Should Transfusion Trigger Thresholds Differ for Critical Care Versus Perioperative Patients? A Meta-Analysis of Randomized Trials

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Objective: To address the significant uncertainty as to whether transfusion thresholds for critical care versus surgical patients should differ.

Design: Meta-analysis of randomized controlled trials.

Setting: Medline, EMBASE, and Cochrane Library searches were performed up to 15 June 2016.

Patients: Trials had to enroll adult surgical or critically ill patients for inclusion.

Interventions: Studies had to compare a liberal versus restrictive threshold for the transfusion of allogeneic packed RBCs.

Measurements and Main Results: The primary outcome was 30-day all-cause mortality, sub-grouped by surgical and critical care patients. Secondary outcomes included myocardial infarction, stroke, renal failure, allogeneic blood exposure, and length of stay.

Odds ratios and weighted mean differences were calculated using random effects meta-analysis. To assess whether subgroups were significantly different, tests for subgroup interaction were used. Subgroup analysis by trials enrolling critically ill versus surgical patients was performed. Twenty-seven randomized controlled trials (10,797 patients) were included. In critical care patients, restrictive transfusion resulted in significantly reduced 30-day mortality compared with liberal transfusion (odds ratio, 0.82; 95% CI, 0.70–0.97). In surgical patients, a restrictive transfusion strategy led to the opposite direction of effect for mortality (odds ratio, 1.31; 95% CI, 0.94–1.82). The subgroup interaction test was significant ($p = 0.04$), suggesting that the effect of restrictive transfusion on mortality is statistically different for critical care (decreased risk) versus surgical patients (potentially increased risk or no difference). Regarding secondary outcomes, for critically ill patients, a restrictive strategy resulted in reduced risk of stroke/transient ischemic attack, packed RBC exposure, transfusion reactions, and hospital length of stay. In surgical patients, restrictive transfusion resulted in reduced packed RBC exposure.

Conclusions: The safety of restrictive transfusion strategies likely differs for critically ill patients versus perioperative patients. Further trials investigating transfusion strategies in the perioperative setting are necessary. (*Crit Care Med* 2018; 46:252–263)

Key Words: blood transfusion; meta-analysis; systematic review

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Dr. Chong extracted the data, performed the data analysis, created the figures/tables, and prepared the article. Contribution: Dr. Krishnan extracted the data, performed the data analysis, created the figures/tables, and revised the article. Dr. Cheng provided resource support in this study, guidance with article preparation, and revised the final article. Dr. Martin conceived the idea of performing a meta-analysis of transfusion triggers, provided guidance with article preparation and data analysis, and revised the final article. All authors attest to the integrity of the original data and analysis, as well as approved the final article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjournal>).

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000002873

After the landmark Transfusion Requirements in Critical Care (TRICC) Trial (1), there has been increasing interest in transfusion thresholds to guide the administration of allogeneic packed RBC (pRBC) in the perioperative and critical care settings. To date, pRBC transfusions remain an important treatment for improving tissue oxygenation in the setting of inadequate oxygen carrying capacity. However, cautious use of allogeneic pRBC transfusions is warranted given that the purported benefits of increased oxygen delivery may not always outweigh the potential harms due to risks of volume overload, transfusion reactions, acute bacterial infection, and chronic infectious disease transmission (2). In addition, the 75 million units of pRBCs

collected worldwide per annum are costly and limited in supply, given the need for administrative systems to screen donors, process whole blood, and store the collected products (3–5).

Given these concerns surrounding pRBC transfusion, there has been high interest in the use of “restrictive” versus “liberal” transfusion triggers to guide administration. Previous systematic reviews and meta-analyses have been published on this topic with conflicting results (6–9). This may be explained by significant methodologic limitations repeated across many existing meta-analyses such as pooling surgical and nonsurgical data (9–11), incorrectly classifying studies as nonsurgical (8), pooling adult and pediatric data (6, 7, 9, 12, 13), including studies wherein transfusion thresholds were not prespecified or were above 10 g/dL in both arms (9, 14), including trials of preautologous donation (11, 12, 14), including duplicate or overlapping studies (15), failing to separate noncardiac and cardiac surgery (8, 10), failing to assess important clinically relevant outcomes such as mortality (7), and inappropriately combining all adverse events into overall morbidity (6).

We performed an updated comprehensive meta-analysis of randomized controlled trials (RCTs) to address the limitations in previously published analyses and to better delineate whether outcomes for restrictive versus liberal transfusion thresholds differ for perioperative (surgical) versus critically ill patients. To further extend the clinical utility of the results, we planned a priori to also separately explore cardiac and noncardiac surgery subgroups given the concerns about presumed excess risk of transfusion restriction in cardiac surgery. We wondered if the mixed conclusions regarding mortality benefit identified by other authors would persist under these conditions of improved methodologic rigor (6, 8–13).

METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement with a protocol defined a priori (16).

Literature Search

Computerized searches of MEDLINE, EMBASE, and the Cochrane Library were conducted from date of inception to June 15, 2016. The full search strategy is detailed in the appendix (**Supplemental Digital Content 1**, <http://links.lww.com/CCM/D45>; **legend**, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Study Selection

Citations were independently screened by at least two authors (M.A.C., R.K., J.M., or a departmental medical librarian). For inclusion, studies must have recruited adult patients and compared a liberal versus restrictive threshold for the transfusion of allogeneic pRBCs using a RCT or quasi-RCT design. The definition for liberal versus restrictive must have been based on either hemoglobin concentration or hematocrit criteria, with or without discretion to transfuse patients with symptoms attributable to anemia (e.g., shock or angina). We did not consider weight-based transfusion triggers or transfusion “policies” where

patients in each arm received a different transfusion trigger as meeting the inclusion criteria. Furthermore, trials comparing autologous donation were not included. The primary outcome was all-cause mortality at 30 days (or closest reported time). Secondary outcomes included patients exposed to allogeneic pRBC transfusion, myocardial infarction (MI), stroke or transient ischemic attack (TIA), congestive heart failure (CHF), renal failure, deep vein thrombosis, pulmonary embolus, infection, and transfusion reactions. In addition, mean volume of pRBCs per patient and length of stay in hospital and the ICU were analyzed.

Data Extraction

Two reviewers (M.A.C., R.K.) independently extracted data related to study descriptors, patient demographics, and predefined clinical outcomes onto standardized study forms. Any discrepancies were resolved by consensus by three authors (M.A.C., R.K., J.M.).

Risk of Bias Assessment

The Cochrane Risk of Bias Tool was used to assess study quality. The specific elements were adequacy of the methods used to minimize bias through: 1) randomization sequence (selection bias), 2) allocation concealment (selection bias), 3) blinding of study personnel and participants (performance bias), 4) blinding of outcome assessors (performance bias), 5) complete reporting of data without arbitrarily excluded patients and with low-to-minimal loss to follow-up (attrition bias), 6) selective reporting bias, and 7) other sources of bias (17). Studies were considered low risk of bias if they adequately met the criteria for low risk of selection bias, performance bias, and attrition bias with no other sources of bias evident. Moderate risk of bias studies met 3–4 of the first criteria on the Cochrane Risk of Bias Tool with no other sources of bias evident. Finally, high risk of bias studies only met 0–2 criteria of the first five items of the Tool. For all significant outcomes, a summary of findings table was created and Grading of Recommendations Assessment, Development and Evaluation was used to assess the overall quality of evidence (18).

Statistical Analysis

Dichotomous outcomes were reported as odds ratios (ORs) and continuous outcomes as weighted mean differences. All analyses were conducted using the random-effects model. For outcomes that reached statistical significance, the number needed to treat to benefit one patient (NNTB) or the number needed to treat to harm one patient (NNTH) was calculated for beneficial and harmful effects, respectively. All results were reported at a significance level of $\alpha = 0.05$, with the corresponding 95% CI. Degree of heterogeneity across studies for each outcome was estimated using χ^2 and P . The continuity correction was used for zero event studies (19). Primary stratification of outcomes based on patient population (perioperative and critical care) was prespecified a priori, as were all secondary subgroup analyses for cardiac versus noncardiac surgery. As recommended for interpretation of subgroup analyses within meta-analysis, the test for interaction across subgroups was performed to determine whether the effect sizes differed significantly across

subgroups, rather than interpretation of subgroup effects by inspection of individual p values for each subgroup alone, which is inherently underpowered when data are divided into subgroups (20, 21). Since the test for interaction may be underpowered, a threshold of p less than 0.10 was used to indicate significant differences across prespecified subgroups. Planned sensitivity analyses included reanalysis of the primary outcome after excluding studies with high risk of bias. Funnel plots and Egger's regression were used to assess for statistical evidence of publication bias.

In meta-analysis, repeated significance testing of pooled data can lead to increased possibility of type 1 errors (22, 23). On the other hand, insufficient power due to inadequate cumulated event rates and sample sizes, together with heterogeneity across study effect sizes, may also result in insufficient "information size" to rule in or rule out a true effect across studies.

