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REVIEW ARTICLE/BRIEF REVIEW

The effect of restrictive *versus* liberal transfusion strategies on longer-term outcomes after cardiac surgery: a systematic review and meta-analysis with trial sequential analysis

Effet des stratégies de transfusion restrictives *vs* libérales sur les devenirs à plus long terme après une chirurgie cardiaque : une revue systématique et méta-analyse avec analyse séquentielle des études

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Abstract

Purpose *Blood transfusions are frequently administered in cardiac surgery. Despite a large number of published studies comparing a "restrictive" strategy with a "liberal" strategy, no clear consensus has emerged to guide blood transfusion practice in cardiac surgery patients. The purpose of this study was to identify, critically appraise, and summarize the evidence on the overall effect of restrictive transfusion strategies compared with liberal transfusion strategies on mortality, other clinical outcomes, and transfusion-related outcomes in adult patients undergoing cardiac surgery.*

Source *We searched MEDLINE (OvidSP), EMBASE (OvidSP) and Cochrane CENTRAL (Wiley) from inception to 1 December 2017 and queried clinical trial registries and conference proceedings for randomized-controlled trials of liberal vs restrictive transfusion strategies in cardiac surgery.*

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Principal findings *From 7,908 citations, we included ten trials (9,101 patients) and eight companion publications. Overall, we found no significant difference in mortality between restrictive and liberal transfusion strategies (risk ratio [RR], 1.08; 95% confidence interval [CI], 0.76 to 1.54; I^2 = 33%; seven trials; 8,661 patients). The use of a restrictive transfusion strategy did not appear to adversely impact any of the secondary clinical outcomes. As expected, the proportion of patients who received red blood cells (RBCs) in the restrictive group was significantly lower than in the liberal group (RR, 0.68; 95% CI, 0.64 to 0.73; I^2 = 56%; 5 trials; 8,534 patients). Among transfused patients, a restrictive transfusion strategy was associated with fewer transfused RBC units per patient than a liberal transfusion strategy.*

Conclusions *In adult patients undergoing cardiac surgery, a restrictive transfusion strategy reduces RBC transfusion without impacting mortality rate or the incidence of other perioperative complications. Nevertheless, further large trials in subgroups of patients, potentially of differing age, are needed to establish firm evidence to guide transfusion in cardiac surgery.*

Trial registration *PROSPERO (CRD42017071440); registered 20 April, 2018.*

Résumé

Objectif *Les transfusions sanguines sont fréquentes après une chirurgie cardiaque. Malgré le nombre important d'études publiées comparant une stratégie « restrictive » à une stratégie « libérale », aucun consensus clair n'est apparu pour guider la pratique de la transfusion sanguine chez les patients de chirurgie cardiaque. L'objectif de cette étude était d'identifier, d'évaluer de façon critique et de résumer les données probantes sur l'effet global des stratégies de transfusion restrictives comparativement aux stratégies libérales sur la mortalité, les autres devenirs cliniques, et les devenirs liés à la transfusion chez des patients adultes subissant une chirurgie cardiaque.*

Source *Nous avons réalisé des recherches dans les bases de données MEDLINE (OvidSP), EMBASE (OvidSP) et Cochrane CENTRAL (Wiley) de leur création jusqu'au 1er décembre 2017 et avons exploré les registres d'études cliniques et les actes de conférence pour en tirer les études randomisées contrôlées évaluant des stratégies transfusionnelles restrictives vs libérales en chirurgie cardiaque.*

Constatations principales *Sur 7908 citations, nous avons inclus dix études (9101 patients) et huit publications connexes. Globalement, nous n'avons observé aucune différence significative en matière de mortalité entre les stratégies transfusionnelles restrictives et libérales (risque relatif [RR], 1,08; intervalle de confiance [IC] 95 %, 0,76 à 1,54; I^2 = 33 %; sept études; 8661 patients). Le recours à une stratégie de transfusion restrictive n'a semblé avoir aucun impact négatif sur quelque résultat clinique secondaire que ce soit. Comme anticipé, la proportion de patients ayant reçu des érythrocytes dans le groupe restrictif était significativement plus basse que dans le groupe libéral (RR, 0,68; IC 95 %, 0,64 à 0,73; I^2 = 56 %; 7 études; 8534 patients). Parmi les patients transfusés, une stratégie de transfusion restrictive a été associée à un nombre moindre d'unités d'érythrocytes transfusées par patient que dans une stratégie transfusionnelle libérale.*

