BJA

British Journal of Anaesthesia, 115 (4): 511–19 (2015)

doi: 10.1093/bja/aev317
Review Article

Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials

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Abstract

Background: Guidelines support the use of a restrictive strategy in blood transfusion management in a variety of clinical settings. However, recent randomized controlled trials (RCTs) performed in the perioperative setting suggest a beneficial effect on survival of a liberal strategy. We aimed to assess the effect of liberal and restrictive blood transfusion strategies on mortality in perioperative and critically ill adult patients through a meta-analysis of RCTs.

Methods: We searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, Transfusion Evidence Library, and Google Scholar up to 27 March 2015, for RCTs performed in perioperative or critically ill adult patients, receiving a restrictive or liberal transfusion strategy, and reporting all-cause mortality. We used a fixed or random-effects model to calculate the odds ratio (OR) and 95% confidence interval (CI) for pooled data. We assessed heterogeneity using Cochrane's Q and I^2 tests. The primary outcome was all-cause mortality within 90-day follow-up.

Results: Patients in the perioperative period receiving a liberal transfusion strategy had lower all-cause mortality when compared with patients allocated to receive a restrictive transfusion strategy (OR 0.81; 95% CI 0.66–1.00; P=0.05; I^2=25%; Number needed to treat=97) with 7552 patients randomized in 17 trials. There was no difference in mortality among critically ill patients receiving a liberal transfusion strategy when compared with the restrictive transfusion strategy (OR 1.10; 95% CI 0.99–1.23; P=0.07; I^2=34%) with 3469 patients randomized in 10 trials.

Conclusion: According to randomized published evidence, perioperative adult patients have an improved survival when receiving a liberal blood transfusion strategy.

Key words: anesthesia; blood transfusion; critical illness; mortality; perioperative care

Accepted: July 9, 2015

Editor's key points

- In this meta-analysis the authors examined the association between blood transfusion strategy (liberal *vs* conservative) and mortality in perioperative and in critically ill patients receiving critical care.
- They found an extensive evidence base, and the data indicated that a liberal transfusion strategy was associated with improved survival in perioperative (but not critically ill) patients.

Blood transfusion is one of the most frequently used treatments in critically ill and surgical patients.[1 2] Approximately, 85 million red blood cell (RBC) units are transfused worldwide annually.[3] However, observational studies suggest that patients who received RBC transfusion are at increased risk of mortality, infection, and organ dysfunction.[4 5] Moreover, data from recent meta-analyses of randomized controlled trials (RCTs) show that a restrictive transfusion approach is as safe as[6–8] or even superior[9] to a liberal transfusion approach. Nevertheless, contemporary knowledge should be considered cautiously as the vast majority of published reviews combine results of studies conducted in different clinical contexts: adults, children, surgical, and critically ill patients.

Recently published RCTs in cardiac surgery,[10] oncology,[11] and hip fracture surgery[12] raised the possibility that mortality is lower using a liberal transfusion strategy when compared with a restrictive strategy. Therefore, we performed a meta-analysis of RCTs to investigate the influence of liberal and restrictive blood transfusion strategies on mortality in perioperative and critically ill adult patients.

Methods

Search strategy

We searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, Transfusion Evidence Library, and Google Scholar for relevant studies up to 27 March 2015, with keyword search terms including 'blood transfusion', 'red blood cell', 'RBC', 'transfusion', 'trigger', 'threshold', 'strategy', 'liberal', and 'restrictive'. The full PubMed search strategy is available in the supplement (Supplementary Digital Content 1). We also searched reference lists of selected articles, conference proceedings, and personal files for relevant citations. We screened ClinicalTrials.gov to ensure identification of relevant ongoing studies. We used no language restrictions.

This systematic review included studies with the following eligibility criteria: (1) population: patients aged more than 18 yr who were in the perioperative period or had critical illness; (2) intervention: allogeneic blood transfusion with the use of liberal (higher transfusion threshold) in one group and restrictive (lower transfusion threshold) protocol in the other group. Thresholds for transfusion were: haemoglobin or haematocrit concentrations, transfusion practice or predefined protocol; (3) outcome: all-cause mortality; (4) study design: randomized controlled trial. We excluded conferences proceedings if the abstracts were not published as full articles in the following 3 yr.