To adequately control for the play of chance and sub-optimal information size, trial sequential analysis (TSA) is recommended to inform whether sufficient evidence has accrued to provide definitive conclusions. TSA allows the creation of trial sequential boundaries within a cumulative meta-analysis to determine when the sample size and p value is sufficient to definitively show an effect (suggesting more research would be futile) versus when the cumulative sample size is insufficient for the associated p value to be definitive (suggesting high risk of false-positive or false-negative results and indicating more research is required before definitive conclusions can be made) (22, 23). For this study, TSA was used to assess 30-day mortality within critical care and perioperative subgroups. The results were calculated using a diversity-adjusted sample size, 80% power, 15% relative risk reduction, and 5% type 1 error. As one of the baseline assumptions for the TSA, the median risk of death from the pool of liberal arms of all included studies was used for the control event rate for each respective subgroup. For further description of TSA, see Thorlund et al (23). Meta-analysis was performed using STATA 14 (24), and TSA was performed with version 0.9.5.5 Beta (23).

RESULTS

Literature Search and Study Selection

The systematic search retrieved 6,055 citations (PRISMA Flowchart, **Supplemental Digital Content 2**, <http://links.lww.com/CCM/D46>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>). Ultimately, 27 RCTs including 10,797 patients met the inclusion criteria (**Table 1**) (1, 25–50). Twelve trials included primarily critically ill patients and 15 included primarily surgical (perioperative) patients. For the restrictive transfusion strategy, the trigger threshold was typically defined as hemoglobin concentration of 7–8 g/dL, and for the liberal transfusion strategy, the trigger was typically between hemoglobin 9 and 10 g/dL (Table 1). Excluded studies are detailed in the online appendix (**Supplemental Digital Content 3**, <http://links.lww.com/CCM/D47>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Risk of Bias

Seventeen studies were deemed at moderate risk of bias, and the remaining 10 were at high risk of bias (Risk of Bias Assessment, **Supplemental Digital Content 4**, <http://links.lww.com/CCM/D48>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Mortality at 30 Days

In critical care patients, the restrictive transfusion strategy resulted in significantly reduced 30-day mortality compared with a liberal transfusion strategy (OR, 0.82; 95% CI, 0.70–0.97; NNTB = 33; $p = 0.019$) (**Fig. 1**). In contrast, in surgical patients, the restrictive transfusion strategy led to the opposite direction of effect for 30-day mortality (OR, 1.31; 95% CI, 0.94–1.82; $p = 0.12$) (**Fig. 1**), though not reaching conventional levels of significance. More importantly, the test for interaction across the critical care and surgical subgroups was significant ($p = 0.04$), suggesting that the effect on mortality is statistically different between the two groups (decreased mortality in critical care patients vs potentially increased risk or no difference in mortality for surgical patients).

The increased risk of 30-day mortality in perioperative patients for the restrictive strategy was confirmed during prespecified sensitivity analyses when limiting to studies at low risk of bias (OR, 1.50; 95% CI, 1.02–2.22; $p = 0.04$; NNTB = 54). Furthermore, the increased risk of 30-day mortality in perioperative patients was intensified when limiting to studies using the lowest category of transfusion threshold (7–7.5 g/dL studies vs 8 g/dL or above studies), where perioperative patients receiving a restrictive strategy of 7–7.5 g/dL experienced significantly greater 30-day mortality (OR, 1.94; 95% CI, 1.24–3.03; $p = 0.003$; NNTB = 48) (**Fig. 2**) compared with the liberal arm. In contrast, critical care patients receiving the lowest threshold of 7–7.5 g/dL experienced a decreased risk of mortality (OR, 0.82; 95% CI, 0.69–0.97; $p = 0.02$; NNTB = 26), whereas 30-day mortality was not significantly different in patients receiving the higher threshold (8 g/dL or above) for both critical care (OR, 1.20; 95% CI, 0.32–4.48; $p = 0.12$) and perioperative (OR, 0.97; 95% CI, 0.71–1.32; $p = 0.84$) patients.

For perioperative patients, additional subgroup analysis by cardiac and noncardiac surgery did not reveal significant differences for 30-day mortality (cardiac surgery: OR, 1.28; 95% CI, 0.82–1.98 vs noncardiac surgery: OR, 1.39; 95% CI, 0.82–2.38; test for subgroup interaction $p = 0.82$). Additional sensitivity analyses are located in Tables S1 and S2 (**Supplemental Digital Content 5**, <http://links.lww.com/CCM/D49>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

TSA was conducted for 30-day mortality for both perioperative and critical care subgroups. Within critical care studies, the cumulative z curve crossed the trial sequential monitoring boundary for benefit (**Supplemental Digital Content 6**, <http://links.lww.com/CCM/D50>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>), inferring that sufficient evidence has accrued to definitively conclude that a restrictive threshold is superior to a liberal threshold strategy