Conclusion *Dans une population de patients adultes subissant une chirurgie cardiaque, une stratégie transfusionnelle restrictive réduit la transfusion d'érythrocytes sans avoir d'impact sur le taux de mortalité ou sur l'incidence d'autres complications périopératoires. D'autres grandes études sur différents sous-groupes de patients, peut-être d'âges différents, sont toutefois nécessaires afin d'établir des données probantes concluantes pour guider les transfusions en chirurgie cardiaque.*

Enregistrement de l'étude *PROSPERO (CRD42017071440); enregistrée le 20 avril 2018.*

Blood transfusions are frequently administered in cardiac surgery with more than 50% of patients receiving a perioperative transfusion.[1] Red blood cell (RBC) transfusions are typically administered to improve oxygen delivery to tissues in situations of anemia or hemorrhage. Under certain conditions (e.g., hemorrhage), RBC transfusion can be lifesaving.[2] Nevertheless, there are risks associated with blood transfusions including acute kidney injury, viral transmission of infection, acute lung injury, and allergic reactions, amongst many others.[3–5] In addition to the adverse events associated with blood transfusion and patient safety, the cost issues are also relevant. In the United States, the estimated price of the transfusion of a unit of blood, when all the activities involved in the blood transfusion are taken into account, is between $700 and $1,200.[6]

Several randomized-controlled trials (RCTs) have compared a restrictive strategy (i.e., RBC transfusion at lower hemoglobin [Hb] concentration or hematocrit [Hct]), with a liberal strategy (i.e., RBC transfusion at a higher Hb concentration or Hct). Results of recently conducted RCTs are inconsistent, including the Transfusion Indication Threshold Reduction (TITRe2) (n = 2,007)[7] and Transfusion Requirements in Cardiac Surgery (TRICS) III (n = 5,243)[8] trials. Accordingly, several systematic

reviews (SRs) and meta-analyses (MAs) have also been published to summate the data and propose meaningful conclusions comparing restrictive and liberal strategies in cardiac surgery. Nevertheless, each of these SR-MAs had important limitations.

Several recent SR-MAs on these transfusion strategies in cardiac surgery[9–11] have focused on the 30-day mortality outcomes in their included trials and did not address the longer follow-up which differed significantly compared with shorter-term outcomes. For example, the 30-day mortality in the TITRe2 trial[7] was not significantly different between restrictive and liberal groups, but the 90-day results showed significantly higher mortality in the restrictive group.

In addition, there was no published protocol or registration for any of these SRs.[9–11] Registering an SR protocol is important as it enables the promotion of transparency and avoidance of potential biases including both selection and selective outcome reporting biases.[12] Therefore, there was a need for an updated and unbiased review on the effectiveness and safety of RBC transfusions in cardiac surgery settings.

Accordingly, we conducted this present SR-MA, including a trial sequential analysis (TSA), using the longest follow-up data from the largest most recently published RCTs to identify, critically appraise, and summarize the evidence on the overall effect of restrictive transfusion strategies compared with liberal transfusion strategies on mortality and other clinical outcomes in adult patients undergoing cardiac surgery.

Methods

Our SR-MA was conducted and reported in accordance with the Methodological Expectations of Cochrane Interventional Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[13,14] The protocol was registered with PROSPERO prior to the start of the review (CRD42017071440) on 20 April 2018.

Search strategy

With assistance from an information specialist (C.N.), we constructed a comprehensive search strategy that was peer-reviewed using the PRESS checklist[15] (available as Electronic Supplementary Material [ESM]). We also reviewed the references of all identified trials and relevant review articles for additional trials (hand-searching for longer follow-ups of included trials, and contacting authors of included studies to find any similar unpublished studies). We searched MEDLINE (OvidSP), EMBASE (OvidSP), and Cochrane Central Register of Clinical Trials (CENTRAL - Wiley), from inception to 1 December 2017. The ESM outlines the complete search strategy used for each database. A separate, supplementary search of clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform was conducted to identify ongoing or unpublished trials.

Eligibility criteria

We included parallel group RCTs of adult patients (≥ 18 yr old) who underwent cardiac surgery with cardiopulmonary bypass (CPB). Patients in the intervention (restrictive) group had to receive RBC transfusion at a lower Hb concentration or Hct level than the comparator (liberal) group, with the various thresholds defined by each study. We excluded observational, quasi-randomized, cross-over, and cluster-randomized trials.

Review outcomes

The primary outcome of our review was mortality at the longest reported follow-up. Our secondary outcomes included: 1) proportion of patients with new onset myocardial infarction (MI), as defined by each study; 2) proportion of patients requiring renal replacement therapy/new onset hemodialysis; 3) proportion of patients with new onset focal neurologic deficit; 4) intensive care unit (ICU) length of stay (LOS) (days); 5) hospital LOS (days); and 6) days on mechanical ventilation. In addition, transfusion-related outcomes studied included: 1) proportion of patients with a transfusion; and 2) rate ratio of RBC units transfused.

