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REVIEW

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Impact of restrictive red blood cell transfusion strategy on thrombosis-related events: A meta-analysis and systematic review

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Abstract

Background and Objectives: There is an ongoing controversy regarding the risks of restrictive and liberal red blood cell (RBC) transfusion strategies. This meta-analysis assessed whether transfusion at a lower threshold was superior to transfusion at a higher threshold, with regard to thrombosis-related events, that is, whether these outcomes can benefit from a restrictive transfusion strategy is debated.

Materials and Methods: We searched PubMed, Cochrane Central Register of Controlled Trials and Scopus from inception up to 31 July 2021. We included randomized controlled trials (RCTs) in any clinical setting that evaluated the effects of restrictive versus liberal RBC transfusion in adults. We used random-effects models to calculate the risk ratios (RRs) and 95% confidence intervals (CIs) based on pooled data.

Results: Thirty RCTs involving 17,334 participants were included. The pooled RR for thromboembolic events was 0.65 (95% CI 0.44–0.94; $p = 0.020$; $I^2 = 0.0\%$, very low-quality evidence), favouring the restrictive strategy. There were no significant differences in cerebrovascular accidents (RR = 0.83; 95% CI 0.64–1.09; $p = 0.180$; $I^2 = 0.0\%$, very low-quality evidence) or myocardial infarction (RR = 1.05; 95% CI 0.87–1.26; $p = 0.620$; $I^2 = 0.0\%$, low-quality evidence). Subgroup analyses showed that a restrictive (relative to liberal) strategy reduced (1) thromboembolic events in RCTs conducted in North America and (2) myocardial infarctions in the subgroup of RCTs where the restrictive transfusion threshold was 7 g/dl but not in the 8 g/dl subgroup (with a liberal transfusion threshold of 10 g/dl in both subgroups).

Conclusions: A restrictive (relative to liberal) transfusion strategy may be effective in reducing venous thrombosis but not arterial thrombosis.

KEYWORDS
cerebrovascular accidents, myocardial infarction, restrictive, thromboembolism, transfusion strategy

Highlights

- A restrictive red blood cell transfusion strategy significantly reduced the risk of thromboembolic events, although the Grading of Recommendations Assessment, Development and Evaluation quality of evidence was very low.
- For cerebrovascular accidents and myocardial infarction, there were no statistically significant differences between restrictive and liberal transfusion strategies.
- Subgroup analyses showed that the restrictive (relative to liberal) transfusion strategy reduced (1) thromboembolic events in trials conducted in North America and (2) myocardial infarctions in the subgroup of trials where the restrictive transfusion threshold was 7 g/dl but not in the 8 g/dl subgroup (with a liberal transfusion threshold of 10 g/dl in both subgroups).

INTRODUCTION

Red blood cell (RBC) transfusion can increase or maintain oxygen levels in tissues [1], improving anaemia, which can save lives [2, 3]. However, transfusion is associated with several adverse events, such as thromboembolism [4, 5], cerebrovascular accidents [6] and myocardial infarction [1, 7]. The mechanisms behind these adverse events include increased circulating RBC mass [1], increased oxidative stress [4], reduced nitric oxide and/or increased inflammatory mediators [6]. Consequently, an appropriate transfusion strategy should be used to reduce the adverse events.

Haemoglobin or haematocrit thresholds are commonly used when deciding whether to perform a transfusion. The most commonly used trigger for transfusion in the twentieth century was haemoglobin of 10 g/dl or haematocrit of 30% [8]. However, several transfusion guidelines suggest that a restrictive transfusion strategy (haemoglobin <7 or 8 g/dl) is suitable in most clinical settings [9–11]. Nevertheless, whether a restrictive transfusion strategy reduces thrombosis-related events compared to a liberal one remains controversial, with some reviews indicating no significant differences [11–14] and others indicating that restrictive strategies decrease cerebrovascular accidents but increase myocardial infarction [15–17]. However, most of these reviews included only a few randomized controlled trials (RCTs) or evaluated composite outcomes.

In order to conduct a comprehensive meta-analysis comparing the restrictive and liberal transfusion strategies with regard to thrombosis-related events in adults, we included all available RCTs reporting these outcomes. In addition, we also performed various subgroup analyses, such as comparing outcomes between different restrictive transfusion thresholds (with a fixed liberal transfusion threshold) and among study areas, which were rarely considered in other meta-analyses.

MATERIALS AND METHODS

Search strategy

We searched PubMed, Cochrane Central Register of Controlled Trials and Scopus from inception to 31 July 2021, using ([blood transfusion*] OR [red blood cell] or RBC or transfus* or haemoglobin) AND (trigger* OR threshold* OR liberal OR restrict* OR strateg*) AND ([randomized controlled trial*] OR [controlled clinical trial*] OR [clinical trial*] OR [randomized trial*] OR trial*). We checked the references of included RCTs for additional relevant articles. The complete search strategy is provided in the Supplementary Material. After records were imported into the EndNote software, duplicate records were removed. Two reviewers (M.M. and C.X.Z.) independently screened the titles and abstracts of the relevant studies. Thereafter, full-text versions were retrieved to further assess eligibility. Disagreements were settled by discussing with other reviewers (J.G.X., Z.C.Z., H.D.L. and O.C.O.).

Study selection

The eligibility criteria were (1) RCT, (2) compared liberal and restrictive transfusion strategies, (3) reported thrombosis-related events and (4) patients aged ≥16 years. For RCTs that generated multiple publications, we excluded duplicate patients and outcome data.

Data extraction

Two authors (M.M. and C.X.Z.) independently extracted information about the first author, year of publication, study area (continent where the patients were recruited from), sample size, transfusion thresholds, demographics, medications and clinical outcomes using a data extraction form. Disagreements were resolved based on reaching a consensus among all authors.

Outcome definitions

Thrombosis-related events can occur in veins or arteries. For venous thrombosis, we included thromboembolic events comprising deep vein thrombosis, pulmonary embolism and thromboembolism. For arterial thrombosis, we included cerebrovascular accidents (stroke or transient ischaemic attack, cerebrovascular attack or cerebral

ischaemia) and myocardial infarction (myocardial infarction, acute myocardial infarction, acute myocardial ischaemia or stent thrombosis). Detailed definitions are provided in Table S1.

Risk of bias and quality

Two authors (M.M. and C.X.Z.) independently assessed the risk of bias (RoB) in the outcomes in the RCTs (categorized as 'low', 'some concerns' or 'high') using the revised Cochrane RoB tool (RoB 2) [18, 19]. As the assessment of each RoB domain for each included outcome in any given RCT was the same, we present the RoB results by RCT instead of by outcome in each RCT. The following domains were assessed: randomization process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result.

We also assessed the overall quality of evidence of each outcome (categorized as 'very low', 'low', 'moderate' or 'high') using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [20].