TABLE 1. Baseline Characteristics of Included Studies

Author	Population			Transfusion Trigger (Hemoglobin [g/dL] or Hematocrit [%])		Total Patients (n)
	Classification	Patient Population	Details	Restrictive	Liberal	
Bergamin et al (33)	Critical care	Critical care	Cancer with septic shock	Hemoglobin < 7 g/dL	Hemoglobin < 9 g/dL	136
Blair et al (27)	Critical care	Upper UGIB	Severe gastrointestinal hemorrhage	Hemoglobin < 8 g/dL or persistent shock within 24 hr admission	At least 2 U of blood within first 24 hr of admission	50
Carson et al (26)	Critical care	Acute coronary syndrome	MI or stable angina with hemoglobin < 10 g/dL	Symptomatic anemia or hemoglobin < 8 g/dL	Hemoglobin < 10 g/dL with maintenance above 10 g/dL	110
Cooper et al (25)	Critical care	Acute coronary syndrome	Acute MI with hematocrit < 30%	Hematocrit < 24% with maintenance between 24% and 27%	Hematocrit < 30% with maintenance between 30% and 33%	45
Hébert et al (30)	Critical care	Critical care	Euvolemic critically ill patients with hemoglobin < 9.0 g/dL	Hemoglobin = 7–7.5 g/dL with maintenance between 7 and 9 g/dL	Hemoglobin = 10–10.5 g/dL with maintenance 10–12 g/dL	69
Hébert et al (1)	Critical care	Critical care	Euvolemic critically ill patients with hemoglobin < 9.0 g/dL	Hemoglobin < 7 g/dL with maintenance between 7 and 9 g/dL	Hemoglobin < 10 g/dL with maintenance between 10 and 12 g/dL	838
Holst et al (32)	Critical care	Critical care	Septic shock with hemoglobin < 9.0 g/dL	Hemoglobin ≤ 7 g/dL	Hemoglobin ≤ 9 g/dL	1005
Jairath et al (29)	Critical care	Upper UGIB	Hematemesis and/or melena	Hemoglobin < 8 g/dL	Hemoglobin < 10 g/dL	936
Mazza et al (50)	Critical care	Critical care	Septic shock with hemoglobin < 9 g/dL	Hemoglobin < 7 g/dL	Hemoglobin < 9 g/dL	46
Robertson et al (34)	Critical care	Traumatic brain injury	Closed head injury	Hemoglobin < 7 g/dL	Hemoglobin < 10 g/dL	98
Villanueva et al (28)	Critical care	Upper UGIB	Hematemesis and/or melena	Hemoglobin < 7 g/dL	Hemoglobin < 9 g/dL	921
Walsh et al (31)	Critical care	Critical care	Older critically ill patients with hemoglobin < 9.0 g/dL	Hemoglobin ≤ 7 g/dL with maintenance between 7.1 and 9 g/dL	Hemoglobin ≤ 9 g/dL with maintenance between 9.1 and 11 g/dL	100
de Almeida et al (44)	Perioperative	Noncardiac surgery	Oncologic surgery	Hemoglobin < 7 g/dL	Hemoglobin < 9 g/dL	198
Bracey et al (35)	Perioperative	Cardiac surgery	CABG	Hemoglobin < 8 g/dL or symptomatic anemia	Hemoglobin < 9 g/dL	428
Bush et al (40)	Perioperative	Noncardiac surgery	Vascular surgery	Hemoglobin < 9 g/dL	Hemoglobin < 10 g/dL	99
Carson et al (41)	Perioperative	Noncardiac surgery	Orthopedic surgery with postoperative hemoglobin ≤ 10 g/dL	Symptomatic anemia or hemoglobin < 8 g/dL	Hemoglobin < 10 g/dL	84

(Continued)