Data extraction and quality assessment

This study was performed at the Department of Anaesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy. Two researchers screened the citations identified by the search strategies. Full text review was done to establish eligibility when screening reviewers believed that a citation potentially met inclusion criteria. Disagreements regarding inclusion were reconciled via consensus.

Two reviewers independently extracted data from the list of included studies. Details of the study design, clinical settings, patient characteristics, transfusion triggers, and mortality were collected. The methodological quality of individual studies (including description of randomization, allocation concealment, blinded assessor, and intention-to-treat data analysis) was assessed. We rated the risk of bias by applying a rating of 'Yes', 'No' or 'Unclear' to denote whether adequate measures were taken to protect against each potential source of bias in each study. The overall risk of bias was expressed as low, moderate, or high.

Data analysis

The primary outcome was 90-day all-cause mortality. If 90-day mortality was not reported we chose the closest mortality data available and reported the follow-up in Table 1. All analyses were done with Review Manager (RevMan, Version 5.3., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We employed the Mantel-Haenszel method with fixed-effect model when the heterogeneity was less than 50%, according to Higgins's I^2 test and the *P* value for Cochrane's Q test had a critical level of significance more than 10%. We used odds ratios (ORs) to pool outcome with a two-sided significance level of 5%. Individual trial and summary results are reported with 95% confidence intervals (CIs). Data from each trial were considered as per the intention-to-treat principle. We also calculated the number needed to treat (NNT). To compare different groups (perioperative and critically ill) with each other, we performed tests for subgroup differences based on random-effects models. To assess for publication bias, we visually examined a funnel plot comparing effect measure for the primary outcome of mortality with study precision for evidence of asymmetry and applied both the Egger's and Begg's regression tests using the metabias command in STATA (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). We performed sensitivity analyses by sequentially removing each study result from the pooled effect estimate. We also repeated analysis including only trials with low risk of bias, with multi-centre design, or trials enrolling more than 100 patients.

Results

Characteristics of included studies

The initial search strategy identified 10 045 citations (Fig. 1). Major exclusions (Supplementary references 1–28) are listed in the Supplementary material together with the reasons of exclusion (Supplementary Digital Content 1). Twenty-seven trials met the inclusion criteria (Table 1) for a total of 11 021 patients: 17 studies enrolled patients in perioperative settings[10–12 15–18 21–23 27–31 33 34] while 10 trials enrolled patients in critically ill settings.[13 14 19 20 24–26 32 35 36] Within the perioperative setting nine trials were in orthopaedic,[12 17 18 21 22 28–30 34] five in cardiac,[10 15 23 27 33] one in vascular,[16] one in oncology surgery,[11] and one trial in obstetrics.[31] Fourteen trials were multicentre[10 17–20 22 24–26 29 31 32 34 36] with 18 trials including more than 100[10–13 15 18 19 21–23 25 26 30–32 34–36] and two trials more than 1000 patients.[10 18] Leucocyte reduced blood was administered in 11

Table 1 Characteristics of included studies. ICU, intensive care unit; NR, not reported; Hb, haemoglobin; RBC, red blood cell; CABG, coronary artery bypass grafting surgery; CVD, cardiovascular disease; Ht, hematocrit; CPB, cardiopulmonary bypass. Haemoglobin values are given in g dl^{-1}. *Symptoms or consequences of anaemia which were defined as chest pain thought to be cardiac in origin; myocardial infarction; congestive heart failure; unexplained tachycardia, hypotension, or decreased urine output that was unresponsive to fluid replacement. †Symptoms of anaemia included definite angina requiring treatment with sublingual nitroglycerin, and unexplained tachycardia or hypotension. ‡Symptoms of anaemia were recurrent vaso-vagal episodes on mobilization, chest pain of cardiac origin, congestive cardiac failure, unexplained tachycardia, hypotension or dyspnoea, decreased urine output unresponsive to fluid replacement. #In restrictive group transfusion policy considering age, time since surgery, cardiovascular comorbidities, pulmonary diseases and diabetes mellitus. In liberal group standard care transfusion policies. ¶Until intracranial pressure monitoring and ventilator support were no longer required. Blood was also given in case of haemodynamic instability because of active bleeding