Statistical analysis

Mantel–Haenszel risk ratios (RRs) with 95% confidence intervals (CIs) were calculated based on pooled data. Thereafter, we performed subgroup analyses by clinical setting, transfusion threshold, transfusion timing (intra- and post-operatively, peri-operatively, post-operatively or during the hospital/intensive care unit [ICU] stay), transfusion type (leucocyte-reduced or non-leucocyte-reduced RBCs) and study area (continent where the patients were recruited from). To test for statistical heterogeneity, I^2 (50% or 85% indicates moderate or substantial heterogeneity, respectively) and χ^2 ($p < 0.05$ indicates significant heterogeneity) were calculated. Random-effect models were used to account for clinical heterogeneity. Several sensitivity analyses were performed to explore various aspects of the trials and review methodology. First, we excluded each trial one at a time and recalculated the pooled effects. Excluding one trial at a time can help investigate how each individual study affects the overall effect size and identify influential studies. Second, we excluded trials with high RoB. Third, we excluded trials from each clinical setting (ICU treatment, cardiac surgery, orthopaedic surgery, vascular surgery, upper gastrointestinal bleeding treatment and cancer treatment) in turn. Fourth, we limited the analysis to trials using specific transfusion thresholds (restrictive transfusion threshold [RTT] = 7, RTT > 7 g/dl, RTT = 7 or 8 g/dl with liberal transfusion threshold [LTT] = 9 g/dl, RTT = 7 or 8 g/dl with LTT = 10 g/dl). Fifth, we excluded trials that involved transfusion during the hospital/ICU stay without a clear indication of transfusion timing. Sixth, we excluded trials that did not report on transfusion type (i.e., whether the RBC transfusion was leucocyte-reduced) and trials that involved either leucocyte-reduced or non-leucocyte-reduced RBCs. Seventh, we excluded trials from each continent in turn.

Funnel plots and Egger's regression were used to assess publication bias. The analyses were performed in Stata 14.0 and Review Manager 5.3.

RESULTS

Included RCTs

The search strategy (Figure S1) identified 2358 articles. After removing duplicates, there were 1750 articles. After screening the titles/abstracts, 119 were selected to be reviewed in full. Thirty RCTs (described in Tables 1 and S2), with 17,334 participants (8576 in restrictive groups and 8637 in liberal groups) were included [21-50]. The RCTs were published between 1992 and 2021. The mean age ranged from 35 to 82.3 years.

Clinical settings varied: 10 involved patients undergoing cardiac surgery [27, 32–35, 37, 40, 47–49], 7 involved patients undergoing orthopaedic surgery [23, 24, 26, 38, 45, 46, 50], 7 involved patients treated in ICUs [21, 22, 25, 28, 29, 39, 42], 3 involved patients undergoing vascular surgery [31, 36, 44], 2 involved patients with upper gastrointestinal bleeding [30, 41] and 1 involved patients undergoing cancer treatment [43]. Additionally, 23 RCTs included cardiovascular disease as a baseline characteristic [21–24, 26–30, 32, 35–38, 40, 42, 44–50], 12 excluded patients with anaemia or bleeding [21, 26–29, 41, 42, 45–49], 1 excluded patients with too high transfusion rate [22] and 1 included patients with high transfusion rates [40].

Regarding RTT and LTT, the haemoglobin RTT ranged from 7.0 to 9.0 g/dl [21–26, 28–30, 33–47, 49, 50], with four additional RCTs specifying haematocrit values of 24% or 25% [27, 31, 32, 48]. The haemoglobin LTT ranged from 8.5 to 10.0 g/dl [21–26, 28–30, 33–47, 49, 50], with four additional RCTs specifying haematocrit values of 28%, 30% or 32% [27, 31, 32, 48]. In four RCTs, transfusion was also permitted for symptoms of anaemia in the restrictive group [45–47, 50]. RCTs were divided into the following pairs of subgroups based on RTT alone or RTT plus LTT: (1) RTT = 7 g/dl versus RTT > 7 g/dl; (2) RTT = 7 g/dl and LTT = 9 g/dl versus RTT = 8 g/dl and LTT = 9 g/dl and (3) RTT = 7 g/dl and LTT = 10 g/dl versus RTT = 8 g/dl and LTT = 10 g/dl.

Specific transfusion timing was reported in 13 RCTs: 3 transfused intra- and post-operatively [35, 40, 44]; 6 transfused post-operatively [31, 33, 36, 37, 45, 46] and 4 transfused peri-operatively [23, 27, 34, 43]. For the remaining RCTs, 12 transfused during the hospital/ICU stay [21, 22, 25, 28, 29, 32, 39, 41, 42, 47–49] and the transfusion timing was not reported by the others [24, 26, 30, 38, 50]. Regarding transfusion type, 12 RCTs used leucocyte-reduced RBCs [21, 22, 26, 29, 36, 39, 41, 42, 46–49], 4 used non-leucocyte-reduced RBCs [23, 25, 27, 28] and the remaining 14 did not provide this information [24, 30–35, 37, 38, 40, 43–45, 50]. Regarding the study area, 12 RCTs were conducted in Europe [23, 24, 26, 29, 30, 34, 36–38, 41, 42, 49], 9 in North America [28, 31, 33, 39, 40, 44, 46–48], 4 in South America [21, 22, 25, 27], 2 in Asia [43, 50] and the remaining 3 recruited patients across several different continents [32, 35, 45].

TABLE 1 Characteristics of included randomized controlled trials

Author (year)	Country	Patient type	Setting	Period	Baseline characteristics	Restrictive threshold (g/dl)	Liberal threshold (g/dl)
Almeida (2015)	Brazil	Surgical oncology	ICU	2012	Age ≥ 18; CVD; cancer; surgery; tobacco use, hypertension, diabetes (excluded pre-existing coagulopathy or anticoagulation therapy, anaemia, and active bleeding)	7	9
Bergamin (2017)	Brazil	Cancer with septic shock	ICU	2012–2014	Age ≥ 18; CVD; cancer; infection; smoking, hypertension, diabetes (excluded patients with too high a transfusion rate)	7	9
Bracey (1999)	USA	Elective primary CABG surgery	Cardiac	1997	Surgery	8	9
Bush (1997)	USA	Elective aortic or infrainguinal arterial reconstruction	Vascular	1995–1996	CVD; surgery; smoking, hypertension, diabetes	9	10
Carson (1998)	USA, UK	Hip fracture	Orthopaedic	1996–1997	Hb < 10 g/dl; CVD; surgery; diabetes (excluded anaemia)	8	10
Carson (2011)	USA, Canada	Hip fracture	Orthopaedic	2004–2009	Age ≥ 50; Hb < 10 g/dl; CVD; surgery; tobacco use, hypertension, diabetes (excluded anaemia and active bleeding)	8	10
Carson (2013)	USA	Coronary syndrome or stable coronary artery disease undergoing catheterization	Cardiac	2010–2012	Age ≥ 18; Hb < 10 g/dl; CVD; surgery; tobacco use, hypertension, diabetes (excluded anaemia and active bleeding)	8	10
Cooper (2011)	USA	AMI	Cardiac	2003–2009	Age ≥ 21; haematocrit ≤ 30%; CVD; surgery; tobacco use, hypertension, diabetes (excluded active bleeding)	24%[a]	30%
Ducrocq (2021)	France, Spain	AMI and anaemia	Cardiac	2016–2019	Age ≥ 18; Hb: 7–10 g/dl; CVD; tobacco use, hypertension, diabetes (excluded massive ongoing bleeding)	8	10
Fan (2014)	China	Total hip replacement	Orthopaedic	2011–2013	Age > 65; CVD; surgery; hypertension, diabetes	8	10
Foss (2009)	Denmark	Hip fracture	Orthopaedic	2004–2006	Age > 65; CVD; surgery; hypertension, diabetes	8	10
Gillies (2020)	UK	Surgery for fractured neck of femur	Orthopaedic	2017–2019	Age ≥ 50; CVD; surgery; hypertension, diabetes	7	9
Gobatto (2019)	Brazil	Moderate or severe traumatic brain injury	ICU	2014–2016	Age > 18; Hb < 9 g/dl; trauma	7	9
Grover (2006)	UK	Elective total knee or hip arthroplasty	Orthopaedic	Not mentioned	Age ≥ 55; CVD; surgery; smoking, hypertension, diabetes (excluded anaemia)	8	10
Hajjar (2010)	Brazil	Elective cardiac surgery	Cardiac	2009–2010	Age ≥ 18; CVD; surgery; smoking, hypertension, diabetes (excluded anaemia)	24%	30%
Hebert (1999)	Canada	Critically ill with euvolemia	ICU	1994–1997	Age ≥ 16; Hb < 9 g/dl; CVD; trauma; infection (excluded anaemia and active bleeding)	7	10