TABLE 1. (Continued). Baseline Characteristics of Included Studies

Author	Population			Transfusion Trigger (Hemoglobin [g/dL] or Hematocrit [%])		Total Patients (n)
	Classification	Patient Population	Details	Restrictive	Liberal	
Carson et al (48)	Perioperative	Noncardiac surgery	Orthopedic surgery with postoperative hemoglobin ≤ 10 g/dL	Symptomatic anemia or physician discretion if hemoglobin < 8 g/dL	Hemoglobin ≤ 10 g/dL	2016
Foss et al (47)	Perioperative	Noncardiac surgery	Orthopedic surgery	Hemoglobin ≤ 8 g/dL	Hemoglobin ≤ 10 g/dL	120
Gregersen et al (45)	Perioperative	Noncardiac surgery	Orthopedic surgery	Hemoglobin < 9.7 g/dL	Hemoglobin < 11.3 g/dL	284
Grover et al (46)	Perioperative	Noncardiac surgery	Orthopedic surgery	Hemoglobin < 8 g/dL with maintenance between 8 and 9.5 g/dL	Hemoglobin < 10 g/dL with maintenance between 10 and 12 g/dL	260
Hajjar et al (36)	Perioperative	Cardiac surgery	CABG and/or valvular surgery	Hematocrit $< 24\%$	Hematocrit $< 30\%$	502
Junio et al (38)	Perioperative	Cardiac surgery	CABG, valvular surgery, or congenital anomaly correction	Hemoglobin ≤ 7 g/dL	Discretion of attending physician	71
Markatou et al (49)	Perioperative	Noncardiac surgery	General surgery	Hemoglobin < 7.7 g/dL	Hemoglobin < 9.9 g/dL	58
Murphy et al (39)	Perioperative	Cardiac surgery	CABG, valvular, or aortic surgery with postoperative hemoglobin ≤ 9 g/dL	Hemoglobin < 7.5 g/dL	Hemoglobin < 9 g/dL	2007
Nielsen et al (43)	Perioperative	Noncardiac surgery	Orthopedic surgery	Hemoglobin < 7.3 g/dL	Hemoglobin < 8.9 g/dL	66
Parker (42)	Perioperative	Noncardiac surgery	Orthopedic surgery with postoperative hemoglobin 8–9.5 g/dL	Symptomatic anemia	Transfusion of at least 1 U packed RBCs to raise hemoglobin > 10 g/dL	200
Shehata et al (37)	Perioperative	Cardiac surgery	CABG and/or valvular surgery	Hemoglobin ≤ 7 g/dL intraoperatively and ≤ 7.5 g/dL postoperatively	Hemoglobin ≤ 9.5 g/dL intraoperatively and ≤ 10 g/dL postoperatively	50

CABG = coronary artery bypass grafting, MI = myocardial infarction, UGIB = upper gastrointestinal bleed.

in critical care patients and that further studies are unnecessary to confirm reduced mortality in this group. In contrast, within perioperative studies, the cumulative z curve neither crossed the trial sequential monitoring boundaries nor entered the futility region. Therefore, the results of this meta-analysis remain inconclusive for perioperative patients, and further studies will be required to reach adequate sample size to clarify the net impact on mortality in the perioperative setting (**Supplemental Digital Content 7**, <http://links.lww.com/CCM/D51>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Late and In-Study Mortality

Only 11 studies reported “late” mortality at 60–365 days. There was no difference between liberal and restrictive transfusion

thresholds for critical care (OR, 0.90; 95% CI, 0.72–1.12) or perioperative patients (OR, 1.31; 95% CI, 0.93–1.87), and the p value for interaction across subgroups was nonsignificant ($p = 0.11$). Similarly, in-study mortality was only detectably different for critical care patients (critical care: OR, 0.84; 95% CI, 0.70–0.99; $p = 0.045$; NNTB = 34 vs perioperative: OR, 1.24; 95% CI, 0.95–1.63), with the p value for interaction being significant ($p = 0.03$).

Secondary Outcomes

Secondary outcomes are summarized in **Table 2**.

Myocardial Infarction

There was no increased rate of MI between the two transfusion strategies for critical care (OR, 0.72; 95% CI, 0.23–2.24;

Figure 1. Forest plot showing the odds ratio (OR) and 95% CIs for the risk of 30-day mortality of patients receiving the liberal versus restrictive transfusion triggers, by critical care and perioperative subgroups. Thirty-day mortality is decreased with a restrictive strategy for critical care patients, but not perioperative patients.

$p = 0.57$) or perioperative patients (OR, 1.58; 95% CI, 0.99–2.49; $p = 0.051$) (Fig. 3 and Table 2). However, subgroup analysis by cardiac or noncardiac surgery revealed more MI with a restrictive strategy in noncardiac surgery patients (OR, 1.66; 95% CI, 1.01–2.70; $p = 0.044$; NNTB = 85; Table 2), although this was not statistically significant after considering the test for interaction p values (interaction $p = 0.63$). Post hoc analysis of critical care studies, without the trials by Holst et al (12) and Walsh et al (31) that reported MI as a composite of acute coronary syndromes, did not reveal significant differences in the risk of MI (OR, 0.37; 95% CI, 0.07–2.08; $p = 0.26$).

Stroke

Critical care patients experienced reduced stroke or TIA with a restrictive strategy (OR, 0.63; 95% CI, 0.40–0.99; NNTB = 79; $p = 0.04$) (Table 2). This significant finding persisted even in post hoc sensitivity analysis without the TRICC trial, which reported stroke as a composite that also included encephalopathy (OR, 0.42; 95% CI, 0.18–0.96; $p = 0.040$). For perioperative

patients, the risk of stroke or TIA was not different between restrictive or liberal transfusion strategies (OR, 1.00; 95% CI, 0.61–1.64).