First author	Year of publication	Journal	Clinical settings	Time of transfusion	Number of patients	Number of trial centers	Transfusion trigger in restrictive *vs* liberal group	Follow-up for mortality data included in the analysis
Bergamin F[13]	2014	*Crit Care (abstract only)*	Patients with cancer admitted to the ICU as a result of septic shock	NR	136	1	Hb 7 *vs* Hb 9	28 days
Blair SD[14]	1986	*Br J Surg*	Acute severe upper gastrointestinal haemorrhage	During first 24 h after hospital admission	50	1	Hb 8 or persistent shock *vs* 2 RBC units	Hospital discharge
Bracey AW[15]	1999	*Transfusion*	Elective CABG surgery	Postoperatively until hospital discharge	437	1	Hb 8 *vs* Hb 9	Hospital discharge
Bush RL[16]	1997	*Am J Surg*	Elective aortic or infrainguinal arterial reconstruction	Intra- and postoperatively	99	1	Hb 9 *vs* Hb 10	30 days
Carson JL[17]	1998	*Transfusion*	Patients with hip fracture who underwent surgical repair	Postoperatively until hospital discharge	84	4	Hb 8 or symptoms of anaemia* *vs* Hb 10	60 days
Carson JL[18]	2011	*N Engl J Med*	Patients ≥50 yr old with risk factors of CVD or CVD undergoing primary surgical repair of a hip fracture	Intra- and postoperatively until hospital discharge or up to 30 days	2016	47	Hb 8 or symptoms of anaemia* *vs* 10	60 days
Carson JL[19]	2013	*Am Heart J*	Patients with acute coronary syndrome or stable angina undergoing cardiac catheterization	Until hospital discharge or up to 30 days	110	8	Hb 8 or symptoms of anaemia† *vs* Hb 10	90 days
Cooper HA[20]	2011	*Am J Cardiol*	Acute myocardial infarction	Until hospital discharge	45	3	Ht 24% *vs* Ht 30%	30 days
de Almeida JP[11]	2015	*Anesthesiology*	Patients who had a major surgical procedure for abdominal cancer and required postoperative care in ICU	ICU up to 30 days	198	1	Hb 7 *vs* Hb 9	60 days
Foss NB[21]	2009	*Transfusion*	Patients >65 yr old with primary hip fracture	Intra- and postoperatively	120	1	Hb 8 *vs* Hb 10	30 days
Gregersen M[12]	2015	*Acta Orthop*	Patients with hip fracture	Postoperatively up to 30 days	284	1	Hb 9.7 *vs* Hb 11.3	90 days
Grover M[22]	2006	*Vox Sang*	Elective hip and knee replacement	Intraoperatively	218	3	Hb 8 *vs* Hb 10	Hospital discharge
Hajjar LA[23]	2010	*JAMA*	CABG and/or valve replacement or repair	Intra- and postoperatively until ICU discharge	512	1	Ht 24% *vs* Ht 30%	30 days
Hébert PC[24]	1995	*JAMA*	Normovolemic critically ill patients	NR	69	5	Hb 7 *vs* Hb 10	30 days
Hébert PC[25]	1999	*N Engl J Med*	Normovolemic critically ill patients	Until ICU discharge	838	25	Hb 7 *vs* Hb 10	60 days

Continued

Table 1 *Continued*

First author	Year of publication	Journal	Clinical settings	Time of transfusion	Number of patients	Number of trial centers	Transfusion trigger in restrictive *vs* liberal group	Follow-up for mortality data included in the analysis
Holst LB[26]	2014	*N Engl J Med*	Septic shock	From ICU admission up to 90 days	1000	32	Hb 7 *vs* Hb 9	90 days
Junio JAE[27]	2012	*Phil Heart Center J*	Elective CABG, valve replacement, correction of congenital cardiac anomaly	Intra- and postoperatively	71	1	Hb 7 *vs* Hb NR	Hospital discharge
Murphy GJ[10]	2015	*N Engl J Med*	Nonemergency cardiac surgery	Postoperatively	2007	17	Hb 7.5 *vs* Hb 9	90 days
Nielsen K[28]	2012	*Transfus Med*	Elective spinal fusion with instrumentation	Intraoperatively	50	1	Hb 7.3 *vs* Hb 8.9	30 days
Nielsen K[29]	2014	*BMC Anesthesiol*	Elective hip revision surgery	Intra- and postoperatively	66	2	Hb 7.3 *vs* Hb 8.9	30 days
Parker MJ[30]	2013	*Injury*	Patients with proximal femoral fracture	Postoperatively	200	1	Symptoms of anaemia[‡] *vs* Hb 10	90 days
Prick BW[31]	2014	*BJOG*	Patients sustained postpartum haemorrhage	Postoperatively	521	37	Symptoms of anaemia *vs* Hb 8.9	42 days
Robertson CS[32]	2014	*JAMA*	Patients with closed head injury	Acute post injury recovery period[¶]	200	2	Hb 7 *vs* Hb 10	28 days
Shehata N[33]	2012	*Transfusion*	Elective cardiac surgery	Intra- and postoperatively until hospital discharge	50	1	Hb 7 during CPB, Hb 7.5 after CPB *vs* Hb 9.5 during CPB, Hb 10 after CPB	Hospital discharge
So-Osman C[34]	2010	*Vox Sang*	Primary or revision total hip or knee replacement	Intra- and postoperatively	619	3	Special protocols in both groups[#]	14 days after surgery or at hospital discharge
Villanueva C[35]	2013	*N Engl J Med*	Severe acute upper gastrointestinal bleeding	Until hospital discharge	921	1	Hb 7 *vs* Hb 9	45 days
Walsh TS[36]	2013	*Crit Care Med*	Critically ill patients ≥55 yr old requiring prolonged mechanical ventilation	14 days from randomization or until ICU discharge	100	6	Hb 7 *vs* Hb 9	60 days

