

A Systematic Review and Meta-analysis of Randomized Controlled Trials Comparing Intraoperative Red Blood Cell Transfusion Strategies

Tori Lenet, MD,*† Laura Baker, MD,*† Lily Park, MD,* Michael Vered, BSc,* Amin Zahrai, BSc,* Risa Shorr, MSc,‡ Alexandra Davis, MSc,‡ Daniel I. McIsaac, MD, FRCPC,†§ Alan Tinmouth, MD, FRCPC,†¶|| Dean A. Fergusson, PhD,*†¶|| and Guillaume Martel, MD, FRCSC, FACS*†☒

Objective: The objective of this work was to carry out a meta-analysis of RCTs comparing intraoperative RBC transfusion strategies to determine their impact on postoperative morbidity, mortality, and blood product use.

Summary of Background Data: RBC transfusions are common in surgery and associated with widespread variability despite adjustment for casemix. Evidence-based recommendations guiding RBC transfusion in the operative setting are limited.

Methods: The search strategy was adapted from a previous Cochrane Review. Electronic databases were searched from January 2016 to February 2021. Included studies from the previous Cochrane Review were considered for eligibility from before 2016. RCTs comparing intraoperative transfusion strategies were considered for inclusion. Co-primary outcomes were 30-day mortality and morbidity. Secondary outcomes included intraoperative and

perioperative RBC transfusion. Meta-analysis was carried out using random-effects models.

Results: Fourteen trials (8641 patients) were included. One cardiac surgery trial accounted for 56% of patients. There was no difference in 30-day mortality [relative risk (RR) 0.96, 95% confidence interval (CI) 0.71–1.29] and pooled postoperative morbidity among the studied outcomes when comparing restrictive and liberal protocols. Two trials reported worse composite outcomes with restrictive triggers. Intraoperative (RR 0.53, 95% CI 0.43–0.64) and perioperative (RR 0.70, 95% CI 0.62–0.79) blood transfusions were significantly lower in the restrictive group compared to the liberal group.

Conclusions: Intraoperative restrictive transfusion strategies decreased perioperative transfusions without added postoperative morbidity and mortality in 12/14 trials. Two trials reported worse outcomes. Given trial design and generalizability limitations, uncertainty remains regarding the safety of broad application of restrictive transfusion triggers in the operating room. Trials specifically designed to address intraoperative transfusions are urgently needed.

Keywords: anesthesiology, blood, decision-making, meta-analysis, randomized controlled trial, surgery, transfusion

(*Ann Surg* 2022;275:456–466)

From the *Department of Surgery, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; †Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; ‡Library Services, The Ottawa Hospital, Ottawa, ON, Canada; §Department of Anesthesiology, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; ¶Department of Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; and ||Canadian Blood Services, Ottawa, ON, Canada.

☒ gumartel@toh.ca.

Protocol registration: PROSPERO CRD42019138397.

Author Contributions: The study was designed by TL, LB, and GM. The protocol was drafted and registered by TL, LB, and GM. GM is the guarantor of the protocol. RS and AD designed and implemented the search strategy. TL, LB, LP, MV, and AV screened citations and performed data abstraction. TL and LP performed the risk of bias assessment. TL and GM analyzed the data. TL, DAF, and GM drafted the manuscript. DIM, AT, DAF, and GM provided content expertise and reviewed the manuscript critically for quality. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors reviewed and approved the final manuscript.

Supported by the Canadian Blood Services Blood Efficiency and Accelerator Award Program 2017 and the Academic Health Science Center Alternative Funding Plan Innovation Fund 2017.

GM is the recipient of the Vered Family Chair in HPB Research at the Ottawa Hospital Research Institute.

GM is the guarantor of this manuscript and he affirms it is an honest, accurate, and transparent account of the study. No important aspects of the study have been omitted. The study has been conducted as originally planned.

The authors report no conflicts of interest.

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 Web site (www.annalsurgery.com).

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

ISSN: 0003-4932/21/27503-0456

DOI: 10.1097/SLA.0000000000004931

Red blood cell (RBC) transfusions are commonly administered in the perioperative setting. In the United States alone, 11 million units of RBCs are administered annually,¹ of which over one quarter are given to surgical patients.² By international estimates, surgical services account for 24%–44% of transfused RBC units among inpatients.^{3,4} Although the need for transfusion is variable, its incidence in the perioperative period can be as high as 50% in procedures associated with a high risk of bleeding.^{5–8}

Although potentially lifesaving, RBC transfusions are not benign interventions. Risks include transfusion-associated acute lung injury, transfusion-associated circulatory overload, hemolytic reactions, bacterial contamination, viral transmission, alloimmunization, and a risk of mistransfusion due to human error.⁹ RBC transfusion may also lead to transfusion-related immunomodulation,¹⁰ which may be associated with worse oncologic outcomes in surgical patients.¹¹ Finally, blood products are a limited and expensive, costing up to 761 US dollars per RBC unit in surgical patients.¹²

There is evidence in the literature of significant variation in transfusion practice in patients undergoing surgery, both in the intraoperative and postoperative settings. Risk-adjusted variation in RBC transfusion has been identified prominently in cardiac surgery⁶ and in major noncardiac surgery.^{7,13–15} Although a certain degree of variation is expected based on casemix, wide variation that cannot be explained by disease severity or patient preference likely reflects unwarranted variation in clinical care.^{16–18} A critical examination of factors contributing to this variation is warranted.

Recommendations guiding the administration of RBCs during surgery exist in the literature.^{19–22} Guidance pertaining to intraoperative transfusion management is generally limited and endorses the use of restrictive transfusion thresholds. However, this endorsement generally relies on evidence from clinical trials conducted in the postoperative and nonoperative settings. The generalizability of these recommendations to patients undergoing a surgical procedure under general anesthesia is limited for several reasons. First, despite a majority of anesthesiologists identifying hemoglobin concentration as the most important factor when deciding on an intraoperative transfusion, it may be less relevant to guide RBC transfusion in the setting of active or rapid blood loss, particularly given the significant variation in hemoglobin concentration with volume of administered crystalloid or colloid fluids.²³ Second, hemodynamic variations in surgical patients are not necessarily reflective of anemia from surgical bleeding, and may result from other factors such as pharmacologic anesthetic agents, patient positioning, mechanical ventilation, neuraxial analgesia, surgical manipulation, and abdominal insufflation.^{24,25} A comprehensive synthesis of randomized trials comparing intraoperative transfusion strategies does not exist, and is thus timely and necessary.

The objective of this work was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing intraoperative allogeneic RBC transfusion strategies in surgical patients and to determine their impact on postoperative morbidity and mortality, and blood product use.

METHODS

A systematic review of RCTs comparing allogeneic RBC transfusion strategies during the intraoperative period was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis statement.²⁶ A protocol was written and registered with PROSPERO (CRD42019138397).

Search Strategy and Data Sources

The search strategy was adopted from an existing 2016 Cochrane Review which assessed the clinical outcomes of medical and surgical patients randomized to restrictive or liberal transfusion strategies.²⁷ The following databases were searched from January 1st, 2016 to February 8th, 2021: EMBASE Classic+, Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, Web of Science, and Transfusion Evidence Library. Before 2016, all included trials from the prior Cochrane review²⁷ were screened for eligibility. References of included trials and systematic reviews were screened for inclusion. There were no language or publication status restrictions. The search strategy is available in Supplemental Digital Content 1, <http://links.lww.com/SLA/D136>.