Study selection and data collection

Two review authors (H.K. and one of C.L., M.J., G.O., or M.K.) independently screened the titles and abstracts. Two review authors (H.K. and C.L.) screened the full-texts of potentially relevant studies extracted data from included trials; disagreements were again resolved by consensus, or by a third reviewer (A.M.A.S.) if needed. If outcome data were unclear or missing, we contacted the corresponding authors of the relevant trials. EndNote™ (version X7; Thomson Reuters, Philadelphia, PA, USA) was used to manage citations.

Risk of bias assessment

Two review authors (H.K. and C.L.) independently assessed the risk of bias in each of the included trials at both the trial and outcome levels[14] using the Cochrane Risk of Bias tool.[16] Information regarding the risk of bias was

used to guide sensitivity analyses and explore sources of heterogeneity. We intended to assess the publication bias using funnel plot techniques.[17]

Data synthesis and analysis

All analyses were performed on the basis of the intention-to-treat principle. We calculated summary treatment effects for dichotomous variables as risk ratio (RR), rate ratio for count data, and mean differences for continuous outcome data along with the 95% confidence intervals (CI).[18]

When only medians were reported, we imputed means and standard deviations for these values by estimation from the median, range, and sample size[19] when all three were reported. If only the median and interquartile range were reported, we instead used the Approximate Bayesian Computation (ABC) method.[20] Statistical heterogeneity of the data was explored and quantified using the I^2 statistic.[21] Random-effects models were used for all analyses.

To decrease type I errors associated with repeated estimates over time, we performed a *post hoc* TSA for the primary outcome (mortality) based on a clinically significant increase in mortality risk of 25%, assuming a 4.5% baseline risk (mortality rate in the control group), a type I error of 0.05, and a power of 80% using a random effects model, accounting for heterogeneity (I^2 = 20%) to calculate the study size needed clarifying whether additional trials were required.[22] RevMan (version 5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for meta-analysis, and R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria) was used for ABC analysis. The TSA was performed using TSA software (version 0.9.5.10 Beta; Copenhagen Trial Unit, Copenhagen, Denmark).

Results

Search results

From 7,906 citations retrieved from the literature search, and two additional citations identified through other resources, we included ten trials[7,8,23–30] (9,101 patients) and eight companion publications[31–37] (Fig. 1).

Trial characteristics

The characteristics of the included RCTs are summarized in Table 1. The principal difference amongst the included trials was the parameter used to set the transfusion threshold. Six trials[7,8,23,27–29] specified a Hb of 70–80 $g{\cdot}L^{-1}$ for the restrictive group and a Hb of 80–100 $g{\cdot}L^{-1}$ for the liberal group. Four trials[24–26,30] specified Hct values of 20–25% for the restrictive group and Hct values of 25–32% for the liberal group.

Risk of bias

The individual risk of bias for each domain is illustrated in Fig. 2. All the trials were categorized as being at a high risk of bias, mainly because lack of blinding was inherent to most transfusion studies. Publication bias assessment using funnel plot techniques was not possible given the small number of included trials.[16]

Primary outcome

There was no significant difference in mortality at the longest follow-up between restrictive and liberal transfusion strategies (RR, 1.08; 95% CI, 0.76 to 1.54; I^2 = 33%; seven trials;[7,8,23,24,26,29,30] 8,661 patients) (Fig. 3). The TSA was performed for mortality based on a clinically significant relative risk reduction of 25%, assuming a 4.5% baseline risk (mortality rate in the control group), a type-I error of 0.05, and a power of 80%. Using a random effects model, accounting for heterogeneity (I^2 = 20%) in our sample, the required information size (30,693 patients) for the outcome of mortality was not reached. The Z-curve did not cross boundaries for benefit, harm, or futility, suggesting a somewhat inconclusive result (Fig. 6).

Secondary morbidity outcomes

The use of a restrictive transfusion threshold did not appear to adversely impact any of the secondary clinical outcomes (Table 2 and eFigs. 1–6 in the ESM).

Secondary transfusion outcomes

The proportion of the patients who received RBCs in the restrictive group was significantly lower than in the liberal group (RR, 0.68; 95% CI, 0.64 to 0.73; I^2 56%; five trials;[7,8,26,29,31] 8,534 patients) (Fig. 4). Also, the rate of RBC units transfused in the restrictive group was significantly lower than in the liberal group (rate ratio, 0.83; 95% CI, 0.77 to 0.90; I^2 = 59%; five trials;[7,8,26,29,31] 8,534 patients) (Fig. 5).