trials[11 13 18–20 22 26 32 34–36] with non-leucocyte reduced RBCs transfused in four trials[12 21 23 25] and with 12 trials not reporting this information.[10 14–17 24 27–31 33]

The transfusion triggers for the restrictive strategy were haemoglobin from 7.0 to 9.7 g dl^{-1}, haematocrit of 24%, symptoms of anaemia or persistent shock. The triggers for liberal transfusion were haemoglobin from 8.9 to 11.3 g dl^{-1} and haematocrit of 30%, while in two trials there was no specific threshold for the liberal group.[14 27] One trial had different thresholds in different subgroups of patients according to age and comorbidities.[34] Out of the 17 perioperative trials, two trials randomized the use of RBCs in the intraoperative period only,[22 28] seven trials randomized the use of RBCs in the postoperatively period only,[10–12 15 17 30 31] and eight trials randomized the use of RBCs both in the intraoperative and postoperative period.[16 18 21 23 27 29 33 34]

The majority of trials reported an appropriate method of randomization. Concealment of allocation was documented in 19 trials. Owing to the nature of interventions used, none of the trials was blinded. However, 14 trials attempted to blind the data collectors. Twenty-six trials presented the results as intention to treat. According to methodological assessment, 13 trials had low, 11 trials had moderate and 2 trials had high risk of bias (Supplementary Table S1 in Supplementary Digital Content 1).

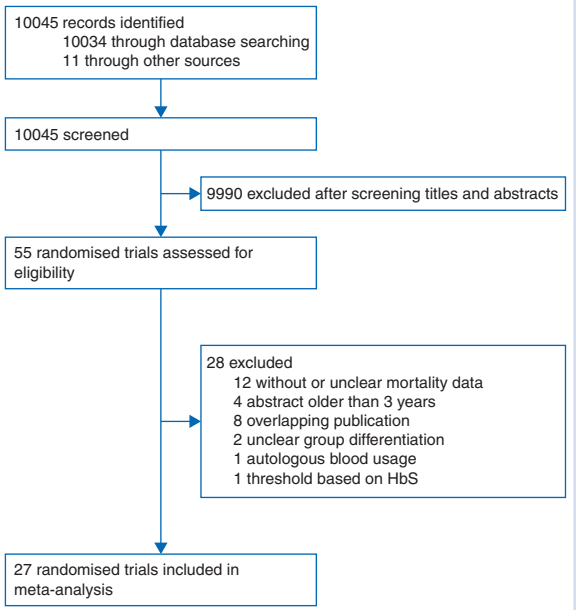

Fig 1 Study flow diagram.

Quantitative data synthesis

Overall, there was no difference in mortality between the liberal and the restrictive transfusion strategy OR 0.96; 95% CI 0.78–1.18; *P* for effect=0.68 (Supplementary Fig. S1 in Supplementary Digital Content 1) with no changes when performing sensitivity analyses (Supplementary Fig. S4) and sub-analyses (Supplementary Table S2 in Supplementary Digital Content 1) and with no evidence of publication bias (Egger's test (*P*=0.83), and Begg's test (*P*=0.21); Supplementary Fig. S2 in Supplementary Digital Content 1).