Infections

No significant difference was found for infectious outcomes (Table 2).

Transfusion Reactions

Critical care patients receiving a restrictive transfusion strategy experienced less transfusion reactions (OR, 0.48; 95% CI, 0.29–0.80; $p = 0.005$; NNTB = 64; Table 2). The data for perioperative patients were not significant (OR, 0.99; 95% CI, 0.10–9.6).

Allogeneic pRBC Utilization

As expected, fewer patients were transfused in the restrictive group compared with the liberal group for both critical care (OR, 0.04; 95% CI, 0.01–0.14; $p < 0.001$; NNTB = 2) and perioperative patients (OR, 0.19; 95% CI, 0.09–0.43; $p < 0.001$;

Figure 2. Forest plot showing the odds ratio (OR) and 95% CIs for the risk of 30-day mortality of patients receiving the liberal versus restrictive transfusion triggers, by restrictiveness of transfusion trigger for the critical care and perioperative subgroups. Thirty-day mortality is decreased with the most restrictive transfusion triggers for critical care patients, but there is an opposite direction of effect for the perioperative patients.

NNTB = 4). Restricted threshold patients also received less units of pRBCs compared with their counterparts in the liberal arm (critical care data: -1.7 U; 95% CI, -2.5 to -0.91 ; $p < 0.001$; and perioperative data: -1.3 U; 95% CI, -1.7 to -0.92 ; $p < 0.001$).

Other Secondary Outcomes

Differences were not detected for other secondary outcomes including cardiac arrest, renal failure, thromboembolism, sepsis or septic shock, cardiogenic shock, acute respiratory distress syndrome, or CHF (Table 2). Hospital length of stay was 1.03 days (95% CI, 0.42–1.64; $p = 0.001$) shorter with a restrictive strategy for critical care patients, with a smaller difference for perioperative patients (-0.32 d; 95% CI, -0.63 to -0.02 ; $p = 0.04$). In contrast, ICU length of stay did not differ between the restrictive and liberal strategy (critical care data: -1.1 d; 95% CI, -3.0 to 0.68; $p = 0.22$ and perioperative data: 0.13 d; 95% CI, -0.06 to 0.32; $p = 0.18$).

Publication Bias

The funnel plot for all-cause mortality for the perioperative studies showed slight asymmetry upon visual inspection (Supplemental Digital Content 8, <http://links.lww.com/CCM/D52>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>). This asymmetry suggests that smaller studies reporting lower risk of mortality with a restrictive transfusion strategy may be selectively missing and that significantly more of the small studies were likely to report an increased risk of mortality. This is indicative of a potential publication bias toward increased reporting of small studies where mortality was increased. However, Egger's regression for these data was not statistically significant ($p = 0.20$). Taken together with the only slight asymmetry of the forest plot, the extent of potential publication bias on the effect estimate for perioperative mortality is likely small and remains underpowered. In contrast, for the critical care studies, the funnel plot appeared

TABLE 2. Summary of Outcomes

Outcome	Subgroup	Odds Ratio (95% CI)	No. Needed to Treat to Benefit One Patient or (No. Needed to Treat to Harm One Patient)	Test for Interaction <i>p</i>
Critical care and perioperative care subgroups				
Mortality	Critical care	0.82 (0.70–0.97)	33	0.04 ^a
	Perioperative	1.31 (0.94–1.82)	—	
Transfused patients	Critical care	0.04 (0.01–0.14)	2	0.10
	Perioperative	0.19 (0.09–0.43)	4	
Myocardial infarction	Critical care	0.72 (0.23–2.24)	—	0.18
	Perioperative	1.58 (0.99–2.49)	—	
Congestive heart failure	Critical care	0.58 (0.26–1.32)	—	0.06
	Perioperative	1.42 (0.88–2.30)	—	
Stroke/transient ischemic attack	Critical care	0.63 (0.40–0.99)	79	0.22
	Perioperative	1.00 (0.61–1.64)	—	
Acute kidney injury	Overall ^b	0.96 (0.73–1.26)	—	—
Renal failure requiring dialysis	Overall ^b	1.21 (0.92–1.60)	—	—
Infections (if reported as composite)	Critical care	0.87 (0.72–1.07)	—	0.23
	Perioperative	1.06 (0.84–1.35)	—	
Wound infection	Perioperative	1.00 (0.71–1.41)	—	—
Pneumonia	Critical care	0.98 (0.75–1.28)	—	0.14
	Perioperative	0.60 (0.31–1.17)	—	
Transfusion reaction	Critical care	0.48 (0.29–0.80)	64	0.83
	Perioperative	0.99 (0.10–9.62)	—	
Thromboembolism	Critical care	0.99 (0.10–9.67)	—	0.95
	Perioperative	0.83 (0.42–1.64)	—	
Cardiac arrest	Overall ^b	0.90 (0.55–1.46)	—	—
Sepsis or septic shock	Overall ^b	1.16 (0.88–1.54)	—	—
Acute respiratory distress syndrome	Overall ^b	0.90 (0.46–1.76)	—	—
Noncardiac surgery and cardiac surgery subgroups				
Mortality	Cardiac	1.28 (0.82–1.98)	—	0.82
	Noncardiac	1.39 (0.82–2.38)	—	
Myocardial infarction	Cardiac	1.15 (0.33–4.03)	—	0.63
	Noncardiac	1.66 (1.01–2.70)	(84)	