(Continues)

TABLE 1 (Continued)

Author (year)	Country	Patient type	Setting	Period	Baseline characteristics	Restrictive threshold (g/dl)	Liberal threshold (g/dl)
Holst (2014)	Denmark, Sweden, Norway, Finland	Septic shock	ICU	2011–2013	Age ≥ 18; Hb < 9 g/dl; CVD; surgery; infection (excluded life-threatening bleeding)	7	9
Jairath (2015)	UK	Acute upper gastrointestinal bleeding	Upper gastrointestinal bleeding	2012–2013	Age ≥ 18; CVD; acute upper gastrointestinal bleeding; hypertension (excluded exsanguinating haemorrhage)	8	10
Johnson (1992)	USA	Elective operations for myocardial revascularization	Vascular	Not mentioned	Surgery	25%	32%
Koch (2017)	USA, India	Cardiac surgery	Cardiac	2007–2014	Age ≥ 18; CVD; surgery; smoking, hypertension, diabetes	24%	28%
Laine (2017)	Finland	Elective open-heart surgery	Cardiac	2014–2015	Surgery	8	10
Mazer (2017)	19 countries	CABG and/or valve	Cardiac	2014–2017	Age ≥ 18; CVD; surgery; diabetes	7.5	8.5, 9.5
Møller (2019)	Denmark	Elective open infra-renal abdominal aortic aneurysm repair or lower-limb bypass	Vascular	2015–2016	Age > 40; CVD; surgery; smoking, hypertension, diabetes	8	9.7
Murphy (2015)	UK	CABG and/or valve or major aortic procedure	Cardiac	2009–2013	Age > 16; CVD; surgery; diabetes	7.5	9
Nielsen (2014)	Denmark	Hip revision surgery	Orthopaedic	2009–2011	Age ≥ 18; CVD; surgery; smoking, hypertension, diabetes	7.3	8.9
Robertson (2014)	USA	Closed head injury	ICU	2006–2012	Trauma; surgery; no comorbidities reported	7	10
Shehata (2012)	Canada	Elective cardiac surgery	Cardiac	2007–2010	CVD; surgery; hypertension, diabetes; high transfusion rates	7, 7.5	9.5, 10
Villanueva (2013)	Spain	Upper gastrointestinal bleeding	Upper gastrointestinal bleeding	2003–2009	Age > 18; upper gastrointestinal bleeding (excluded massive exsanguinating bleeding, major CVD or a recent history of trauma or surgery)	7	9
Walsh (2013)	UK	Mechanically ventilated	ICU	2009–2010	Age ≥ 55; Hb < 9 g/dl; CVD (excluded active bleeding)	7	9
Zhang (2020)	China	Cancer surgery	Oncologic	2012–2016	Hb < 10 g/dl; surgery; cancer	7	10

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CVD, cardiovascular disease; Hb, haemoglobin; ICU, intensive care unit.
[a]Transfusion was indicated by haematocrit value.

Outcomes

Thromboembolic events

Based on 13 RCTs (3976 participants) reporting on thromboembolic events, the risk was significantly lower in the restrictive group than the liberal group (RR = 0.65; 95% CI 0.44–0.94; $p = 0.020$; Figure 1). Study heterogeneity was not significant ($\chi^2 = 10.79$; degrees of freedom [df] = 12 [$p = 0.55$]; $I^2 = 0.0\%$). Subgroup analyses were then performed. Regarding the clinical setting, there was no significant difference in thromboembolic events between the two transfusion strategies in any clinical setting subgroup assessed (Figure S2).

Regarding transfusion threshold, there was no significant difference in thromboembolic events between the two transfusion strategies in the RTT = 7 g/dl or RTT > 7 g/dl subgroups (Figure S3). However, the risk of thromboembolic events was significantly lower in the restrictive (relative to liberal) transfusion group in the RTT = 7 g/dl and LTT = 10 g/dl subgroup (RR = 0.37; 95% CI 0.17–0.79; Figure S4) but not the RTT = 8 g/dl and LTT = 10 g/dl subgroup; nevertheless, there was only one RCT included in the former subgroup.

Regarding transfusion timing, no significant difference was observed in thromboembolic events between the two transfusion strategies in the intra- and post-operative, peri-operative or post-operative subgroups (Figure S5). Regarding transfusion type, there was no significant difference in thromboembolic events between the two transfusion strategies in the non-leucocyte-reduced or leucocyte-reduced RBC subgroups (Figure S6). Lastly, regarding the study area, there were fewer thromboembolic events in the restrictive (relative to liberal) group in trials conducted in North America (RR = 0.50; 95% CI 0.28–0.87; Figure S7) but not in trials conducted in Europe, South America and Asia.

Sensitivity analysis showed that, after removing the trial by Robertson et al. [39] or Jairath et al. [30], there was no longer a significant difference in thromboembolism between the restrictive and liberal groups. Likewise, there was no longer a significant difference in thromboembolism after removing trials involving ICU treatment, orthopaedic surgery, or upper gastrointestinal bleeding treatment, or after limiting the analysis to trials reporting on transfusion timing (intra- and post-operative, peri-operative or post-operative), trials reporting on transfusion type (leucocyte-reduced or non-leucocyte-reduced RBCs) and non-North American trials. Limiting the analysis to trials involving 'low'/'some concerns' RoB; RTT = 7 or 8 g/dl with LTT = 10 g/dl; and RTT = 7 g/dl and LTT = 10 g/dl maintained the significant decrease in thromboembolism for the restrictive (relative to liberal) strategy.

Cerebrovascular accidents

Based on 21 RCTs (14,509 participants) reporting on cerebrovascular accidents, the risk did not differ by restrictive versus liberal strategy (RR = 0.83; 95% CI 0.64–1.09; $p = 0.180$) (Figure 2). Study heterogeneity was not significant ($\chi^2 = 13.47$; df = 20 [$p = 0.860$]; $I^2 = 0.0\%$). There were no differences in cerebrovascular accidents between the transfusion strategies in any of the subgroup analyses (Figures S8–S14).