In the perioperative setting all-cause mortality was reduced in patients randomized to receive a liberal transfusion strategy when compared with those receiving a restrictive transfusion strategy OR 0.81; 95% CI 0.66–1.00; *P* for effect=0.05; NNT=97 (Fig. 2) with 7552 patients and 17 trials included. Heterogeneity between trials was low (χ^2=16.09, *P* for heterogeneity=0.19; I^2=25%). Visual inspection of the funnel plot (Fig. 3), Egger's test

Study or subgroup	Liberal Events	Liberal Total	Restrictive Events	Restrictive Total	Weight	Odds ratio M-H, fixed, 95% CI
Bracey AW 1999	6	222	3	215	1.5%	1.96 (0.48, 7.95)
Bush RL 1997	4	49	4	50	1.8%	1.02 (0.24, 4.34)
Carson JL 1998	2	42	5	42	2.4%	0.37 (0.07, 2.02)
Carson JL 2011	76	1007	66	1009	30.5%	1.17 (0.83, 1.64)
de Almeida JP 2015	11	97	24	101	10.4%	0.41 (0.19, 0.89)
Foss NB 2009	0	60	5	60	2.7%	0.08 (0.00, 1.54)
Gregersen M 2015	30	140	40	144	15.5%	0.71 (0.41, 1.22)
Grover M 2006	1	109	0	109	0.2%	3.03 (0.12, 75.14)
Hajjar LA 2010	12	257	15	255	7.2%	0.78 (0.36, 1.71)
Junio JAE 2012	0	37	0	34		Not estimable
Murphy GJ 2015	26	1003	42	1004	20.4%	0.61 (0.37, 1.00)
Nielsen K 2012	0	25	0	25		Not estimable
Nielsen K 2014	0	33	0	33		Not estimable
Parker MJ 2013	10	100	11	100	4.9%	0.90 (0.36, 2.22)
Prick BW 2014	0	259	0	262		Not estimable
Shehata N 2012	1	25	4	25	1.9%	0.22 (0.02, 2.11)
So-Osman C 2010	2	310	1	309	0.5%	2.00 (0.18, 22.17)
Total (95% CI)		3775		3777	100.0%	0.81 (0.66, 1.00)
Total events	181		220			

Heterogeneity: χ^2=16.09, df=12 (*P*=0.19); I^2=25%
Test for overall effect: Z=1.96 (*P*=0.05)

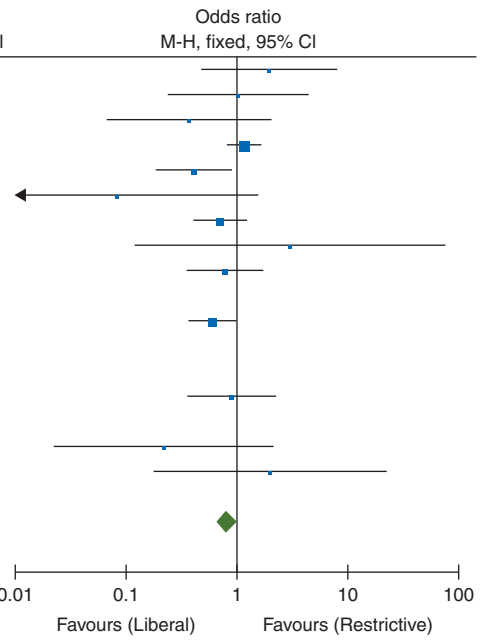

Fig 2 Forest plot of all-cause mortality in the perioperative setting.

(P=0.39), and Begg's test (P=0.86), showed no evidence of small study publication bias.

In the critically ill setting there was no difference in all-cause mortality in patients randomized to receive a liberal transfusion strategy when compared with those receiving a restrictive transfusion strategy OR 1.10; 95% CI 0.99–1.23; P for effect=0.07 (Fig. 4). Heterogeneity between trials was low (χ^2=13.66, P for heterogeneity=0.13; I^2=34%). Visual inspection of the funnel plot, Egger's test (P=0.78), and Begg's test (P=0.86), showed no evidence of small study publication bias (Supplementary Fig. S3 in Supplementary Digital Content 1).

Tests for comparison between perioperative and critically ill subgroups based on random-effects models revealed that blood transfusion intervention had a statistically significant different effect on survival in different clinical settings: χ^2=4.51, P for effect=0.03; I^2=77.9%.

