin and colleagues focused on cancer patients who developed septic shock in

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

### 17 **Strengths and limitations**

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



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

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



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3 1 those with septic shock basing on a lack of sufficient evidence.  
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8 3 **Conclusions and clinical implications**  
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10 4 The present meta-analysis of RCTs focused on the effect of RBC transfusions at  
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12 5 the threshold of hemoglobin < 7 g/dl on the survival and prognosis of ICU patients.  
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14 6 RBC transfusions at the threshold of hemoglobin < 7 g/dl did not result in significant  
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16 7 difference in short-term mortality when compared with transfusions administered at a  
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18 8 more liberal threshold. However, it might associate with decreased MI events,  
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20 9 suggesting its potentially protecting role for critically ill patients. Besides, regarding  
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22 10 ICU patient with septic shock, RBC transfusions at the restrictive threshold did not  
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24 11 improve short-term mortality compared with transfusions at the more liberal threshold.  
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26 12 Therefore, we recommend a hemoglobin trigger of 7 g/dL for critically ill patients  
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28 13 with or without septic shock due to the cost and resource saving effect, as well as its  
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30 14 latent value in reducing severe adverse effect. Still, further studies are required to  
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32 15 validate our findings. This study indeed provides novel conclusions on the impact of  
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34 16 blood transfusion on short-term outcomes of critically ill patients as well as patients  
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36 17 with septic shock. Even though it was hard to determine that the hemoglobin trigger  
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38 18 of 7 g/dL was the optimal strategy for RBC transfusion, but it did show advantages in  
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40 19 managing the use of RBC units and urged prudent decision-making in blood  
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42 20 transfusion for critically ill patients.  
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## 2 **Data Availability Statement**

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

5  
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## 6 **Conflicts of Interest**

7 The authors have no conflicts of interest to declare.

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## 9 **Acknowledgement**

10 We greatly appreciated the excellent job and kind share of professor Holst in  
11 providing important evidence on the impact of blood transfusion with liberal and  
12 restrictive hemoglobin thresholds on short-term mortality.

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## 14 **Abbreviations**

15 RBC: Red blood cell; ICU: Intensive care unit; TRICC: Transfusion  
16 requirements in critical care; APACHE: Acute physiology and chronic health  
17 evaluation; DO<sub>2</sub>: oxygen delivery; VO<sub>2</sub>: oxygen consumption; RCT: Randomized  
18 controlled trial; TRISS: The transfusion requirements in septic shock; SOFA:  
19 sequential organ failure assessment; PRISMA: Preferred items for systematic reviews  
20 and meta-analyses; MeSH: Medical Subject Heading; MI: Myocardial infarction;  
21 GRADE: Grading of recommendations, assessment, development and evaluation;  
22 ORs: Odds ratios; SMDs: standardized mean differences; CIs: Confidence intervals;  
23 M-H: Mantel-Haenszel; TRICOP: Transfusion requirements in critically ill  
24 oncological patients; TIA: Transient ischemic attack; TRAHT: Transfusion  
25 requirements after head trauma; SCC: Surviving sepsis campaign; ACCM: American

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

2

### 3 **Author contributions**

4 YMY and ZFX conceived the meta-analysis. RQY and CR extracted all data.

5 YBZ and ZCZ undertook and refined the searches. RQY and CR co-wrote the paper.

6 RQY undertook the statistical analyses. All authors contributed to and revised the

7 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

1 myocardial infarction compared with the more liberal threshold.

2

3 **Figure 6. Forest plot of ischemic events/thromboembolic events in ICU patients**

4 **after RBC transfusions.** The odds ratios and 95% CI for ischemic/thromboembolic

5 events are presented in the forest plot. No significant difference was noted in

6 ischemic/thromboembolic events between the group with the threshold of 7 g/dl

7 hemoglobin compared with the group with the more liberal threshold.