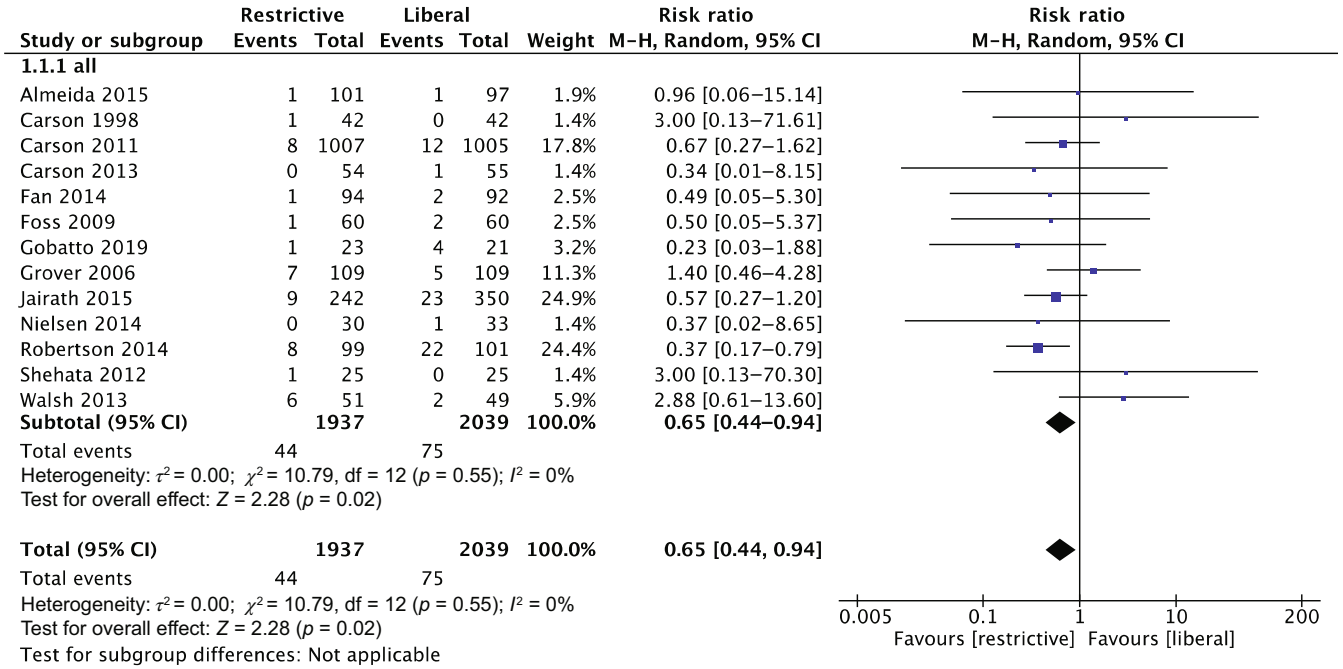

FIGURE 1 Comparison of thromboembolic events between restrictive and liberal transfusion strategies in randomized controlled trials (RCTs). Size of squares for risk ratio reflects weight of RCT in pooled analysis. Horizontal bars represent 95% confidence intervals (CIs). Risk ratio >1.0 favours liberal transfusion strategy. df, degrees of freedom; M–H, Mantel–Haenszel; Random, random-effects model

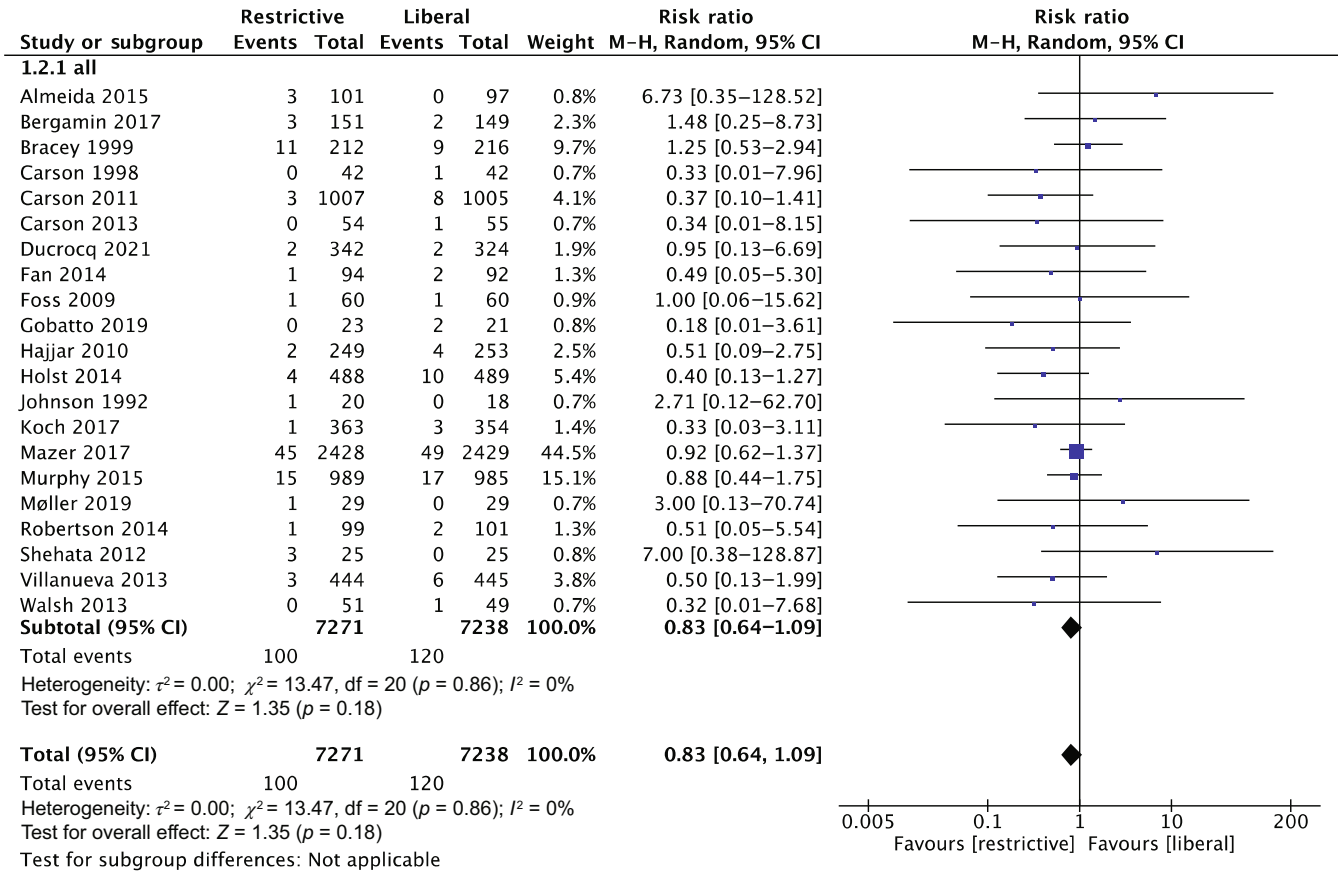

FIGURE 2 Comparison of cerebrovascular accidents between restrictive and liberal transfusion strategies in randomized controlled trials (RCTs). Size of squares for risk ratio reflects weight of RCT in pooled analysis. Horizontal bars represent 95% confidence intervals (CIs). Risk ratio >1.0 favours liberal transfusion strategy. df, degrees of freedom; M–H, Mantel–Haenszel; Random, random-effects model

The risk of cerebrovascular accidents became significantly lower in the restrictive (relative to liberal) group when limiting that analysis to trials that reported on transfusion type (leucocyte-reduced or non-leucocyte-reduced RBCs); however, removing trials involving either leucocyte-reduced RBCs or non-leucocyte-reduced RBCs resulted in no significant difference. Other sensitivity analyses for cerebrovascular accidents did not differ from the overall pooled results.

The difference in myocardial infarction between the restrictive and liberal groups was still non-significant when limiting the analysis to trials involving RTT = 7 or 8 g/dl with LTT = 10 g/dl, but further limiting the analysis to trials involving RTT = 7 g/dl and LTT = 10 g/dl showed that the restrictive (relative to liberal) group had a significantly reduced risk of myocardial infarction. Other sensitivity analyses for myocardial infarction did not show differences from the overall pooled results.