^aIndicates statistically significant *p* value.^bIndicates not enough studies to perform subgroup analysis by critical care versus perioperative.

Other clinical outcomes did not differ for cardiac and noncardiac subgroups.

Dashes indicate value is not applicable.

symmetrical (**Supplemental Digital Content 9**, <http://links.lww.com/CCM/D53>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>) and Egger's regression was also not significant ($p = 0.28$). Both these findings suggest a low likelihood of publication bias for the critical care data.

Summary of Findings and GRADE'd Level of Evidence

The summary of findings for significant results and the GRADE level of evidence is provided in Table S3 (**Supplemental Digital Content 10**, <http://links.lww.com/CCM/D54>;

Figure 3. Forest plot showing the odds ratio (OR) and 95% CIs for the risk of myocardial infarction (MI) of patients receiving the liberal versus restrictive transfusion triggers, by critical care and perioperative subgroups. There is a trend toward increased MI in perioperative patients receiving the restrictive strategy.

legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

DISCUSSION

Major Findings

Evidence suggests that the safety of restrictive transfusion thresholds differs for critically ill patients versus perioperative patients. In critical care patients, a restrictive transfusion strategy (transfusion trigger ~7–8 g/dL in the majority of studies) significantly reduced mortality, stroke/TIA, transfusion reactions, allogeneic blood exposure, and hospital length of stay. In contrast, for perioperative patients, current evidence suggests that a restrictive transfusion strategy may increase the risk of mortality, although the overall results were not statistically significant and lack of power prevents definitive conclusions.

In sum, these numbers suggest that for every 1,000 critical care patients treated with a restrictive transfusion strategy instead of a liberal strategy, a total of 31 (95% CI, 6–55) fewer patients would die at 30 days, 13 (95% CI, 1–21) fewer patients would experience stroke/TIA, 16 (95% CI, 7–22) fewer would experience transfusion reactions, 663 (95% CI, 429–771) fewer would be exposed to

allogeneic RBC transfusion, and more than 1,000 hospital days would be saved. In contrast, in perioperative patients, the evidence for mortality is less definitive due to lower power. However, acknowledging that the overall data were not statistically significant, there are perhaps signals toward harm, given the significant test for subgroup interaction and significant findings in subgroup analysis by transfusion trigger value (7–7.5 g/dL studies vs 8 g/dL or above studies). This is analogous to a dose-related effect (lower threshold was increasingly worse for mortality differences than more moderate thresholds). Specifically, perioperative patients in trials that administered a restrictive trigger of 7–7.5 g/dL experienced 22 extra deaths (95% CI, 6–45) per 1,000 patients, which reached statistical significance. Furthermore, there were no other differences in the secondary outcomes for perioperative patients, apart from significantly reducing allogeneic pRBC exposure by 317 fewer patients (95% CI, 135–512) per 1,000 treated. Finally, when subgroup analysis was conducted by study quality, the increased risk of mortality in surgical patients reached statistical significance for perioperative studies (Table S1, Supplemental Digital Content 5, <http://links.lww.com/CCM/D49>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Thus, the implications are clear that a restrictive transfusion strategy (transfusion trigger 7–8 g/dL, unless otherwise symptomatic) is recommended for critical care patients, with the evidence being less clear for surgical patients. Important limitations to our analysis include the moderate-to-high risk of bias of all included studies and possibility of publication bias among the perioperative studies. The specific GRADE recommendations corresponding to each of the outcomes of interest are located in the Summary of Findings Table (Table S3, Supplemental Digital Content 10, <http://links.lww.com/CCM/D54>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>). In general and in reference to Table S3, the quality of evidence for each outcome ranged from moderate to low (18).