Study Selection and Data Collection

Citation titles and abstracts were screened independently and in duplicate. Articles advanced to full-text review were reviewed in duplicate, independently, by the same team. Disagreements were resolved by consensus.

Relevant data were then extracted using a data extraction form (Supplemental Digital Content 2, <http://links.lww.com/SLA/D136>). The data extraction form was piloted on 5 studies; modifications were made as appropriate. Data extraction was conducted in duplicate, independently. Disagreements were resolved by consensus.

Data Items

The following variables were extracted: patient population demographics and comorbidities, intervention and comparison details, primary and secondary outcomes, protocol deviation, randomization and allocation methods, blinding, follow-up, and number of participating centers. RBC transfusions reported in mL were

converted to units by dividing by 300.²⁸ Hematocrit (%) was converted to hemoglobin (g/dL) by dividing by 3.²⁹

Study Eligibility Criteria

The population studied included adult patients undergoing surgery for any indication. The intervention of interest was the implementation of a transfusion strategy in the intraoperative period based on specified hemoglobin or hematocrit thresholds/targets, blood loss, physiological parameters, or any other predefined rules or algorithms. The comparison arm included patients undergoing surgery with a different transfusion strategy or usual care applied in the intraoperative period. Co-primary outcomes were 30-day mortality and morbidity. Secondary outcomes included intraoperative and overall incidence of RBC transfusion, postoperative hemoglobin, hospital length of stay (LOS), and intensive care unit (ICU) LOS. Postoperative hemoglobin values were recorded in the immediate postoperative period and on postoperative days 1, 2, 3, and 7.

All RCTs comparing a minimum of 2 intraoperative transfusion strategies and reporting on at least 1 outcome of interest were considered for eligibility. Studies that did not apply the transfusion strategy during the intraoperative period were excluded.

Risk of Bias and Quality Assessment

Risk of bias at the outcome level was assessed using the Revised Cochrane Risk of Bias instrument.³⁰ The instrument was applied independently by 2 reviewers. Disagreements were resolved by consensus. The quality of the results of the primary outcomes were assessed using the Grading of Recommendations Assessment, Development and Evaluation system.³¹ Publication bias was assessed using funnel plots.

Statistical Analysis

Studies were sorted into 3 hierarchies of analysis to determine the effect of the intraoperative intervention on studied outcomes. Level 1 studies only implemented an intraoperative transfusion intervention against a control, without use of a postoperative protocol (ie, usual care). Level 2 studies implemented an intraoperative transfusion intervention against a control, and implemented a common postoperative transfusion protocol in both groups. Level 3 studies implemented an intraoperative transfusion intervention against a control, and carried the different intervention and control protocols forward to the postoperative period. Studies in each hierarchy were analyzed separately.

Outcomes reported by 3 or more studies were pooled for meta-analysis. The unit of analysis was the individual study level. Principal summary measures were risk ratios and mean differences, with 95% confidence intervals (CIs), for dichotomous and continuous variables, respectively. Relative risks (RRs) were calculated as the percentage of patients with events in the restrictive group divided by the percentage of patients with events in the liberal group. Therefore, a RR greater than 1 indicates a higher risk in the restrictive group, whereas a RR less than 1 indicates a lower risk in the restrictive group. Mean difference is calculated as mean in the restrictive group minus the mean in the liberal group. A positive mean difference would, therefore, indicate a higher mean in the restrictive group, whereas a negative mean difference would indicate a lower mean in the restrictive group. Where means and standard deviations could not be extracted from included trials, they were estimated from medians and interquartile ranges using the method of Wan et al.³² Standard deviations were estimated from standard errors and CIs using standard methods.³³ Random effects models were used given expected differences between study populations, transfusion strategies, and types of surgical interventions. The I^2 statistic was used to estimate statistical heterogeneity. The threshold for interpretation was defined according to the Cochrane Handbook for Systematic Reviews of Interventions.³³

Prespecified subgroup analyses were planned for patients undergoing noncardiac surgery and for studies at low risk of bias for 30-day mortality. Further subgroup analysis for studies comparing transfusion strategies based solely on hemoglobin or hematocrit trigger values was performed for 30-day mortality. For 3-armed studies, restrictive transfusion strategies were pooled together and compared against the most liberal transfusion strategy to avoid a unit-of-analysis error. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using Review Manager 5.3.³⁴

RESULTS

Following de-duplication, 5699 studies were screened. After full text review of 49 studies, a total of 14 RCTs met eligibility criteria and were included in this review (Fig. 1).

Study Characteristics

Table 1 provides the characteristics of included trials. Overall, a total of 8641 patients were included. Five studies had under 100

patients,^{3,35–38} and 1 trial accounted for 56% of patients.³⁹ Studies were conducted in variable surgical populations: cardiac surgery (n = 6, 6709 patients, 78%),^{3,37,39–42} orthopedic surgery (n = 4, 1007 patients, 12%),^{35,43–45} vascular surgery (n = 2, 157 patients, 2%),^{36,38} oncologic surgery (n = 1, 423 patients, 5%),⁴⁶ and burn surgery (n = 1, 345 patients, 4%).⁴⁷ All trials had a traditional 2-arm parallel design except for 1.⁴⁶ Eleven studies tested restrictive hemoglobin or hematocrit triggers against liberal triggers to guide RBC transfusion. Restrictive hemoglobin transfusion triggers ranged from 7 g/dL to 9 g/dL, and liberal triggers ranged from 8.9 g/dL to 10 g/dL. Two studies utilized a perioperative transfusion trigger score to guide perioperative blood transfusion.^{42,46} This score assessed factors such as markers of cardiac ischemia and vasopressor requirement before each transfusion to allow for dynamic changes in the hemoglobin transfusion trigger point. One study compared this score against usual care,⁴² whereas the other study was a 3-armed study with a restrictive and liberal hemoglobin trigger as the other 2 arms.⁴⁶ For analysis purposes, outcome data for the perioperative transfusion trigger score group and the restrictive transfusion trigger group were