Discussion

This SR-MA that included ten RCTs[7,8,23–30] comprising 9,101 adult patients undergoing cardiac surgery indicates that there was no significant difference in mortality between restrictive and liberal transfusion strategies.

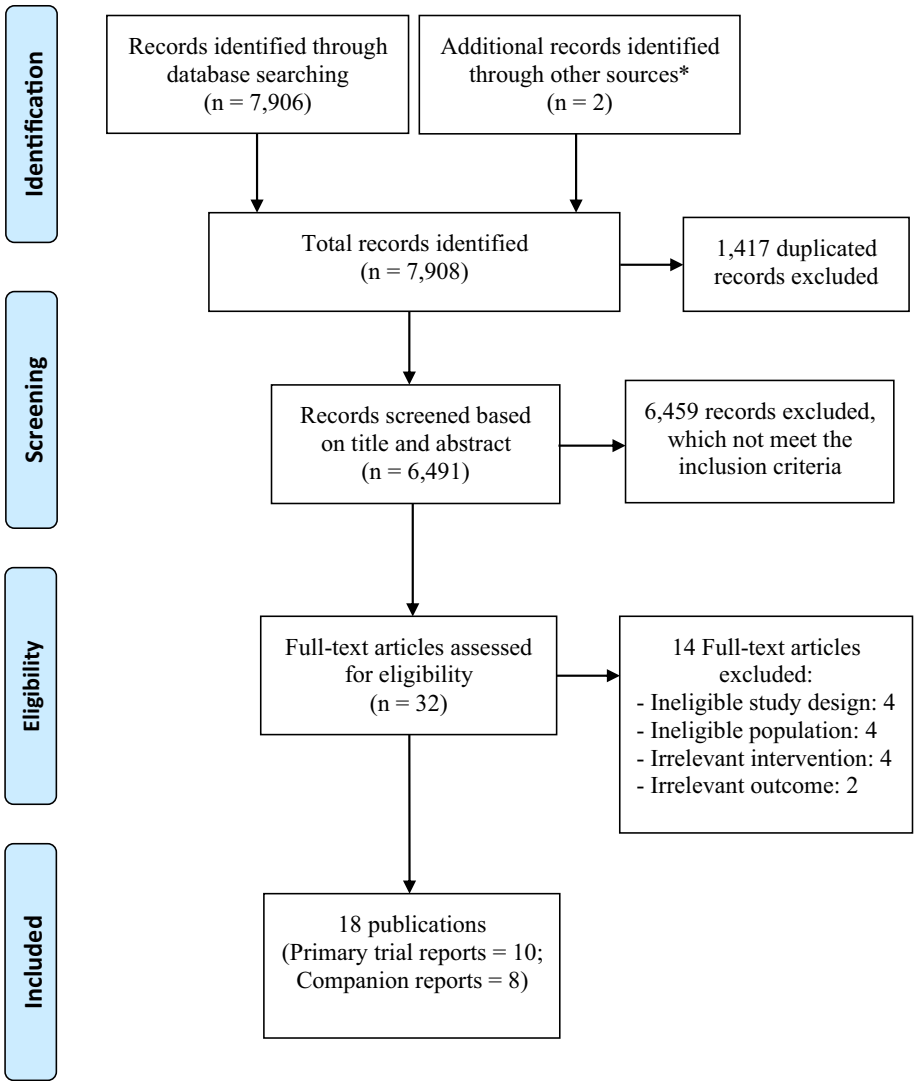

Fig. 1 Summary of literature review and screening process (Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram)

Nevertheless, the TSA showed that the cumulative Z-curve (i.e., number of patients needed to be enrolled to definitively answer the question) did not cross any of the inferiority, superiority, or futility boundaries, and with only 30% of the required information size being reached, suggests that the true effect, though unlikely to be clinically important, is not conclusively known (Fig. 6).

As with the other SR-MAs, we found that a restrictive strategy did not impact the secondary clinical outcomes (MI, renal failure, stroke, ICU LOS, hospital LOS, and days on mechanical ventilation). On the other hand, it was associated with a 30% decrease in exposure to RBC transfusion. In addition, the rate of RBC units transfused in the restrictive group was 0.83 the rate of transfusion in the liberal group.