Myocardial infarction

Based on 25 RCTs (14,829 participants) reporting on myocardial infarction, the risk did not differ by restrictive versus liberal strategy (RR = 1.05; 95% CI 0.87–1.26; $p = 0.620$) (Figure 3). Study heterogeneity was not significant ($\chi^2 = 21.13$; df = 22 [$p = 0.510$]; $I^2 = 0\%$). The risk of myocardial infarction was significantly lower in the restrictive (relative to liberal) transfusion group in the RTT = 7 g/dl and LTT = 10 g/dl subgroup (RR = 0.32; 95% CI 0.11–0.93) but not in the RTT = 8 g/dl and LTT = 10 g/dl subgroup (Figure S18). Regarding the other subgroup analyses, there were no differences in myocardial infarction between the transfusion strategies (Figures S15–S17 and S19–S21).

RoB and quality

Twenty trials (66.7%) had 'some concerns' or 'high' RoB [21, 23, 24, 26, 29–33, 35–38, 40, 41, 43, 46, 47, 49, 50] (Figures 4 and 5). The main category for some concerns and high RoB was deviations from intended interventions, which included lack of blinding of participants, caregivers or outcome assessors (as the nature of blood transfusion makes it hard to blind them) and insufficient information provided about the appropriateness of the analysis. The GRADE quality of evidence was judged to be 'very low' for thromboembolic events and cerebrovascular accidents, and 'low' for myocardial infarction (Figure 6). The reasons included inadequate blinding, large variation in effect and the small number of events.

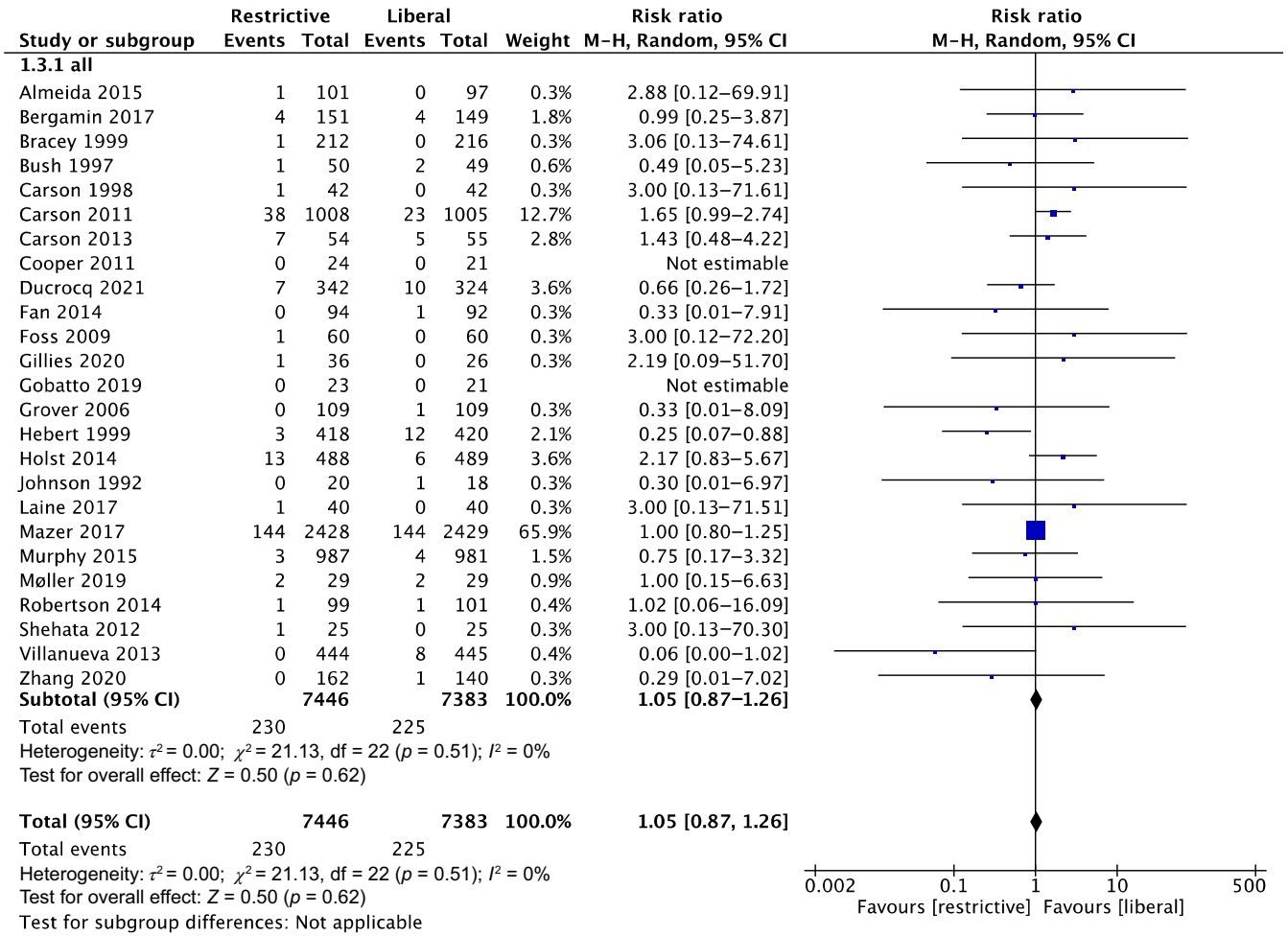

FIGURE 3 Comparison of myocardial infarction between restrictive and liberal transfusion strategies in randomized controlled trials (RCTs). Size of squares for risk ratio reflects weight of RCT in pooled analysis. Horizontal bars represent 95% confidence intervals (CIs). Risk ratio >1.0 favours liberal transfusion strategy. df, degrees of freedom; M–H, Mantel–Haenszel; Random, random-effects model

Publication bias

Regarding thromboembolic events and cerebrovascular accidents, no publication bias was found according to the funnel plots or Egger's test (Figures S22 and S23). However, the funnel plot for myocardial infarction showed slight asymmetry (Figure S24), suggesting publication bias. Nevertheless, Egger's test for myocardial infarction was not significant ($p = 0.578$). Overall, the publication bias regarding this outcome appears to be small.

DISCUSSION

Our meta-analysis of 30 RCTs compared thrombosis-related complications between restrictive and liberal transfusion strategies. The incidence of thromboembolic events was lower in the restrictive (relative to liberal) transfusion group, but there were no differences in cerebrovascular accidents or myocardial infarction.

A 2016 Cochrane review reported that restrictive transfusion strategies decrease the proportion of transfused patients across many clinical settings without worsening clinical outcomes [51]. Similar statements were made by Brunskill et al. [15] and Shehata et al. [52] in their systematic reviews of transfusion thresholds for patients with hip fractures and patients undergoing cardiac surgery, respectively. The findings of these reviews suggested that restrictive transfusion strategies can also effectively reduce adverse events, such as mortality and infections.