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9 **Figure 7. Forest plot for short-term mortality following subgroup analysis.** The

10 forest plot shows the odds ratios and 95% CI for the all-cause short-term mortality of

11 patients receiving RBC transfusions at various thresholds according to the subgroup

12 analysis of the septic shock and non-sepsis groups. Restrictive transfusion was

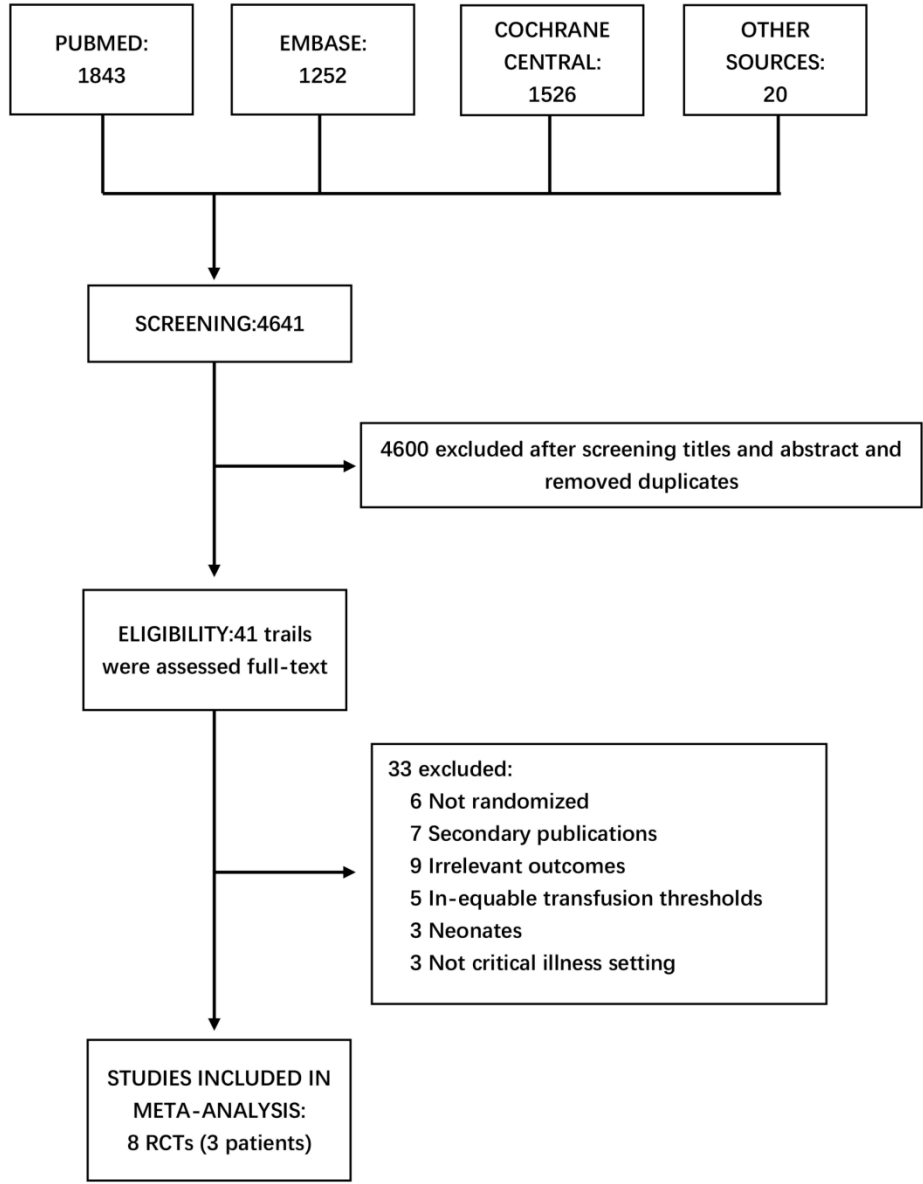
13 incapable of decreasing short-term mortality in septic ICU patients.