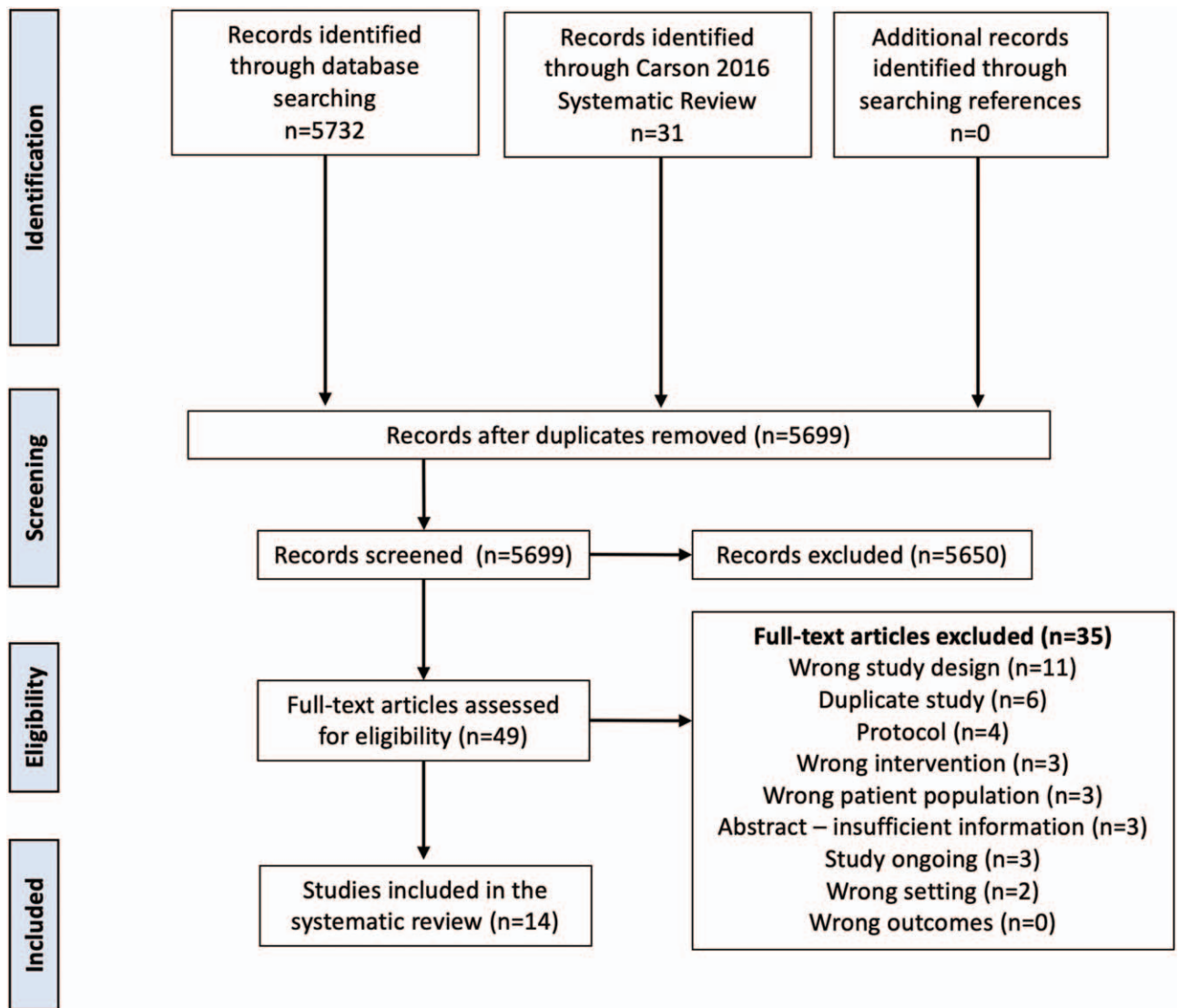


FIGURE 1. PRISMA flow diagram. PRISMA indicates preferred reporting items for systematic reviews and meta-analysis.

TABLE 1. Characteristics of Included Trials

Author, Year	Patient Population	N	Intervention	Restrictive Protocol	Liberal Protocol	Study Design	Primary Outcome(s)
Bush 1997	Vascular	99	Restrictive vs. liberal Hb trigger	Hb <9 g/dL	Hb <10 g/dL	Noninferiority	Cardiac morbidity, mortality
Grover 2006	Orthopedic	218	Restrictive versus liberal Hb trigger	Hb <8 g/dL	Hb <10 g/dL	Equivalence	Silent cardiac ischemia, mean ischemia load
Foss 2009	Orthopedic	120	Restrictive versus liberal Hb trigger	Hb <8 g/dL	Hb <10 g/dL	Superiority	Functional outcomes, anemia symptoms
Hajjar 2010	Cardiac	502	Restrictive versus liberal Hct trigger	Hct <24%	Hct <30%	Noninferiority	Composite 30 d all cause morbidity and mortality
So-Osman 2010	Orthopedic	603	New versus standard care transfusion protocol	Hb 6.4–8.9 g/dL depending on patient risk and timing from surgery	Hb 6.4–9.7 g/dL depending on patient risk and timing from surgery	Superiority	RBC transfusion, hospital LOS
Shehata 2012	Cardiac	50	Restrictive versus liberal Hb trigger	Hb <7 g/dL during CPB <7.5 g/dL after CPB	Hb <9.5 g/dL during CPB <10.0 g/dL after CPB	Pilot	Enrollment rate and overall adherence
Nielsen 2014	Orthopedic	66	Restrictive versus liberal Hb trigger	Hb <7.3 g/dL	Hb <8.9 g/dL	Superiority	Postoperative ambulation (timed up and go test)
Koch 2017	Cardiac	717	Restrictive versus liberal Hct trigger	Hct <24%	Hct <28%	Superiority	Composite in-hospital postoperative morbidity/mortality, average relative effect OR
Laine 2017	Cardiac	80	Restrictive versus liberal Hb trigger	Hb <8 g/dL	Hb <10 g/dL	Superiority	ROTEM/FibTEM coagulation parameters
Palmieri 2017	Burn	345	Restrictive versus liberal Hb trigger	Hb <7 g/dL	Hb <10 g/dL	Superiority	Blood stream infection
Mazer 2018	Cardiac	4860	Restrictive versus liberal Hb trigger	Hb <7.5 g/dL	Hb <9.5 g/dL	Noninferiority	Morbidity/mortality composite outcome (in-hospital, at 6 mo)
Møller 2019	Vascular	58	Restrictive versus liberal Hb trigger	Hb <8 g/dL	Hb <9.7 g/dL	Superiority	Mean postoperative hemoglobin (POD 0–15)
Zhang 2020	Oncologic	423	Perioperative transfusion trigger score versus restrictive Hb trigger versus liberal Hb trigger	POTTS Hb <7 g/dL	Hb <10 g/dL	Superiority	Mortality, 30 d postoperative morbidity, survival rate after discharge
Ma 2021	Cardiac	500	Cardiac perioperative transfusion trigger score versus usual care	cPOTTS	Usual care	Superiority	30-d and 1-yr mortality, perioperative ischemic cardiac events

cPOTTS indicates cardiac perioperative transfusion trigger score; FibTEM, fibrinogen-based thromboelastometry; Hb, hemoglobin; Hct, hematocrit; LOS, length of stay; OR, odds ratio; POD, postoperative day; POTTS, perioperative transfusion trigger score; RBC, red blood cell; ROTEM, rotational thromboelastometry.

combined and compared against the liberal transfusion trigger group. The restrictive and liberal hemoglobin trigger arms of this trial were included in the subgroup analysis of studies comparing hemoglobin or hematocrit triggers. One study, So-Osman et al, risk-stratified patients based on age and medical comorbidities and applied different hemoglobin triggers depending on the perioperative phase of care.⁴⁸ All intraoperative transfusion protocols were part of a broader perioperative transfusion protocol that extended to the postoperative period. In all studies, the intraoperative intervention and control transfusion protocols were carried forward to the postoperative setting. All were thus hierarchy level 3 studies and were analyzed together. None of the trials specified the timing, indication, or method of intraoperative hemoglobin testing. Study participants were individually randomized to intervention groups. There were no cluster-randomized trials.

Risk of Bias

Risk of bias assessment for included trials is presented in Supplemental Digital Content 3 and 4, <http://links.lww.com/SLA/D136>. Overall, 2 studies^{3,35} were considered to be at high risk of bias, 7 studies^{37,40,42–46} had some concerns for bias, and 5 studies^{36,38,39,41,47} were considered to be at low risk for bias. Of note, risk of bias assessment for 2 trials^{42,46} was limited due to insufficient information provided in the manuscript for aspects such as randomization, allocation concealment, protocol adherence or suspension, and blinding. Both of these papers were considered to have concerns for potential bias across multiple domains.