Our meta-analysis focused on the effects of transfusion strategies on thrombosis-related events. Several meta-analyses have assessed the effects of different transfusion strategies on thromboembolic events in various clinical settings [12, 15, 51, 53–55]. For example, one found no difference in venous thromboembolism between transfusion strategies in adult and paediatric patients (RR = 0.76; 95% CI 0.41–1.41; $p = 0.920$) [12]. A study of hip fracture patients also reported no significant difference in thromboembolism between transfusion strategies (RR = 1.15; 95% CI 0.56–2.37; $p = 0.710$) (based on low-quality evidence) [15]. Another study on hip fracture patients similarly reported no difference in thromboembolic events between transfusion strategies (RR = 0.71; 95% CI 0.34–1.45; $p = 0.350$) [53]. However, these reviews included studies other than

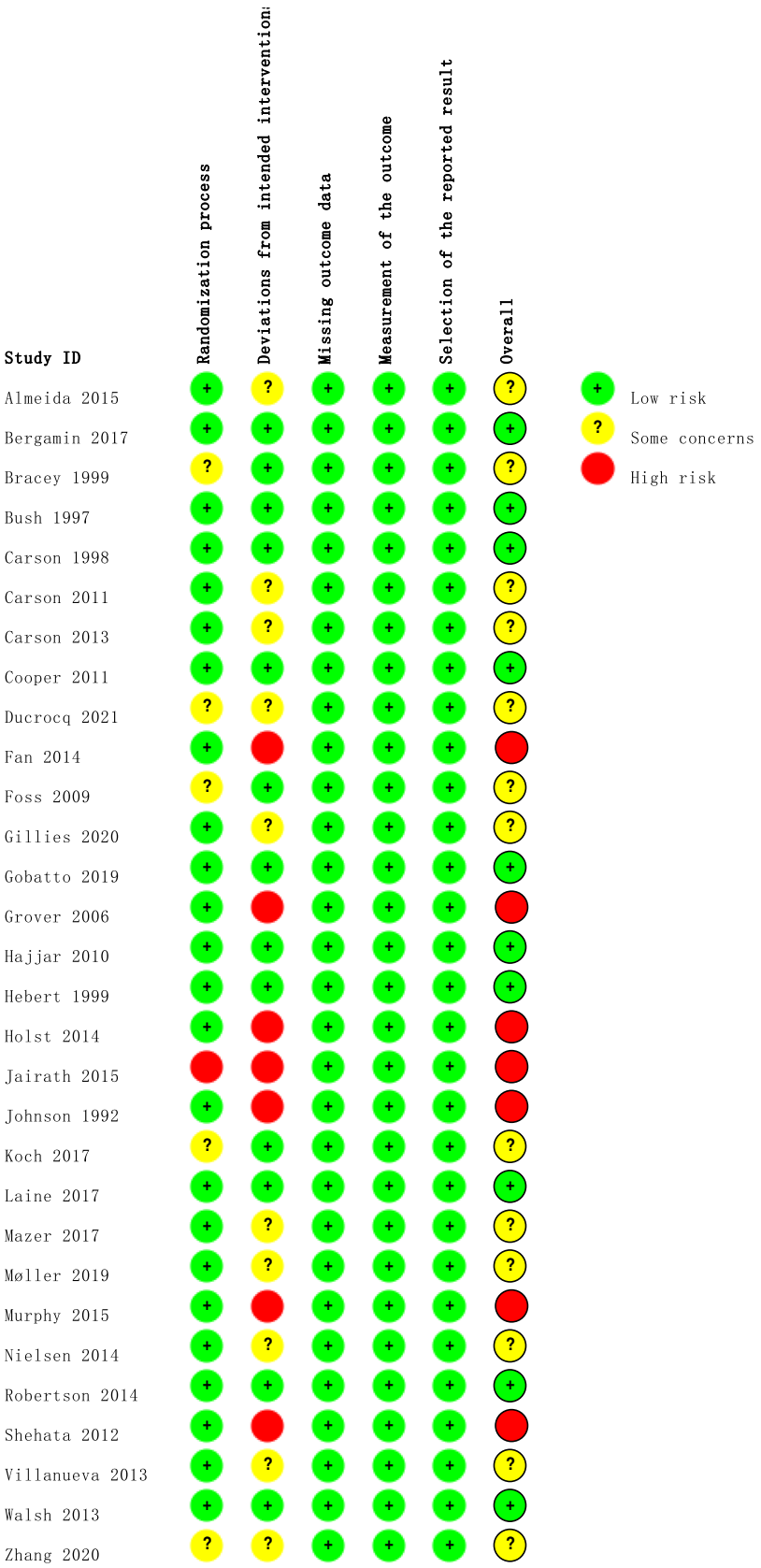

FIGURE 4 Risk of bias assessment of included randomized controlled trials

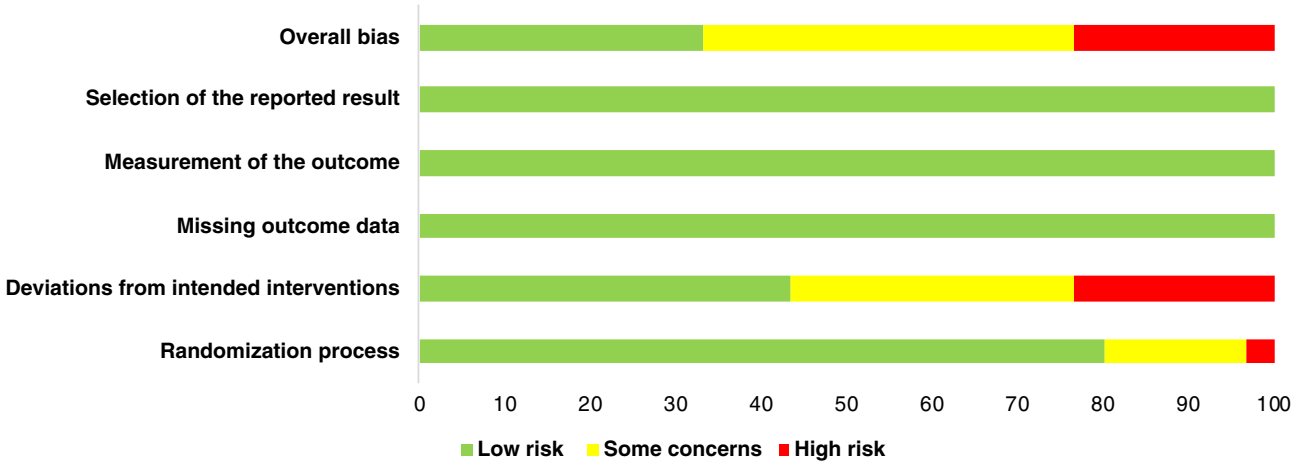

FIGURE 5 Risk of bias summary

Summary of findings:

Restrictive transfusion strategy compared to liberal transfusion strategy in adult patients

Patient or population: adult patients
Setting: inpatient
Intervention: restrictive transfusion strategy
Comparison: liberal transfusion strategy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with liberal transfusion strategy	Risk with restrictive transfusion strategy				
Thromboembolic events	37 per 1000	**24 per 1,000** (16–35)	**RR 0.65** (0.44–0.94)	3976 (13 RCTs)	⨁◯◯◯ VERY LOW a,b,c	
Cerebrovascular accidents	17 per 1000	**14 per 1,000** (11–18)	**RR 0.83** (0.64–1.09)	14,509 (21 RCTs)	⨁◯◯◯ VERY LOW a,b,c	
Myocardial infarction	30 per 1000	**32 per 1,000** (27–38)	**RR 1.05** (0.87–1.26)	14,829 (25 RCTs)	⨁⨁◯◯ LOW a,b	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI, confidence interval; **RR,** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Most studies were not adequately blinded (including participants, personnel, and outcome assessors).
b. Point estimates varied widely across studies.
c. The small number of events occurred in two transfusion groups.