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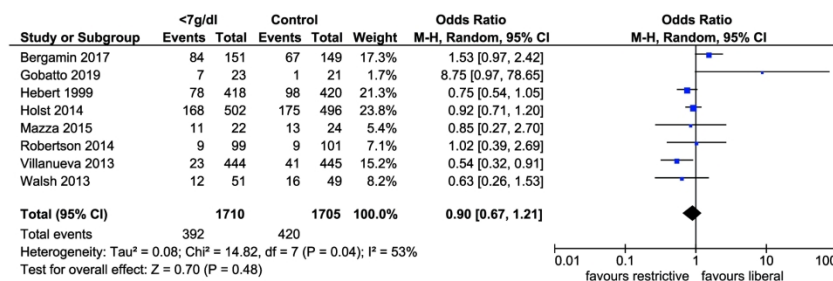


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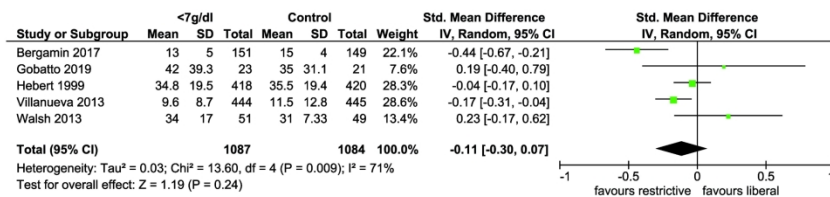
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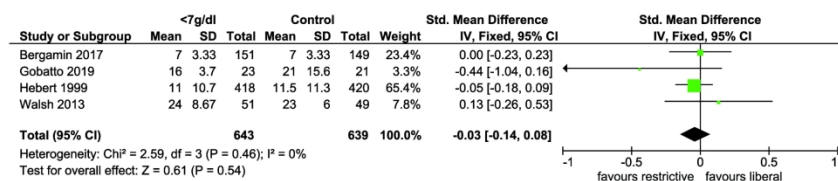
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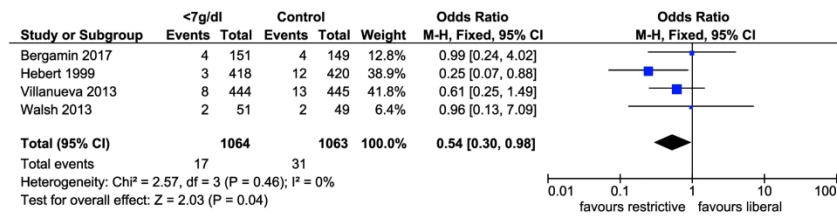