Table 2 describes study design and methodology. Protocol suspension and nonadherence were variably reported among included trials. These referred to transfusions given while the trial protocol was suspended during surgery or for thresholds or indications other than that specified in the trial protocol. Failure to transfuse below the allocated threshold was also considered protocol nonadherence. Six studies reported rates of protocol suspension.^{36,38–41,45} These ranged from 0.28% to 28% in restrictive arms, and 0% to 14% in liberal arms. Common reasons included uncontrolled hemorrhage, end organ ischemia, and hemodynamic instability. Six studies reported rates of protocol nonadherence.^{3,35,38,39,43,47} These ranged from 0.59% to 28% in restrictive arms, and 3.8% to 59% in liberal arms.

Primary Outcomes

Perioperative Mortality

Thirty-day postoperative mortality was reported in 12 studies (7945 patients) (Supplemental Digital Content 5, <http://links.lww.com/SLA/D136>).^{3,35,36,38–41,43–47} One study had no events in either arm and could, therefore, not be included in the analysis.³⁵ Meta-analysis demonstrated no significant difference between intervention groups (RR 0.96, 95% CI 0.71–1.29, $P = 0.77$) (Fig. 2). Statistical heterogeneity was low ($I^2 = 7\%$). This result was judged to warrant low certainty using the GRADE framework (rated down for potential bias among studies and indirectness of evidence). After examination of the corresponding funnel plot, there was no indication of publication bias.

Subgroup analysis of noncardiac surgery trials^{38,43–47} noted no significant difference in 30-day mortality (RR 1.00, 95% CI 0.51–1.98, $P = 0.99$, $I^2 = 14\%$) (Supplemental Digital Content 6, <http://links.lww.com/SLA/D136>). Subgroup analysis of studies that used hemoglobin/hematocrit transfusion triggers^{3,36,38–41,43,44,46,47} yielded similar results (RR 0.90, 95% CI 0.53–1.54, $P = 0.71$, $I^2 = 51\%$) (Supplemental Digital Content 7, <http://links.lww.com/SLA/D136>). Similarly, sensitivity analysis of studies at low risk of bias^{36,38,39,41,47} found no significant difference (RR 0.94, 95% CI

0.73–1.21, $P = 0.64$, $I^2 = 0\%$) (Supplemental Digital Content 8, <http://links.lww.com/SLA/D136>).

Perioperative Morbidity

Given the clinical heterogeneity and variable reporting of morbidity outcomes across trials, meta-analysis of overall postoperative adverse events was not performed. Many studies reported a composite outcome of mortality and major postoperative morbidity. Two trials reported a statistically significant increase in postoperative adverse events among patients in the restrictive transfusion trigger group. Foss et al,⁴³ a study of 120 patients >65 years old admitted for orthopedic surgery following a hip fracture, reported a significant increase in any cardiovascular event or death within 30 days of surgery among patients in the restrictive (8 g/dL) transfusion group. Similarly, Møller et al,³⁸ which included 58 patients undergoing vascular surgery, found that death or any major vascular complication within 90 days of the index operation was significantly higher among patients in the restrictive (8 g/dL) transfusion trigger group.

Specific postoperative morbidity outcomes reported by 3 or more studies were pooled. These included cardiac morbidity ($n = 5$, RR 1.24, 95% CI 0.88–1.75, $P = 0.22$, $I^2 = 20\%$), acute myocardial infarction ($n = 9$, RR 1.02, 95% CI 0.83–1.27, $P = 0.83$, $I^2 = 0\%$), cardiac arrhythmia ($n = 4$, RR 0.70, 95% CI 0.48–1.04, $P = 0.08$, $I^2 = 0\%$), acute kidney injury ($n = 5$, RR 0.99, 95% CI 0.92–1.08, $P = 0.88$, $I^2 = 0\%$), need for renal replacement therapy ($n = 3$, RR 0.83, 95% CI 0.61–1.13, $P = 0.84$, $I^2 = 0\%$), neurologic morbidity ($n = 3$, RR 0.86, 95% CI 0.45–1.64, $P = 0.64$, $I^2 = 0\%$), stroke ($n = 4$, RR 1.00, 95% CI 0.65–1.53, $P = 0.98$, $I^2 = 1\%$), pulmonary morbidity ($n = 5$, RR 1.00, 95% CI 0.70–1.44, $P = 0.98$, $I^2 = 20\%$), pneumonia ($n = 6$, RR 0.87, 95% CI 0.52–1.45, $P = 0.29$, $I^2 = 19\%$), infectious morbidity ($n = 6$, RR 1.03, 95% CI 0.72–1.49, $P = 0.86$, $I^2 = 51\%$), sepsis ($n = 3$, RR 1.66, 95% CI 0.33–8.41, $P = 0.54$, $I^2 = 0\%$), wound infection ($n = 5$, RR 0.82, 95% CI 0.50–1.36, $P = 0.45$, $I^2 = 0\%$), GI morbidity ($n = 3$, RR 1.08, 95% CI 0.63–1.77, $P = 0.83$, $I^2 = 0\%$), ICU LOS ($n = 6$, mean difference (MD) 0.13, 95% CI 0.02–0.25, $P = 0.02$, $I^2 = 26\%$), and hospital LOS ($n = 11$, MD –0.12, 95% CI –0.53 to 0.29, $P = 0.57$, $I^2 = 61\%$). No significant difference in any of the postoperative outcomes was identified when comparing restrictive and liberal transfusion groups (Supplemental Digital Content 9A–O, <http://links.lww.com/SLA/D136>), with the exception of ICU LOS.

Secondary Outcomes

Intraoperative Transfusion

Eight studies^{3,38–41,43,46,47} (7071 patients) were included for meta-analysis (Fig. 3). Other studies could not be included as they did not separately report patients receiving blood transfusions in the different phases of care. There were significantly fewer patients receiving intraoperative blood transfusions in the restrictive transfusion groups compared to the liberal transfusion groups (RR 0.53, 95% CI 0.43–0.64, $P < 0.00001$). Statistical heterogeneity was high ($I^2 = 89\%$). The study by Palmieri et al⁴⁷ was noted to be an outlier; when this study was removed, statistical heterogeneity decreased significantly and effect size was slightly larger ($n = 7$, RR 0.50, 95% CI 0.46–0.54, $I^2 = 25\%$). A similar effect size was noted in a subgroup analysis of noncardiac surgery trials, with high heterogeneity ($n = 4$, RR 0.54, 95% CI 0.34–0.87, $P < 0.00001$, $I^2 = 94\%$). Once again, statistical heterogeneity was driven exclusively by Palmieri et al, as when this study was removed, I^2 dropped to 0% ($n = 3$, RR 0.44, 95% CI 0.38–0.51, $I^2 = 0\%$).