Discussion

The most important finding of this meta-analysis of RCTs is to suggest that the effect of transfusion strategies on patients' survival depends on the studied setting. In adult perioperative patients a restrictive strategy seems to be detrimental and to increase mortality. In critically ill patients there was no difference in mortality, we revealed only the trend in favour of restrictive strategy. While a restrictive transfusion strategy is endorsed by several guidelines[37–39] especially because of reduced resource utilization, the increase in mortality with a restrictive strategy in the perioperative setting is a novel finding.

Heterogeneity in blood transfusion management exists despite the recommendation of several guidelines for a restrictive (rather than liberal) strategy for blood management in various clinical environments.[37–39] It should be noted that some of the clinical practice guidelines have a low level of evidence and are based on expert opinion.[37] Other guidelines based their suggestions using the evidence coming from a single RCT[38] or based their assumption on previous guidelines.[39] The updated guidelines by the American Society of Anesthesiologists task force on perioperative blood management, concluded that a restrictive RBC transfusion strategy may be used to reduce the usage of blood products, while recognizing that findings for mortality, cardiac, neurologic and pulmonary complications, and length of hospital stay were equivocal.[40]

Large multicentre RCTs in critically ill patients with normovolaemia (TRICC),[25] in patients with septic shock (TRISS),[26] in high-risk patients after hip surgery (FOCUS),[18] and one large single-centre RCT in elective cardiac surgery patients (TRACS)[23] showed similar rates of mortality between patients with restrictive and liberal transfusion strategies. These RCTs influenced the general recommendation for preferable use of restrictive strategy over liberal transfusion in the above mentioned guidelines. However, the results of these trials should be interpreted cautiously. The TRICC and FOCUS trials had low level of enrolment of the eligible patients that raises concerns about selection bias. In the TRICC, TRACS, and TRISS trials patients in the restrictive group were transfused at haemoglobin concentrations that were higher than that of the protocolized thresholds.

Our findings are different from those of five previously published meta-analyses. We are the first to document a mortality reduction with the use of a liberal transfusion strategy in patients in the perioperative period. This difference is driven by the inclusion in our meta-analysis of three RCTs[10–12] published in 2015,

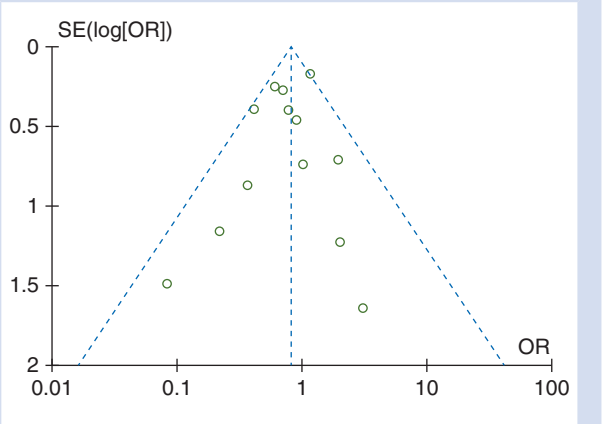

Fig 3 Funnel plot of all-cause mortality in the perioperative setting.

Study or subgroup	Liberal Events	Liberal Total	Restrictive Events	Restrictive Total	Weight	Risk ratio M-H, fixed, 95% CI
Bergamin F 2014	34	63	41	73	9.1%	0.96 (0.71, 1.30)
Blair SD 1986	2	24	0	26	0.1%	5.40 (0.27, 107.09)
Carson JL 2013	2	55	9	55	2.2%	0.22 (0.05, 0.98)
Cooper HA 2011	1	21	2	24	0.4%	0.57 (0.06, 5.86)
Hebert PC 1995	9	36	8	33	2.0%	1.03 (0.45, 2.36)
Hebert PC 1999	111	420	95	418	22.9%	1.16 (0.92, 1.48)
Holst LB 2014	223	497	216	503	51.6%	1.04 (0.91, 1.20)
Robertson CS 2014	10	101	12	99	2.9%	0.82 (0.37, 1.80)
Villanueva C 2013	41	460	23	461	5.5%	1.79 (1.09, 2.93)
Walsh TS 2013	22	49	14	51	3.3%	1.64 (0.95, 2.92)
Total (95% CI)		1726		1743	100.0%	1.10 (0.99, 1.23)
Total events	455		420			

Heterogeneity: χ^2=13.66, df=9 (P=0.13); I^2=34%
Test for overall effect: Z=1.80 (P=0.07)