For surgical patients, the perioperative setting offers different challenges in managing blood transfusion. Patients undergoing surgery have different risks than the critically ill, including surgery-related blood loss, vasoregulatory changes from anesthesia, and fluid shifts that are inherent to complex surgical procedures (51). Therefore, the acuity and time course of oxygen demands in perioperative patients may differ from those who are critically ill (52). For the outcome of 30-day mortality, the test for interaction between perioperative and critically ill patients was significant, suggesting that the direction of the effect sizes differ. Furthermore, subgroup analysis of low risk of bias perioperative studies, as well as those employing restrictive transfusion triggers of 7–7.5 g/dL (compared to 8 g/dL or higher), did demonstrate a higher risk of 30-day mortality. Taken together, these findings may potentially place perioperative patients at an increased risk of 30-day mortality with a restrictive transfusion strategy. Given divergent effect sizes and the low power in the accumulated sample size for surgical patients, our analysis calls into question the current American Society of Anesthesiologists guidelines (53), which advocate for a restrictive transfusion threshold in perioperative patients. In addition, our findings provide reason to reassess the American Association of Blood Banks recommendations related to surgery, which suggest that “a restrictive RBC transfusion threshold of 8 g/dL is recommended for patients undergoing orthopedic surgery, cardiac surgery, and those with preexisting cardiovascular disease (strong recommendation, moderate quality evidence). The restrictive transfusion threshold of 7 g/dL is likely comparable with 8 g/dL, but RCT evidence is not available for all patient categories” (9).

Fortunately, relevant research is ongoing, including the international Transfusion Requirements in Cardiac Surgery III trial of cardiac surgery patients randomized to restrictive versus liberal transfusion thresholds (NCT02042898), which should help to clarify the appropriate threshold in this subgroup.

Differences From Prior Meta-Analyses

This meta-analysis improves on pre-existing meta-analyses, due to our strict inclusion criteria and clear demarcation of surgical and critical care patients. Furthermore, we avoided pooling secondary outcomes into an overall composite (as employed in another analysis) (6) since this practice may lead

to double-counting of patients within the same composite outcome who have related events across subcomponents of the artificially combined composite outcome across studies. Furthermore, this approach allows us to identify significant differences for individual secondary outcomes of interest, which would have been lost in a composite. A number of studies included in other meta-analyses were excluded from our meta-analysis in order to improve clinical homogeneity and more clearly differentiate the potential differences of predefined restrictive transfusion thresholds across more uniform populations. For transparency, we have outlined our excluded studies and reasons for exclusion (Supplemental Digital Content 3, <http://links.lww.com/CCM/D47>; legend, Supplemental Digital Content 11, <http://links.lww.com/CCM/D55>).

Notable RCTs that did not meet our inclusion criteria but were included by authors of other meta-analyses, include the trials by Prick et al (54) and So-Osman et al (55). The former recruited parturients with anemia, and mortality was not reported (54). Furthermore, as more than 80% of their patients underwent vaginal delivery (and not c-section), the patient population is arguably not “perioperative” or “critically ill” (54). The trial by So-Osman et al (55) also did not meet the inclusion criteria because their intervention incorporated mandatory risk stratification by arbitrary patient characteristics and their comparator was the standard of care at each study site, rather than a liberal transfusion trigger. Furthermore, one study employed a weight-based transfusion trigger versus control, and depending on the patient’s weight, there could be overlap between the transfusion triggers in the intervention arm versus control arm (56). Finally, we excluded pediatric studies and studies of ambulatory cancer patients.

CONCLUSIONS

Evidence suggests that the safety of restrictive transfusion thresholds differs for critically ill patients versus perioperative patients. In critical care patients, a restrictive transfusion strategy (transfusion trigger ~ 7–8 g/dL) reduces the risk of overall mortality, stroke/TIA, transfusion reactions, length of stay, and allogeneic blood exposure. In contrast, for perioperative patients, current evidence suggests a restrictive transfusion strategy may increase the risk of mortality, particularly with transfusion triggers of 7–7.5 g/dL. While the evidence base is sufficiently robust to provide definitive conclusions for critically ill patients due to large accumulated sample size, the existing evidence base for the perioperative population remains less robust due to insufficiently accumulated sample size. Consequently, further research is encouraged in perioperative patients to define safe transfusion thresholds, especially for cardiac surgical patients or high-risk patients undergoing noncardiac surgery.

ACKNOWLEDGMENTS

This meta-analysis was awarded second place in the oral competition at the Midwest Anesthesia Residents’ Conference, and an earlier version of the analysis was presented as a poster

presentation at the annual Canadian Anesthesiologists Meeting (June 2016). We thank Jessica Moodie (MLIS) and Amy Newitt (MLIS) for performing the systematic searches. Finally, we appreciate the assistance of Dr. Yun-Hee Choi (Assistant Professor, Department of Epidemiology and Biostatistics, Western University) with reviewing the statistical methodology of the article.

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