Perioperative Transfusion

Data from all but 1 study³⁷ were pooled (8566 patients) (Fig. 4). The overall incidence of transfusion in the perioperative

TABLE 2. Study Design and Methodology

Author, Year	Protocol for Intraoperative Hb/Hct Monitoring	Intraoperative Transfusion Reporting	Indications for Protocol Suspension	Protocol Suspensions No. (%)	Reasons for Protocol Nonadherence	Protocol Nonadherence No. (%)
Bush 1997	NR	✓	Uncontrolled hemorrhage or evidence of MI (MI, angina, ST-segment elevation or depression, CHF)	Restrictive (n = 50) 3 (6)	NR	—
Grover 2006	If signs of hypovolemia due to blood loss	—	NR	Liberal (n = 49) Overall (n = 99)	2 (4.1) 5 (5.1)	—
Foss 2009	When excessive blood loss observed	✓	NR	—	Development of acute cardiac condition, transfer to another ward	Restrictive (n = 60) Liberal (n = 60) Overall (n = 120)
Hajjar 2010	After each transfused unit, at least 3 times in the OR	✓	Status considered to be life threatening (hemorrhagic or other forms of circulatory shock)	Restrictive (n = 249) 4 (1.6)	NR	—
So-Osman 2010	NR	—	NR	Liberal (n = 253) Overall (n = 502) Restrictive (n = 299) Liberal (n = 304) Overall (n = 603) NR	0 (0) 4 (0.80) NR NR 27 (4.5)	—
Shehata 2012	NR	✓	Rapid blood loss	—	Patient refusal, use of hemococoncentration, hemorrhage, Hct being used to transfuse, confusion about protocol, hyperkalemia, perfusionist occupied	Restrictive (n = 25) 4 (16)
Nielsen 2014	NR	✓	NR	—	Gastric bleeding, fatigue, dizziness, pallor, nausea, dyspnea, atrial fibrillation	Liberal (n = 25) Overall (n = 50) Restrictive (n = 33) 6 (18.1)
Koch 2017	NR	✓	Actively bleeding patients	Restrictive (n = 365) Liberal (n = 357) Overall (n = 722)	1 (0.28) 1 (0.27) 2 (0.28)	3 (9.1) 9 (13.6)
Laine 2017	Beginning of surgery, q30 min during CPB, q1h during surgery, immediately after transfusion	✓	NR	—	NR	—
Palmieri 2017	Within 8h of surgery, before and immediately after transfusion, within 30 min post-op	✓	NR	—	Acute intraoperative bleeding or hypotension	Restrictive (n = 168) 1 (0.59)
Mazer 2017	Preoperatively, before CPB, during CPB, after CPB, after transfusion	✓	Rapid blood loss, hemodynamic instability due to blood loss, resumed when hemostasis achieved or at a maximum of 24 h after suspension	Restrictive (n = 2430) 348 (14.3)	Transfusion given without Hb trigger being met; transfusion not initiated after trigger met or repeat Hb value above trigger not measured	Liberal (n = 177) Overall (n = 345) Restrictive (n = 2621) 117 (4.5)*
Møller 2019	q30 min during active surgical bleeding, after every transfusion	✓	Uncontrollable surgical bleeding, hypotension unresponsive to fluid replacement (MAP <65), stroke, limb/intestinal ischemia, suspected HF	Liberal (n = 2430) Overall (n = 4860) Restrictive (n = 29) 270 (11.1) 618 (12.7) 8 (28)	Transfusion at a Hb level above the allocated trigger or for indications not defined in protocol; failure to transfuse when the Hb level was below the allocated threshold	Liberal (n = 2622) Overall (n = 5243) Restrictive (n = 29) 99 (3.8)* 216 (4.1)* 8 (28)
Zhang 2020	NR	✓	NR	Liberal (n = 29) Overall (n = 58)	4 (14) 12 (20.7)	Liberal (n = 29) Overall (n = 58)
Ma 2021	NR	—	NR	—	NR	—

*Patients with <90% protocol adherence. CPB indicates cardiopulmonary bypass; Hb, hemoglobin; HD, hemodynamic; HF, heart failure; ICU, intensive care unit; MI, myocardial infarction; NR, not reported; OR, operating room; RBC, red blood cell.

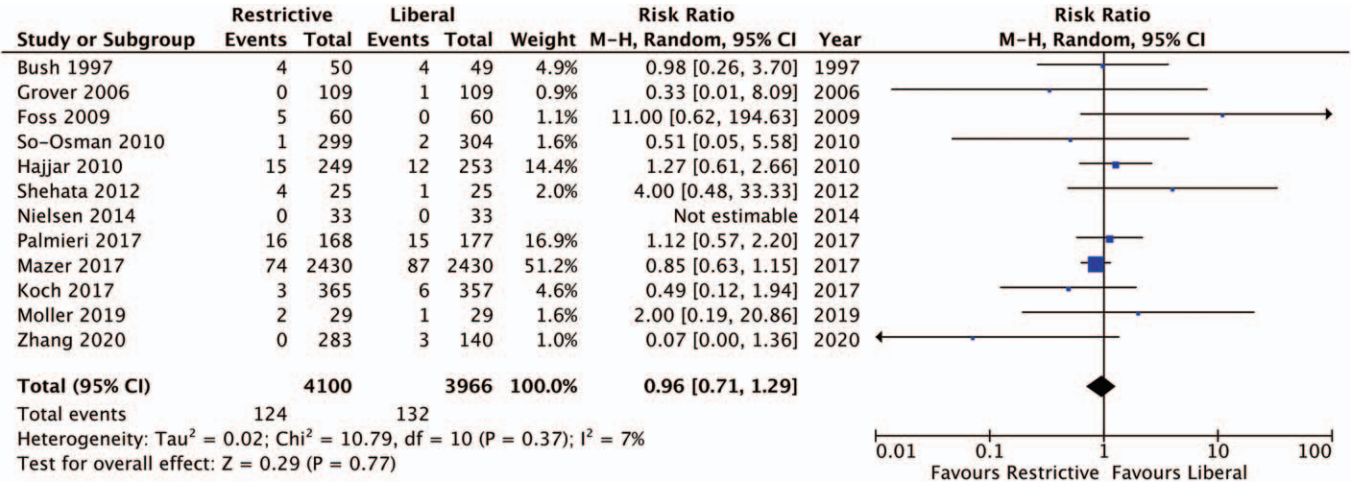


FIGURE 2. Forest plot 30-d mortality.

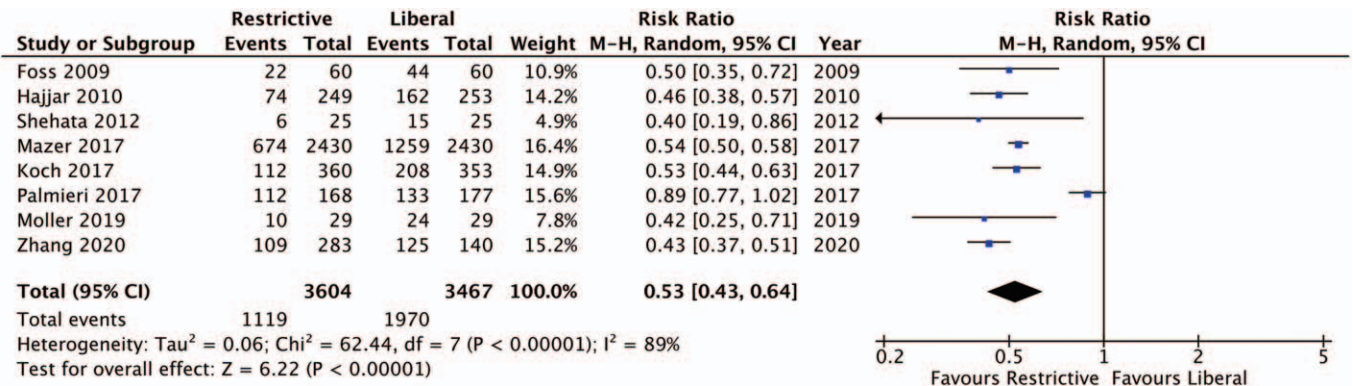


FIGURE 3. Forest plot incidence of intraoperative transfusion.