Although this is the fourth SR-MA to be published on this topic, our study differs significantly in its results and conclusions. This resulted from using a somewhat different methodology, according to the Cochrane Handbook,[13] including a pre-registered protocol, a non-restricted up-to-date literature search, and encompassing data of the longest follow-up time available for all the trials. For example, the TSA of this SR-MA indicates that further trials would be needed to more definitively understand the true impact of these transfusion strategies on mortality. This is in contrast to the TSA results of the two recent SR-MAs.[9,10] Indeed, the TSA of Chen *et al.*[10] stated that their data were sufficient to conclude that a restrictive transfusion strategy is as effective and safe as a liberal strategy. Chen *et al.*[10] noted that they performed a TSA with a two-sided boundary with an alpha of 5% and a power of 80%, based on the mortality incidence of 1.42% in the restrictive group and 2.78% in the liberal group, but did not report the threshold for relative risk. The mortality

Table 1 Baseline characteristics of included trials

Trial	Follow-up time	Urgency of surgery	Type of surgery	Transfusion Threshold		N		Age (yr)		Sex (% male)	
				R	L	R	L	R	L	R	L
Chkhaidze *et al.* 2013[23]	30 days	Elective	CABG	Hb<80	Hb<100	38	35	-	-	-	-
Hajjar *et al.* 2010[24]	30 days	Elective	CABG or valve or CABG + valve	Hct<24%	Hct<30%	255	257	58 (12.5)	61 (1.0)	60	64
Johnson *et al.* 1992[25]	Hospital discharge	Elective	CABG	Hct<25%	Hct<32%	21	18	58.2 ± 7.5	60.5 ± 6.9	100	89
Koch *et al.* 2017[26]	Hospital discharge	-	-	Hct<24%	Hct<28%	365	357	59 (15)	60 (13)	63	66
Laine *et al.* 2017[28]	7 days	Elective and urgent	CABG or valve or CABG + valve	Hb<80	Hb<100	40	40	70.5 [67.8–73.2]	64.5 [60.6–68.3]	72	70
Mazer *et al.* 2017[8]	6 months	Elective and emergent	CABG or valve or CABG + valve or other	Hb<75	Hb<95 in OR and ICU; 85 in ward	2621	2622	72 (10)	72 (10)	64	65
Murphy *et al.* 2007[28]	1 month	Elective and urgent	CABG or valve or CABG + valve	Hb<70	Hb<80	162	159	67 [60–74]	66 [58–73]	81.5	77.4
Murphy *et al.* 2015[7]	3 months	Elective and urgent	CABG or valve or CABG + valve or other	Hb<75	Hb<90	1004	1003	69.9 [63.1–76]	70.8 [64.1–76.7]	69.3	67.8
Shehata *et al.* 2012[29]	Hospital discharge	-	CABG or valve or CABG + valve	Hb<75 in OR and 70 after OR	Hb<95 in OR; 100 after OR	25	25	67.2 (11.2)	68.8 (9.2)	68	80
von Heyman *et al.* 2006[30]	ICU discharge	Elective	CABG	Hct<20%	Hct<25%	26	28	65 [58–71]	60 [55–67]	67	67

Data are presented as mean (standard deviation) or median [interquartile range]

CABG = coronary artery bypass grafting; Hb = hemoglobin ($g \cdot L^{-1}$); Hct = hematocrit; ICU = intensive care unit; L = liberal; N = number of randomized patients (intention-to-treat); OR= operating room; R = restrictive