FIGURE 6 Summary of findings (including Grading of Recommendations Assessment, Development and Evaluation [GRADE] quality of evidence) in included randomized controlled trials

RCTs, and some of the included RCTs did not report specific haemoglobin- or haematocrit-based transfusion thresholds. We found a lower risk of thromboembolic events with the restrictive strategy (RR = 0.65; 95% CI 0.44–0.94; $p = 0.020$). RBC transfusions may result in thrombosis by altering the rheologic variables and due to the infusion of pro-inflammatory and pro-thrombotic microparticles [56]; thus, lowering the transfusion threshold may reduce the risk. Subgroup analysis also showed that a restrictive (relative to liberal)

strategy reduced thromboembolic events in RCTs conducted in North America (RR = 0.50; 95% CI 0.28–0.87; $p = 0.010$). The incidence of venous thrombosis varies among ethnic groups, with lower rates in Asians, Pacific Islanders and Hispanics than in Whites in the United States [57]. However, the association between transfusion strategies and ethnicity needs further investigation. Nevertheless, we should be cautious when interpreting the effect of a restrictive strategy on thromboembolic events. Sensitivity analyses showed that there was no longer a difference in thromboembolism between the restrictive and liberal groups after excluding the trial by Robertson et al. [39] (conducted in the United States) or Jairath et al. [30] (conducted in the United Kingdom).

We found no significant difference in cerebrovascular accidents between the restrictive and liberal strategies (RR = 0.83; 95% CI 0.64–1.09; $p = 0.180$). Curley et al. [58] reported that transfusion threshold was not associated with the risk of stroke among five RCTs (RR = 1.15; 95% CI 0.57–2.32; $p = 0.510$). Likewise, there was no significant difference in cerebrovascular accidents between restrictive and liberal strategies in cardiac patients [59] (RR = 0.97; 95% CI 0.72–1.30; $p = 0.840$); however, the review included only seven RCTs and used neurological complications as the cerebrovascular accident outcome. In contrast to other reviews, a review by Chong et al. [17] found that restrictive transfusion strategies were associated with fewer cerebrovascular accidents in critically ill patients based on six included RCTs (OR = 0.63; 95% CI 0.40–0.99; $p = 0.040$).

We also found that a restrictive strategy did not significantly affect myocardial infarction (RR = 1.05; 95% CI 0.87–1.26; $p = 0.620$), which is supported by previous meta-analyses [52, 59, 60]. Chen et al. [59] demonstrated that there was no difference in acute myocardial infarction between restrictive and liberal strategies in patients undergoing cardiac surgery. Similarly, Simon et al. [60] found no significant difference in myocardial infarction between the two transfusion strategies in older patients. However, Yao et al. [61] found that the incidence of myocardial infarction was lower with a restrictive (relative to liberal) transfusion strategy in ICU patients (OR = 0.54; 95% CI 0.30–0.98; $p = 0.040$). One of their included RCTs, conducted by Villanueva et al. [41], had only a small percentage of patients who were admitted to the ICU, despite the study having the greatest weight in the meta-analysis. After removing this study, the significant positive effect of the restrictive transfusion strategy on myocardial infarction in the review [61] became non-significant, indicating the instability of the effect.

Regarding transfusion type, we found no difference in the risk of thrombosis-related events between the transfusion strategies in either the leucocyte-reduced or non-leucocyte-reduced RBC subgroups. Regarding study area, the restrictive (relative to liberal) transfusion strategy reduced the risk of thromboembolic events in North America. This may have occurred because different areas have different ethnic groups who had varying levels of thrombosis risks after transfusion [57], different transfusion guidelines were employed in different regions and/or the perception of the risk of transfusion varied across areas [62–65].

Our meta-analysis has several strengths. First, we conducted a comprehensive search for RCTs that reported on thrombosis-related events (thromboembolic events, cerebrovascular accidents and myocardial infarction), which have not been fully analysed in previous meta-analyses [17, 55]. Second, we included the five most recent RCTs (published in 2019–2021) conducted in patients with traumatic brain injury [25], patients undergoing vascular surgery [36], patients in orthopaedic units [24], patients with acute myocardial infarction and anaemia [49] and patients undergoing cancer treatment [43]. Lastly, we used the latest Cochrane RoB tool, RoB 2, to evaluate RoB.

Our meta-analysis also has several limitations. First, the included RCTs had different RTTs; most were based on haemoglobin level, while some were based on haematocrit level. Furthermore, the RTTs varied among RCTs, even though they were based on haemoglobin level. Most trials used RTTs of 7–8 g/dl, but others used higher RTTs, potentially causing clinical heterogeneity. Second, the participants came from various clinical settings, leading to different tolerances for transfusion strategies. Third, thrombosis-related complications (such as thromboembolic events) were pre-specified as outcomes in only 25 of the 30 RCTs. Fourth, the definitions and follow-up time of each outcome varied across trials. Lastly, the transfusion timing (intra-operative, post-operative and during hospital/ICU stay) differed among the RCTs.

In conclusion, this meta-analysis demonstrated that restrictive transfusion strategies had a lower risk of thromboembolic events. The incidences of cerebrovascular accidents and myocardial infarction were unaffected by the transfusion strategy. Subgroup analyses indicated that restrictive (relative to liberal) strategies led to (1) fewer thromboembolic events in RCTs conducted in North America and (2) fewer myocardial infarctions in the RTT = 7 g/dl and LTT = 10 g/dl subgroup but not in the RTT = 8 g/dl and LTT = 10 g/dl subgroup. Restrictive (relative to liberal) transfusion strategies may be effective at reducing venous thrombosis but not arterial thrombosis. Other interventions are needed to reduce the incidence of thrombosis-related complications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation. 2007;116:2544–52.