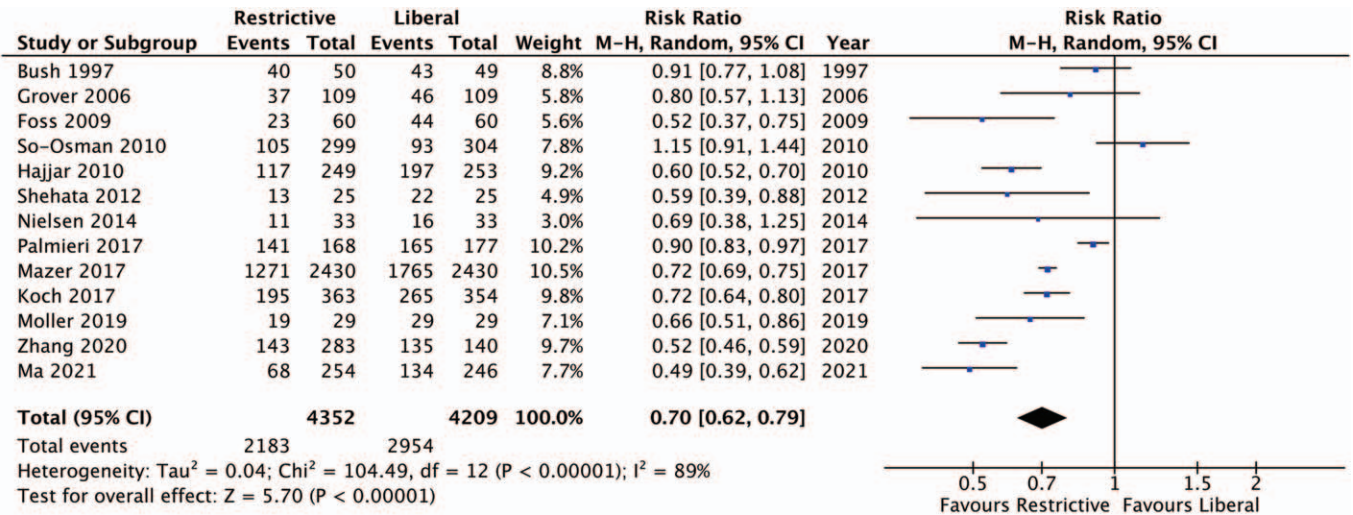


FIGURE 4. Forest plot incidence of overall transfusion.

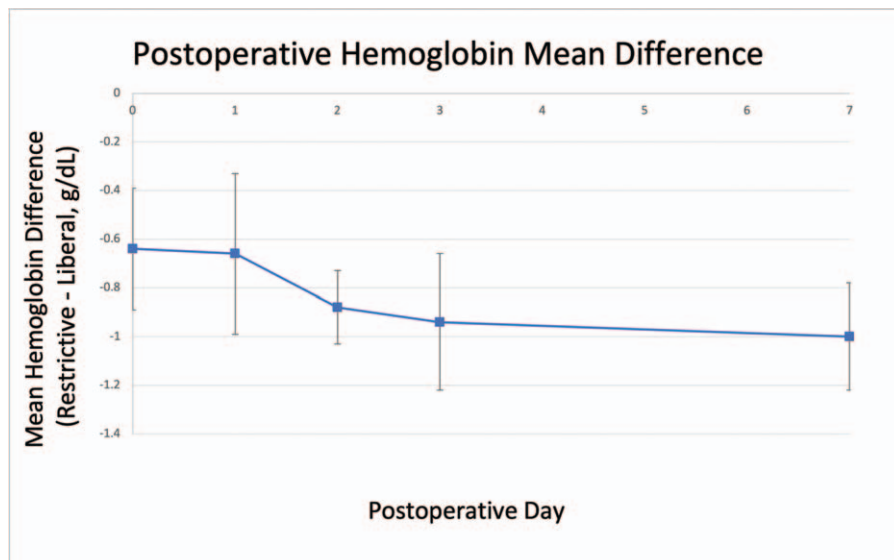


FIGURE 5. Postoperative mean hemoglobin difference.

period was significantly reduced in the restrictive transfusion protocol group (RR 0.70, 95% CI 0.62–0.79, $P < 0.00001$). Statistical heterogeneity was high ($I^2 = 89\%$). Subgroup analysis of noncardiac surgery trials yielded similar results ($n = 8$, RR 0.75, 95% CI 0.60–0.94, $P = 0.01$, $I^2 = 91\%$).

Hemoglobin

Mean hemoglobin differences were significantly lower among restrictive groups at all studied times, with mean differences of -0.64 g/dL ($n = 7$, 95% CI -0.89 to -0.39 , $P < 0.00001$, $I^2 = 79\%$) in the immediate postoperative period, -0.66 g/dL ($n = 10$, 95% CI -0.99 to -0.33 , $P = 0.0001$, $I^2 = 93\%$) on day 1, -0.88 g/dL ($n = 6$, 95% CI -1.03 to -0.73 , $P < 0.00001$, $I^2 = 40\%$) on day 2, -0.94 g/dL ($n = 6$, 95% CI -1.22 to -0.66 , $P < 0.00001$, $I^2 = 80\%$) on day 3, and -1.00 g/dL ($n = 5$, 95% CI -1.22 to -0.79 , $P < 0.00001$, $I^2 = 56\%$) on day 7 (Fig. 5, Supplemental Digital Content 10A-E, <http://links.lww.com/SLA/D136>).

DISCUSSION

This review identified 14 trials comparing transfusion strategies during the intraoperative period. Pooled data suggest that restrictive transfusion strategies decrease intraoperative and overall RBC transfusions, thereby reducing the number of patients exposed to blood products. There was no clear signal of differences in postoperative mortality or morbidity, although conclusions about the primary outcomes are limited due to the rarity of perioperative mortality events, the heterogeneity of interventions, patient populations, and morbidity outcome definitions. Furthermore, the impact of the intraoperative period on postoperative outcomes could not be determined given that all intraoperative interventions were part of a broader perioperative transfusion strategy.

The majority of eligible studies were in cardiac ($n = 6$) and orthopedic surgery ($n = 4$). There was only 1 low-quality study investigating intraoperative transfusion strategies in thoracic, general, urologic, or gynecologic surgery. This highlights a major knowledge gap in the literature, given that these specialties are frequent users of blood products and perform the bulk of oncologic operations. Transfusion strategies were categorized as restrictive or liberal, and were largely exclusively reliant on hemoglobin or hematocrit concentration. Physiologic parameters were incorporated

into the transfusion algorithm of only 2 trials, but were frequently cited as indications for protocol suspension or nonadherence.

Meta-analysis of included trials demonstrated no significant difference in 30-day mortality or any specific postoperative outcome, with the exception of ICU LOS. A small increase of 0.13 days in ICU LOS among restrictive transfusion patients was noted, although it is unlikely to be clinically significant. No study was adequately powered to detect differences in morbidity outcomes, making it challenging to meaningfully interpret the available data, especially outside of cardiac and orthopedic surgery.

Two studies reported an increased incidence in postoperative adverse events in the restrictive groups. Foss et al⁴³ reported a lower composite 30-day mortality and cardiovascular event rate within the liberal arm (2%) compared with the restrictive arm (18%) ($P < 0.01$). Møller et al³⁸ reported an increase in a composite of perioperative death and major vascular complications, noting incidences of 66% and 28% in the restrictive and liberal groups, respectively ($P = 0.003$). Finally, meta-analysis identified a nonsignificant increased risk of cardiac morbidity among patients in the restrictive strategy group (RR 1.24, 95% CI 0.88–1.75, $P = 0.22$, $I^2 = 20\%$). Further trials evaluating the safety of restrictive transfusion strategies, particularly among patients with underlying cardiovascular comorbidities who may have a higher perioperative cardiac risk, are warranted.