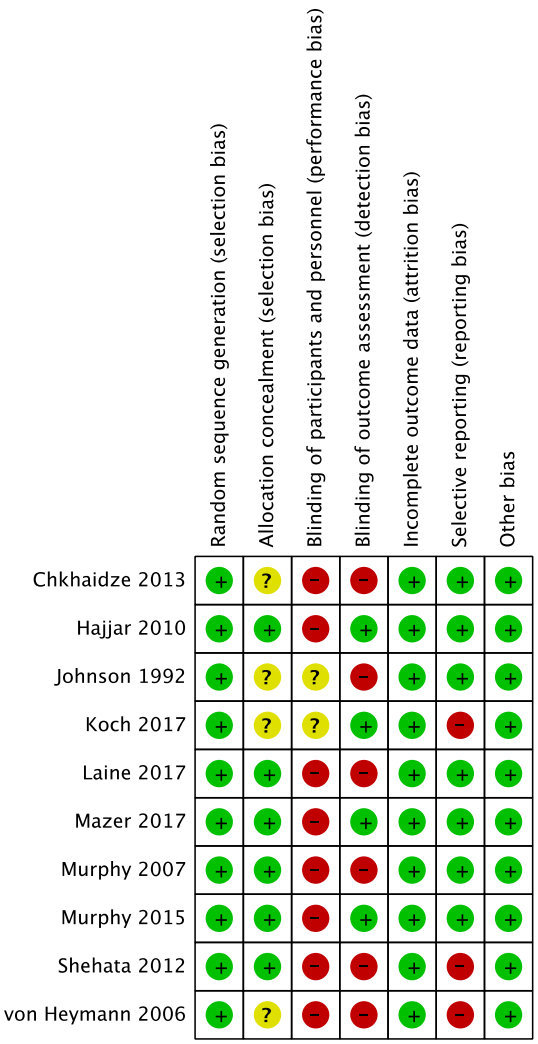

Fig. 2 Risk of bias for each included trial

rate that was used for TSA was different from the rate reported in their MA, which was 3.19% in the restrictive group and 3.13% in the liberal group. Using different rates for the mortality and relative risk changes might explain the difference observed between the "required information size" of Chen *et al.* (5,206) and our study (30,693). Furthermore, Shehata *et al.*[9] calculated 12,904 as a critical sample size (alpha of 5% and power of 80%) to detect a 30% relative risk increase in mortality (with a one-sided alpha of 2.5%, assuming a mortality rate in the liberal transfusion group of 3%). Shehata *et al.*[9] also indicated that the sample size of 8,565 was sufficient to conclude that the two strategies were not inferior to each other as the futility boundary was crossed in the TSA for mortality within 30 days. This is in contrast to our results and conclusion where we noted that the rate of mortality was higher (4.5% *vs* 3%) because a longer follow-up time was used. Moreover, we used a two-sided model as we were looking for any difference between restrictive and liberal transfusion strategies' effect on mortality, as opposed to only looking at non-inferiority. In addition, Shehata *et al.* did not consider the heterogeneity of their sample (I^2 = 30%), which decreased the sample size of 18,434 to 12,094.[9]

Our review methodology also had additional safeguards in place to avoid the possible introduction of bias; the prior SR-MAs[9–11] did not adequately account for these.[12] For example, our protocol was registered with PROSPERO prior to the start of the review. While four research groups (including our own) studied this subject almost simultaneously, we were the only ones that registered the protocol with PROSPERO as it is highly recommended to prevent redundant research and unnecessary duplication of efforts by other reviewers.[14] Thus, considerable resources and effort were arguably unnecessarily duplicated by having multiple SR-MAs on the topic. Also, prospective registration enables the researchers to carefully establish the outline and structure of the paper before beginning the review, thus permitting readers to appraise the protocol and compare it with the published review, as well as to establish whether the methods are replicable and valid.[13] Lastly, with no registered protocol to compare against, the risk of selective outcome reporting bias is high (such as excluding the results of longer follow-ups in other recent SR-MAs).[9–11]

A strength of our SR-MA was the non-restricted and up-to-date comprehensive literature search that ensured that all

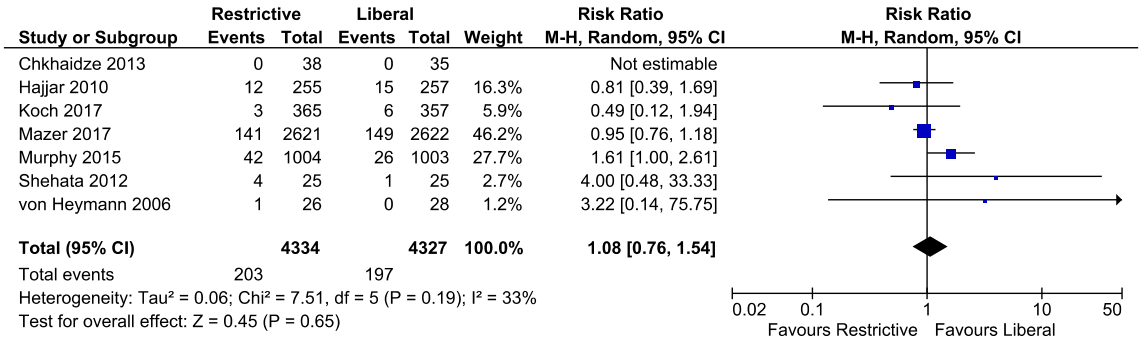

Fig. 3 Forest plot of all-cause mortality at the longest follow-up time

Table 2 Secondary morbidity outcomes (clinical)