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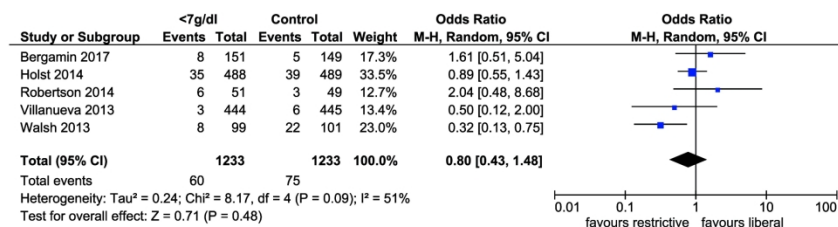
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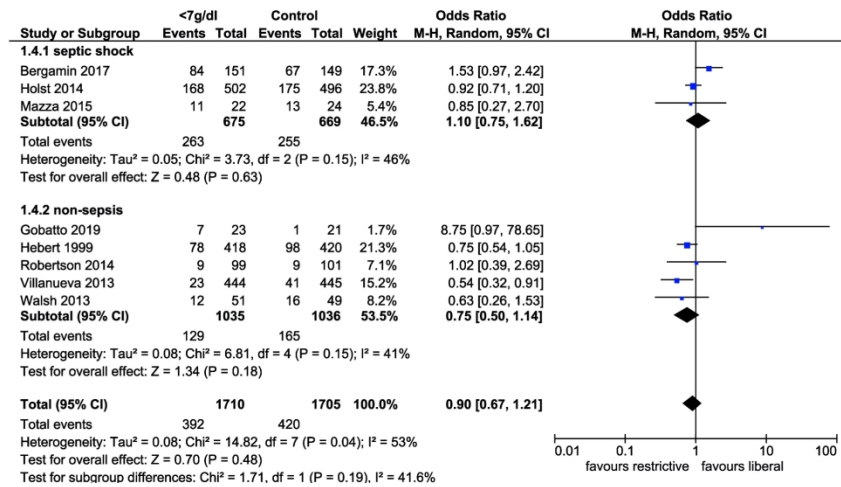
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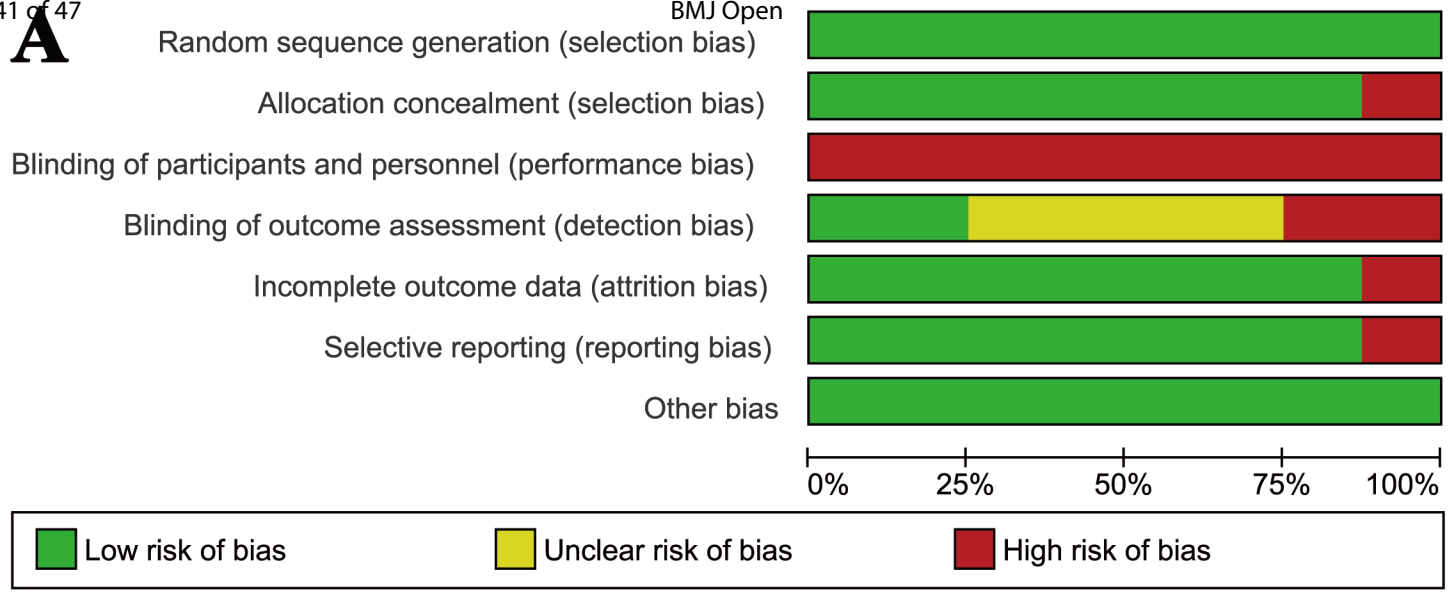
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### Search strategy

((((((((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]))