The incidence of RBC transfusion was significantly lower in the restrictive group compared to the liberal group. A larger effect size was observed in the intraoperative period compared to the perioperative period, with respective risk ratios of 0.53 and 0.70. This suggests that restrictive transfusion protocols can effectively reduce unnecessary transfusions during surgery. This decrease was reflected in significantly lower hemoglobin values among patients in the restrictive group compared to the liberal group throughout the postoperative period.

Protocol suspension and nonadherence were common, but variably reported. For instance, in Nielsen et al,³⁵ half of the restrictive patients who received RBC transfusions and almost one-fifth of liberal patients who received transfusions did so outside of study protocol. Reasons for nonadherence included intraoperative events such as acute surgical bleeding. Although poorly reported, the majority of these non-protocol transfusions likely occurred in the operating room as opposed to the postoperative period, where

patients were presumably more stable. The high rate of protocol suspension and nonadherence must inform future trials and suggests that intraoperative transfusion protocols should include provisions for major blood loss and anesthesiologist judgement. Despite the large number of non-protocol transfusions, intraoperative and overall blood product use was significantly lower in the restrictive group, suggesting that pragmatic restrictive transfusion rules based on hemoglobin measurement during surgery may be effective.

The current review adds to a growing body of evidence that supports restrictive transfusion strategies to avoid unnecessary RBC transfusions. These findings are largely in keeping with the aforementioned Cochrane review by Carson et al,²⁷ which found that restrictive transfusion strategies in all spheres of practice successfully decreased participants exposure to blood transfusions. There was no evidence of increased morbidity or mortality among patients transfused based on a restrictive protocol. This systematic review forms the basis of the Clinical Practice Guidelines published by the AABB.¹⁹ However, the evidence base surrounding intraoperative transfusion decision-making that is referred to in this document is very limited. Despite including 7 of the studies included in the current review, Carson et al were not specific to the operative setting. The only recommendation pertaining to surgical patients in the AABB guidelines proposes a transfusion trigger of 8 g/dL in patients “undergoing orthopedic surgery.”

Similarly, The Frankfurt Consensus Committee²² recommends a transfusion trigger of 8 g/dL in patients “with a hip fracture and cardiovascular disease,” stating that they found no increase in critical outcomes including 30-day mortality and various morbidity outcomes. It is unclear whether this recommendation is meant to encompass the intraoperative period, as the evidence base supporting this recommendation is drawn largely from the postoperative period.

The Perioperative Blood Management Guidelines published by the American Society of Anesthesiology Task Force²⁰ suggest that restrictive transfusion strategies lead to fewer blood transfusions, with equivocal findings regarding mortality and perioperative complications. They state that “the determination of whether hemoglobin concentration between 6 and 10 g/dL justify or require RBC transfusion should be based on potential or actual ongoing bleeding, intravascular volume status, signs of organ ischemia, and adequacy of cardiopulmonary reserve.” Similarly, guidelines from the European Society of Anesthesiology²¹ recommend a target hemoglobin concentration of 7–9 g/dL during active bleeding. They recommended the implementation of restrictive transfusion strategies to reduce exposure to blood products. Again, much of the evidence base supporting these recommendations is derived from the critical care literature and is not necessarily transferable to the operative setting.

The results of the current study lend support to these guidelines, but further caution against the widespread use of restrictive triggers during surgery owing to the limited number of trials conducted in the intraoperative period.

Strengths of this systematic review include its comprehensive nature and search strategy. It tackles a highly focused and important clinical question that affects millions of patients every year, and it seeks to fill a major knowledge gap in the literature that no other systematic review has directly addressed.

This study was limited by the heterogeneity of the patients populations, study interventions, and outcome reporting between trials. Although this was mitigated to some degree by using random-effects models for meta-analysis, the variability in baseline patient populations and study interventions introduced significant heterogeneity in several meta-analyses that persisted despite subgroup analysis. For example, potential for blood loss is very different among patients undergoing different operative interventions. This was illustrated when exploring heterogeneity in the intraoperative transfusion

meta-analysis, whereby excluding a study done in patients undergoing skin grafting for major burns significantly decreased statistical heterogeneity. Outcome selection was also heterogeneous between studies. In particular, definitions of postoperative adverse events were highly variable, at times precluding meaningful meta-analysis.

Moreover, despite a significant reduction in both intraoperative and postoperative RBC transfusion, mean postoperative hemoglobin differences were actually relatively small (although statistically significant at all studied points). This failure to achieve separation in postoperative hemoglobin values may be related to the fact that not all patients in a given trial would have reached a transfusion threshold, thus diluting the effect difference. That being said, this small degree of separation may also explain in part the lack of significant postoperative outcome differences between the restrictive and liberal transfusion strategy groups.

Furthermore, the definition of liberal and restrictive transfusion triggers varied considerably across included studies. Restrictive transfusion triggers ranged from hemoglobin values of 7.0 g/dL to 9.0 g/dL, whereas liberal triggers ranged from 8.9 g/dL to 10 g/dL. Many studies did not provide rationales for choosing transfusion triggers. Some studies cited previous trials such as transfusion requirements in critical care (TRICC),⁴⁹ transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS),⁵⁰ and transfusion indication threshold reduction (TITRe2)⁵¹ to justify their selection, all of which included postoperative or nonoperative patients. These results may, therefore, not be appropriately applied to patients undergoing general anesthesia with mechanical ventilation, experiencing major fluid shifts, and possibly major blood loss. It is clear that the optimal transfusion threshold to be used in the operating room has yet to be defined.

No included studies were designed to specifically address blood transfusion in the operating room. Protocols were part of a broader effort to demonstrate the safety and efficacy of restrictive transfusion programs in the perioperative period. Trials were classified into 3 hierarchies to specifically study the effect of the intraoperative intervention on the studied outcomes. All included studies fell into the third hierarchy, meaning that they implemented the same intraoperative and postoperative transfusion strategy versus a control throughout their study period. Therefore, it is impossible to tease out the effect of the intraoperative intervention on postoperative morbidity and mortality. This limits the applicability of the study results to specifically guide intraoperative transfusion decision-making.

Although all studies compared transfusion protocols incorporating hemoglobin measurements, no study reported the methods used to measure intraoperative hemoglobin. Several techniques can be used to measure hemoglobin during surgery, including central laboratory complete blood counts, blood gas analysis, and a multitude of point-of-care testing devices. The reliability and accuracy of point-of-care testing for transfusion decision-making during surgery is debated.⁵² Use of these devices may have plausibly resulted in non-protocol transfusions.

Finally, pooled analyses including data from Mazer et al³⁹ are heavily influenced by its large sample size ($n = 4860$), which may limit generalizability. Subgroup analyses performed in noncardiac surgery patients revealed similar mortality and specific morbidity results, although these may have been underpowered to detect small and medium effect size differences.

CONCLUSIONS

This review sought to compare the safety and effectiveness of intraoperative transfusion strategies in surgical patients. Currently available literature suggests that restrictive transfusion strategies are associated with fewer intra- and perioperative transfusions, without

increased morbidity or mortality in all but 2 small trials. All included trials tested transfusion protocols that carried forward to the postoperative setting, making it impossible to tease out the effect of intraoperative interventions on morbidity and mortality. Uncertainty remains regarding the safety of broad application of restrictive transfusion triggers in the operating room. Trials specifically designed to address intraoperative transfusion are urgently needed.