Clinical outcomes	Number of studies	Reference numbers	Number of patients		Effect estimate (95% CI)	Heterogeneity
			Restrictive	Liberal		
MI	6	7, 8, 25, 27, 29, 30	3,737	3,736	RR = 0.99 (0.80 to 1.21)	$\chi2$ = 7.51, df = 5 (*P* = 0.19); I^2 = 33%
Renal failure	6	7, 8, 24, 26, 29, 30	3,547	3,546	RR = 0.97 (0.79 to 1.20)	$\chi2$ = 1.41, df = 5 (*P* = 0.92); I^2 = 0%
Neurologic deficit	7	7, 8, 24, 25, 26, 29, 30	4,317	4,310	RR = 0.94 (0.69 to 1.27)	$\chi2$ = 3.16, df = 5 (*P* = 0.68); I^2 = 0%
ICU LOS	6	7, 8, 23, 24, 25, 30	3,884	3,893	MD = −0.01 (−0.08 to 0.06)	$\chi2$ = 3.93, df = 5 (*P* = 0.56); I^2 = 0%
Hospital LOS	4	7, 8, 24, 25	3,818	3,832	MD = −0.13, (−0.35 to 0.10)	$\chi2$ = 5.39, df = 3 (*P* = 0.15); I^2 = 44%
Days on mechanical ventilation	2	23, 30	66	61	MD = −0.57 (0.79 to 1.93)	$\chi2$ = 4.66, df = 1 (*P* = 0.03); I^2 = 79%

CI = confidence interval; df: degrees of freedom; ICU = intensive care unit; LOS = length of stay; MD = mean difference; MI = myocardial infarction; RR = risk ratio

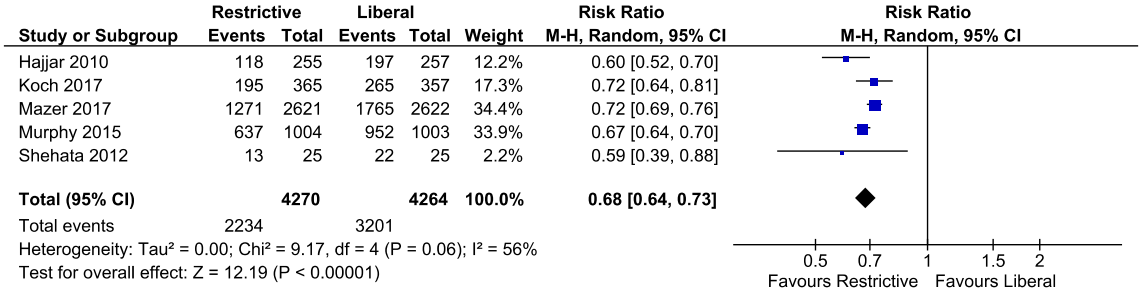

Fig. 4 Forest plot of proportion of patients who received red blood cell transfusion

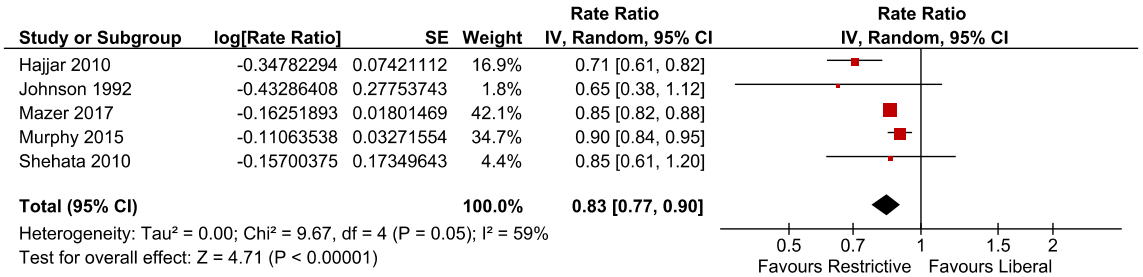

Fig. 5 Forest plot of rate ratio of red blood cell units transfused

the pertinent trials were identified. For example, other recent SRs[9,10] did not identify the trial by Johnson *et al.*[25] even though it met their inclusion criteria. Also, we excluded any low-quality RCTs that would have increased the risk of bias. Accordingly, we excluded the Bracey *et al.* study[38] (included in the other SR-Mas),[9–11] which was a quasi-randomized trial and had a high risk of bias regarding randomization.