# A

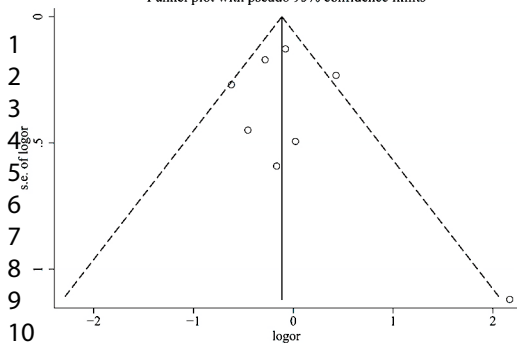


# B

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bergamin 2017	+	+	-	-	+	+	+
Gobatto 2019	+	+	-	?	+	+	+
Hebert 1999	+	+	-	?	+	+	+
Holst 2014	+	+	-	+	+	+	+
Mazza 2015	+	-	-	?	-	-	+
Robertson 2014	+	+	-	+	+	+	+
Villanueva 2013	+	+	-	-	+	+	+
Walsh 2013	+	+	-	?	+	+	+

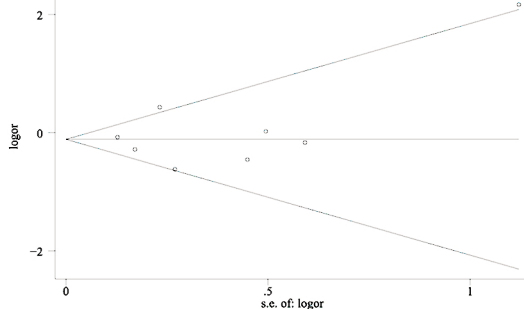
**A**

Funnel plot with pseudo 95% confidence limits

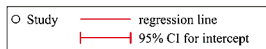
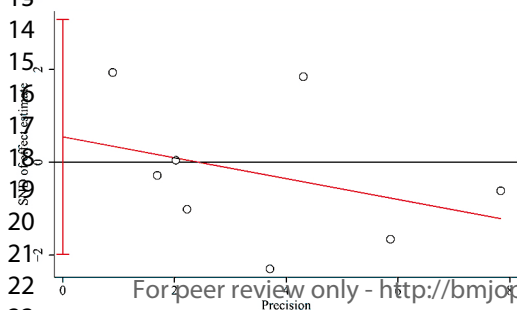


**B**

Begg's funnel plot with pseudo 95% confidence limits



**C**



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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 <sup>1</sup>	
	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 <b>0.11 standard deviations lower</b> (0.30 lower to 0.07 higher)		SMD -0.11 (-0.30 to 0.07)	2171 (5 studies)	⊕⊕⊕⊖ low <sup>1</sup>	
ICU length of stay	The mean icu length of stay in the intervention groups was <b>0.03 standard deviations lower</b> (0.14 lower to 0.08 higher)		SMD -0.03 (-0.14 to 0.08)	1282 (4 studies)	⊕⊕⊕⊖ low <sup>1</sup>	
Myocardial Infraction	Study population		OR 0.54 (0.3 to 0.98)	2127 (4 studies)	⊕⊕⊕⊖ moderate <sup>1</sup>	
	29 per 1000	16 per 1000 (9 to 29)				
	Moderate					
	29 per 1000	16 per 1000 (9 to 28)				
Ischemic event	Study population					

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	<b>61 per 1000</b>	<b>49 per 1000</b>			
		(27 to 87)			
	<b>Moderate</b>		<b>OR 0.8</b>	2466	⊕⊕⊕⊖
			(0.43 to 1.48)	(5 studies)	<b>moderate</b> <sup>1</sup>
	<b>61 per 1000</b>	<b>49 per 1000</b>			
		(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.

<sup>1</sup> No explanation was provided



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

[www.prisma-statement.org](http://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.
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
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.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
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.	
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.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
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.	

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).	
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.	
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).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
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.	
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.	
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).	
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.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
<b>DISCUSSION</b>			
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).	
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).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			

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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.	

*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

**Once you have completed this checklist, please save a copy and upload it as part of your submission. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

For peer review only