2. Li Y, Cheang I, Zhang Z, Zuo X, Cao Q, Li J. Prognostic association between perioperative red blood cell transfusion and postoperative cardiac surgery outcomes. Front Cardiovasc Med. 2021;8:1–8.
3. World Health Organization The clinical use of blood [cited 2021 Dec 31]. Available from: https://www.who.int/bloodsafety/clinical_use/en/Handbook_EN.pdf
4. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008;168:2377–81.
5. Neumayer LA. Association between venous thromboembolism and perioperative allogeneic transfusion: commentary. Arch Surg. 2007;142:126–32.
6. Mariscalco G, Biancari F, Juvonen T, Zanobini M, Cottini M, Banach M, et al. Red blood cell transfusion is a determinant of neurological complications after cardiac surgery. Interact Cardiovasc Thorac Surg. 2015;20:166–71.
7. Bursi F, Barbieri A, Politi L, Di Girolamo A, Malagoli A, Grimaldi T, et al. Perioperative red blood cell transfusion and outcome in stable patients after elective major vascular surgery. Eur J Vasc Endovasc Surg. 2009;37:311–8.
8. Nicol G, Hunt E, Manji M. When to give blood. Dent Traumatol. 2001;3:221–33.
9. World Health Organization Clinical transfusion practice: guidelines for medical interns [cited 2021 Dec 31]. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/bloodsafety/transfusion_services/ClinicalTransfusionPracticeGuidelinesforMedicalInternsBangladesh.pdf
10. Baciewicz FA. Blood transfusion. J Thorac Cardiovasc Surg. 2020;159:e85.
11. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016;316:2025–35.
12. Desborough MJR, Colman KS, Prick BW, Duvekot JJ, Sweeney C, Odutayo A, et al. Effect of restrictive versus liberal red cell transfusion strategies on haemostasis: systematic review and meta-analysis. Thromb Haemost. 2017;117:889–98.
13. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JAC, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol. 2015;2:e543–53.
14. Kheiri B, Abdalla A, Osman M, Haykal T, Chintalapati S, Cranford J, et al. Restrictive versus liberal red blood cell transfusion for cardiac surgery: a systematic review and meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2019;47:179–85.
15. Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev. 2015;CD009699.
16. Gu WJ, Gu XP, Wu XD, Chen H, Kwong JSW, Zhou LY, et al. Restrictive versus liberal strategy for red blood-cell transfusion: a systematic review and meta-analysis in orthopaedic patients. J Bone Joint Surg. 2018;100:686–95.
17. Chong MA, Krishnan R, Cheng D, Martin J. Should transfusion trigger thresholds differ for critical care versus perioperative patients? A meta-analysis of randomized trials. Crit Care Med. 2018;46:252–63.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
19. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC, et al. Assessing risk of bias in a randomized trial. Cochrane handbook for systematic reviews of interventions 2nd edition. 2019;205–28. Chichester, UK: John Wiley & Sons.
20. Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Completing 'summary of findings' tables and grading the certainty of the evidence. Cochrane handbook for systematic reviews of interventions; 2019;2:375–402. Chichester, UK: John Wiley & Sons.
21. De Almeida JP, Vincent JL, Galas FRBG, De Almeida EPM, Fukushima JT, Osawa EA, et al. Transfusion requirements in surgical oncology patients: a prospective, randomized controlled trial. Anesthesiology. 2015;122:29–38.
22. Bergamin FS, Almeida JP, Landoni G, Galas FRBG, Fukushima JT, Fominskiy E, et al. Liberal versus restrictive transfusion strategy in critically III oncologic patients: the transfusion requirements in critically III oncologic patients randomized controlled trial. Crit Care Med. 2017;45:766–73.
23. Foss NB, Kristensen MT, Jensen PS, Palm H, Krasheninnikoff M, Kehlet H. The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. Transfusion. 2009;49:227–34.
24. Gillies MA, Ghaffar S, Moppett IK, Docherty AB, Clarke S, Rea N, et al. A restrictive versus liberal transfusion strategy to prevent myocardial injury in patients undergoing surgery for fractured neck of femur: a feasibility randomised trial (RESULT-NOF). Br J Anaesth. 2021;126:77–86.
25. Gobatto ALN, Link MA, Solla DJ, Bassi E, Tierno PF, Paiva W, et al. Transfusion requirements after head trauma: a randomized feasibility controlled trial. Crit Care. 2019;23:1–10.
26. Grover M, Talwalkar S, Casbard A, Boralessa H, Contreras M, Boralessa H, et al. Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. Vox Sang. 2006;90:105–12.
27. Hajjar LA, Vincent JL, Galas FRBG, Nakamura RE, Silva CMP, Santos MH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010;304:1559–67.
28. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340:409–17.
29. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371:1381–91.
30. Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet. 2015;386:137–44.
31. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg. 1992;104:307–14.
32. Koch CG, Sessler DI, Mascha EJ, Sabik JF, Li L, Duncan AI, et al. A randomized clinical trial of red blood cell transfusion triggers in cardiac surgery. Ann Thorac Surg. 2017;104:1243–50.
33. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion. 1999;39:1070–7.
34. 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;32:131–9.
35. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.
36. Møller A, Nielsen HB, Wetterslev J, Pedersen OB, Hellemann D, Winkel P, et al. Low vs high hemoglobin trigger for transfusion in vascular surgery: a randomized clinical feasibility trial. Blood. 2019;133:2639–50.
37. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372:997–1008.
38. Nielsen K, Johansson PI, Dahl B, Wagner M, Frausing B, Børglum J, et al. Perioperative transfusion threshold and ambulation after hip revision surgery – a randomized trial. BMC Anesthesiol. 2014;14:1–9.

39. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC, et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA. 2014;312:36–47.
40. Shehata N, Burns LA, Nathan H, Hebert P, Hare GMT, Fergusson D, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion. 2012;52:91–9.
41. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21.
42. Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med. 2013;41:2354–63.
43. Zhang F, Zheng ZB, Zhu ZQ, Liu DX, Liu J. Application of perioperative transfusion trigger score in patients undergoing surgical treatment of malignant tumor. Indian J Hematol Blood Transfus. 2020;36:156–63.
44. Bush RL, Pevec WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. Am J Surg. 1997;174:143–8.
45. Carson JL, Terrin ML, Barton FB, Aaron R, Greenburg AG, Heck DA, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. Transfusion. 1998;38:522–9.
46. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011;365:2453–62.
47. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, et al. Coronary artery disease liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013;165:964–971.e1.
48. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol. 2011;108:1108–11.
49. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical rrial. JAMA. 2021;325:552–60.
50. Fan YX, Liu FF, Jia M, Yang JJ, Shen JC, Zhu GM, et al. Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: a preliminary study. Arch Gerontol Geriatr. 2014;59:181–5.
51. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016;CD002042.
52. Shehata N, Mistry N, Da Costa BR, Pereira TV, Whitlock R, Curley GF, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. Eur Heart J. 2019;40:1081–8.
53. Zhu C, Yin J, Wang B, Xue Q, Gao S, Xing L, et al. Restrictive versus liberal strategy for red blood-cell transfusion in hip fracture patients: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98:e16795.
54. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ. 2015;350:h1354.
55. Müller S, Oberle D, Drechsel-Bäuerle U, Pavel J, Keller-Stanislawski B, Funk MB. Mortality, morbidity and related outcomes following perioperative blood transfusion in patients with major orthopaedic surgery: a systematic review. Transfus Med Hemother. 2018;45:355–67.
56. Goel R, Patel EU, Cushing MM, Frank SM, Ness PM, Takemoto CM, et al. Association of perioperative red blood cell transfusions with venous thromboembolism in a North American Registry. JAMA Surg. 2018;153:826–33.
57. Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol. 2007;44:62–9.
58. Curley GF, Shehata N, Mazer CD, Hare GMT, Friedrich JO. Transfusion triggers for guiding RBC transfusion for cardiovascular surgery: a systematic review and meta-analysis. Crit Care Med. 2014;42:2611–24.
59. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. Crit Care. 2018;22:1–9.
60. Simon GI, Craswell A, Thom O, Fung YL. Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials: a systematic review and meta-analysis. Lancet Haematol. 2017;4:e465–74.
61. Yao RQ, Ren C, Zhang ZC, Zhu YB, Xia ZF, Yao YM. Is haemoglobin below 7.0 g/dL an optimal trigger for allogenic red blood cell transfusion in patients admitted to intensive care units? A meta-analysis and systematic review. BMJ Open. 2020;10:e030854.
62. Badenes R, Oddo M, Suarez JI, Antonelli M, Lipman J, Citerio G, et al. Hemoglobin concentrations and RBC transfusion thresholds in patients with acute brain injury: an international survey. Crit Care. 2017;21:1–10.
63. Franchini M, Marano G, Mengoli C, Pupella S, Vaglio S, Muñoz M, et al. Red blood cell transfusion policy: a critical literature review. Blood Transfus. 2017;15:307–17.
64. Merz EM, Zijlstra BJH, de Kort WLAM. Perceived blood transfusion safety: a cross-European comparison. Vox Sang. 2016;110:258–65.
65. Vincent JL, Jaschinski U, Wittebole X, Lefrant JY, Jakob SM, Almekhlafi GA, et al. Worldwide audit of blood transfusion practice in critically ill patients. Crit Care. 2018;22:1–9.

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