REFERENCES

- Ellingson KD, Sapiano MRP, Haass KA, et al. Continued decline in blood collection and transfusion in the United States-2015. *Transfusion (Paris)*. 2017;57(Suppl 2):1588–1598.
- Whitaker B. 2013 AABB blood survey report. December 2015:88. Available at: https://www.aabb.org/docs/default-source/default-document-library/resources/2013-aabb-blood-survey-report.pdf?sfvrsn=17317db0_0. Accessed May 14, 2021.
- Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. *Transfusion (Paris)*. 2012;52:91–99.
- Dhingra N. Estimate Blood Requirements – Search for a Global Standard. WHO. PDF. Presented at the Geneva. Available at: https://www.who.int/bloodsafety/transfusion_services/estimation_presentations.pdf. Accessed August 2, 2020.
- Lu Q, Zhang J, Gao W-M, et al. Intraoperative blood transfusion and postoperative morbidity following liver resection. *Med Sci Monit Int Med J Exp Clin Res*. 2018;24:8469–8480.
- Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA*. 2010;304:1568–1575.
- Osborne Z, Hanson K, Brooke BS, et al. Variation in transfusion practices and the association with perioperative adverse events in patients undergoing open abdominal aortic aneurysm repair and lower extremity arterial bypass in the vascular quality initiative. *J Vasc Surg*. 2018;67:675.
- Verlicchi F, Desalvo F, Zanotti G, et al. Red cell transfusion in orthopaedic surgery: a benchmark study performed combining data from different data sources. *Blood Transfus*. 2011;9:383–387.
- Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. *Br J Anaesth*. 2005;95:33–42.
- Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. *Blood Rev*. 2007;21:327–348.
- Bennett S, Baker LK, Martel G, et al. The impact of perioperative red blood cell transfusions in patients undergoing liver resection: a systematic review. *HPB*. 2017;19:321–330.
- Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion (Paris)*. 2010;50:753–765.
- Qian F, Osler TM, Eaton MP, et al. Variation of blood transfusion in patients undergoing major noncardiac surgery. *Ann Surg*. 2013;257:266–278.
- Chen A, Trivedi AN, Jiang L, et al. Hospital blood transfusion patterns during major noncardiac surgery and surgical mortality. *Medicine (Baltimore)*. 2015;94:e1342.
- Ejaz A, Spolverato G, Kim Y, et al. Variation in triggers and use of perioperative blood transfusion in major gastrointestinal surgery. *Br J Surg*. 2014;101:1424–1433.
- Wennberg JE. Unwarranted variations in healthcare delivery: implications for academic medical centres. *BMJ*. 2002;325:961–964.
- Partington A, Chew DP, Ben-Tovim D, et al. Screening for important unwarranted variation in clinical practice: a triple-test of processes of care, costs and patient outcomes. *Aust Health Rev Publ Aust Hosp Assoc*. 2017;41:104–110.
- Harrison R, Manias E, Mears S, et al. Addressing unwarranted clinical variation: a rapid review of current evidence. *J Eval Clin Pract*. 2019;25:53–65.
- Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*. 2016;316:2025–2035.
- American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists task force on perioperative blood management. *Anesthesiol J Am Soc Anesthesiol*. 2015;122:241–275.
- Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update. *Eur J Anaesthesiol EJA*. 2017;34:332.
- Patient Blood Management: Recommendations from the 2018 Frankfurt Consensus Conference. Available at: <https://jamanetwork-com.proxy.bib.uot-tawa.ca/journals/jama/fullarticle/2727453>. Accessed July 13, 2020.
- Bennett S, Ayoub A, Tran A, et al. Current practices in perioperative blood management for patients undergoing liver resection: a survey of surgeons and anesthesiologists: transfusion in liver resection. *Transfusion (Paris)*. 2018;58:781–787.
- Baker L, Park L, Gilbert R, et al. Intraoperative red blood cell transfusion decision-making: a systematic review of guidelines. *Ann Surg*. 2021;274:86–96.
- Barash P. *Clinical Anesthesia Fundamentals*. Philadelphia, PA: Lippincott Williams & Wilkins; 2015.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2016;10:CD002042.
- Elzik ME, Dirschl DR, Dahners LE. Correlation of transfusion volume to change in hematocrit. *Am J Hematol*. 2006;81:145–146.
- Quintó L, Aponte JJ, Menéndez C, et al. Relationship between haemoglobin and haematocrit in the definition of anaemia. *Trop Med Int Health TM IH*. 2006;11:1295–1302.
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898.
- GRADEpro GDT, McMaster University and Evidence Prime Inc. Available at: <https://gradepro.org/>. Accessed May 14, 2021.
- Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
- Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.2. The Cochrane Collaboration; 2021. Available at: www.handbook.cochrane.org.
- Review Manager, Cochrane RevMan. Available at: <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>. Accessed May 14, 2021.
- Nielsen K, Johansson PI, Dahl B, et al. Perioperative transfusion threshold and ambulation after hip revision surgery—a randomized trial. *BMC Anesthesiol*. 2014;14:89.
- Bush RL, Pevco WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am J Surg*. 1997;174:143–148.
- Laine A, Niemi T, Schramko A. Transfusion threshold of hemoglobin 80 g/l is comparable to 100 g/l in terms of bleeding in cardiac surgery: a prospective randomized study. *J Cardiothorac Vasc Anesth*. 2018;32:131–139.
- Møller A, Nielsen HB, Wetterslev J, et al. Low vs high hemoglobin trigger for transfusion in vascular surgery: a randomized clinical feasibility trial. *Blood*. 2019;133:2639–2650.
- Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med*. 2017;377:2133–2144.
- Koch CG, Sessler DI, Mascha EJ, et al. A randomized clinical trial of red blood cell transfusion triggers in cardiac surgery. *Ann Thorac Surg*. 2017;104:1243–1250.
- Hajjar LA, Vincent J-L, Galas FRBG, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*. 2010;304:1559–1567.
- Ma H-P, Zhang L, Chen C-L, et al. Evaluation of a novel cardiac peri-operative transfusion trigger scoring system in patients with coronary artery disease. *BMC Cardiovasc Disord*. 2021;21:40.
- Foss NB, Kristensen MT, Jensen PS, et al. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion (Paris)*. 2009;49:227–234.
- Grover M, Talwalkar S, Casbard A, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Vox Sang*. 2006;90:105–112.
- So-Osman C, Nelissen R, Brand R, et al. The impact of a restrictive transfusion trigger on post-operative complication rate and well-being following elective orthopaedic surgery: a post-hoc analysis of a randomised study. *Blood Transfus*. 2013;11:289–295.

46. Zhang F, Zheng Z-B, Zhu Z-Q, et al. Application of perioperative transfusion trigger score in patients undergoing surgical treatment of malignant tumor. *Indian J Hematol Blood Transfus.* 2020;36:156–163.
47. Palmieri TL, Holmes JH, Arnoldo B, et al. Transfusion requirement in burn care evaluation (TRIBE): a multicenter randomized prospective trial of blood transfusion in major burn injury. *Ann Surg.* 2017;266:595–602.
48. So-Osman C, Nelissen R, Te Slaa R, et al. A randomized comparison of transfusion triggers in elective orthopaedic surgery using leucocyte-depleted red blood cells. *Vox Sang.* 2010;98:56–64.
49. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med.* 1999;340:409–417.
50. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med.* 2011;365:2453–2462.
51. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med.* 2015;372:997–1008.
52. Rice MJ, Gravenstein N, Morey TE. Noninvasive hemoglobin monitoring: how accurate is enough? *Anesth Analg.* 2013;117:902–907.