A potentially important difference in our SR-MA compared with the others also related to the screening and data extraction, which were done in duplicate by independent authors in our review. The authors of the Shehata *et al.*[9] SR-MA were also authors of two included trials[8,29] (carrying the most weight in the analyses), which may have introduced the risk of confirmation bias and selective outcome reporting.[12]

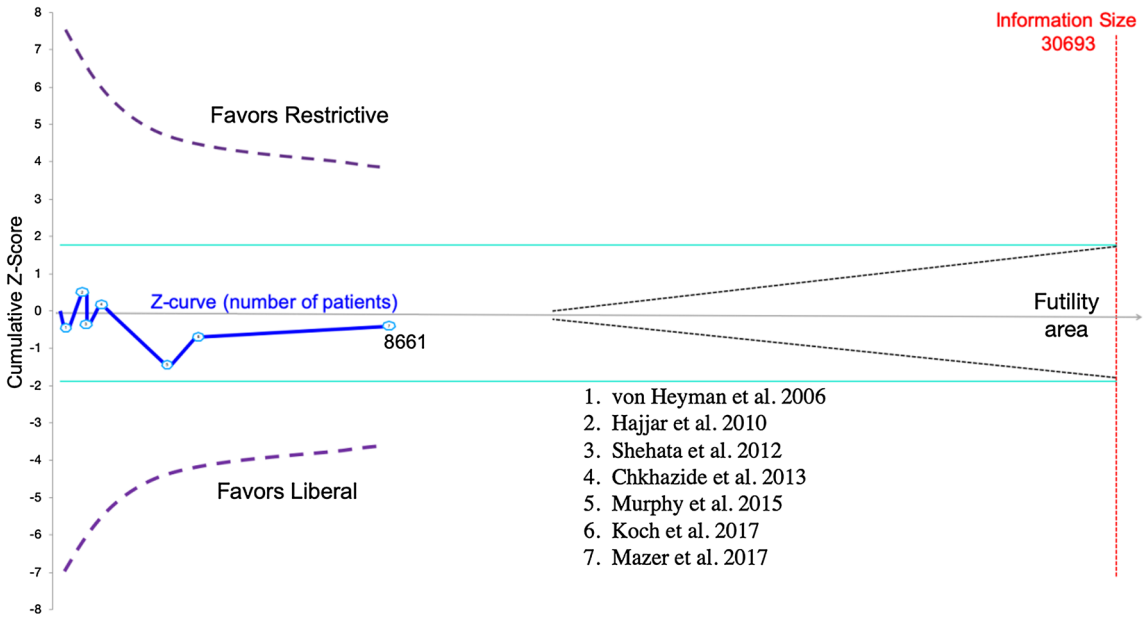

Fig. 6 Trial sequential analysis for mortality at the longest follow-up time (type I error of 0.05, power of 80%, and a clinically significant increase in mortality risk of 25%). The purple lines on the left are the trial sequential boundaries and show a significant increase in mortality (above for the restrictive and below for the liberal group). The blue lines show the Z-statistic for the cumulative meta-analyses with the dots on the blue lines representing the trials in chronological order. The inside of the grey lines at the far right indicates the futility region. Horizontal green lines represent a Z score of +1.96 and −1.96, indicating a conventional significant $P = 0.05$. The cumulative Z-curve did not cross any of the inferiority, superiority, or futility boundaries, and with only 30% of the required information size being reached, suggests that the true effect, though unlikely to be clinically important, is not conclusively known

Our period of longest mortality follow-up also resulted in point estimate differences compared with the other SR-MAs. While the mortality rate for the restrictive and liberal groups in the other SRs[9–11] is approximately 3%, our SR with its longer follow-up periods indicated an overall mortality rate of 4.5%.

Despite our best efforts, the present SR-MA also has some limitations. First, the thresholds of restrictive and liberal transfusion strategies varied among the included RCTs, which reduced the validity of pooling data across all trials and increased the clinical heterogeneity. Second, we did not perform any subgroup analyses as the included trials did not systematically report treatment effects in clinically meaningful subgroups, such as procedure urgency, which could potentially delineate higher blood transfusions for emergency surgery[39] and a potential divergent effect of age on clinical outcomes. For example, Nakamura *et al*. reported that a restrictive transfusion strategy may increase the rate of cardiogenic shock in elderly patients,[33] but Mazer *et al*. showed that a restrictive strategy decreased the risk of the composite outcome (mortality, MI, stroke, or new-onset renal failure) among older patients.[32,33] Third, the overall risk of bias in our SR-MA was similarly high as in the other SR-MAs as all of the included trials had a high risk of bias associated with the lack of blinding owing to the nature of the transfusion intervention.

Conclusions

Our SR-MA provides the highest-quality evidence with the longest follow-up to date that a restrictive transfusion strategy decreases blood transfusion without impacting mortality and morbidity after cardiac surgery. Nevertheless, the required sample sizes were not reached based on the TSA to definitely determine the full impact of these strategies. Accordingly, further large trials in subgroups of patients, potentially of differing age, are needed to establish firm evidence to guide transfusion in cardiac surgery.

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served as a content expert. All authors critically revised the article for important intellectual content.

Conflicts of interest None.

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