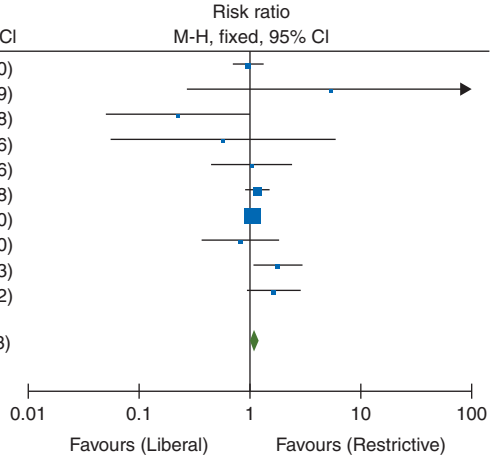

Fig 4 Forest plot of all-cause mortality in the critically ill setting.

independently showing a mortality reduction in this setting when using a liberal approach. Furthermore, we limited our analysis to adult patients and we were the first to focus on the perioperative setting. A 2012 Cochrane review of RCTs showed that patients receiving liberal transfusion had higher in-hospital mortality compared with those with restrictive strategy,[6] but 97% of weight for in-hospital mortality outcome derived from only two trials (TRICC and FOCUS). The meta-analysis of three RCTs by Salpeter and colleagues[9] revealed higher mortality in a mixed population with liberal strategy compared with restrictive of <7 g dl^{-1} including paediatric and adult patients. A meta-analysis of seven RCTs in adult patients undergoing cardiovascular surgery did not determine any difference in mortality between liberal and restrictive blood transfusion strategies.[7] Chatterjee and colleagues[41] summarized the findings from one RCT and nine observational trials in patients with an acute myocardial infarction and showed that blood transfusion was associated with higher mortality. However, this study was not able to adequately manage the unbalance in patients' characteristics in the included trials and there was a great interdependence in the level of pooled risk from anaemia or from blood transfusions. Finally, a recently published comprehensive systematic review and meta-analysis of 31 RCTs by Holst and colleagues[8] revealed a reduction in the number of units and number of patients transfused in restrictive group compared with liberal, but there was no difference in mortality and morbidity between the groups. Even if this manuscript was recently published, it did not include the three recent RCTs[10–12] that were all published in 2015 showing mortality reduction in cardiac, orthopaedic and oncology surgery with the use of a liberal strategy. Further differences with this meta-analysis are the following: we included only adult patients; we excluded trials with autologous blood transfusion; we limited the follow up to 90 days; we considered one trial[35] performed in acute gastrointestinal bleeding patients admitted in the ICU as pertaining to the 'critically ill' setting and not as 'perioperative'; we extrapolated data strictly following the intention to treat principle.

Physicians have, in general, a negative opinion on the effects of RBCs on clinically relevant outcomes because of the huge number of published observational reports suggest a worsened outcome in patients receiving RBC transfusion. Two systematic reviews summarize a large part of observational trials.[4 5] Marik and colleagues[4] evaluated 45 trials with multivariate assessment and suggested that RBCs transfusion was an independent predictor of death based on a meta-analysis of 12 studies (OR 1.7; 95% CI, 1.4–1.9). Pooling 15 large-scale observational studies published between 2006 and 2010 Hopewell and colleagues[5] used adjusted analysis and found a higher rate of mortality in patients receiving RBCs compared with those who did not. At the same time, in the recently published observational study of about 1.6 million patients, perioperative transfusion of a single unit of packed red cells was significantly associated only with unadjusted mortality.[42]

Nevertheless, our findings are in accordance with the results of a recently published large multicentre RCT in nonemergency cardiac surgery.[10] Patients were randomized to receive transfusion when their haemoglobin concentration was less than 9 g dl^{-1} or when it was less than 7.5 g dl^{-1}. There was no difference between the groups in terms of morbidity. However, 90-day mortality rate was significantly higher in the restrictive compared with the liberal transfusion group (4.2% *vs* 2.6%; hazard ratio 1.64; 95% CI: 1.00–2.67; *P*=0.045).

In our meta-analysis we investigated mortality in RCTs of blood transfusion strategy taking into account the important role of the clinical context. Because of pathophysiological differences between surgery and critical illness, outcome data associated with RBCs transfusions and the thresholds cannot be generalized. Important differences exist in the anaemia of surgical patients and of critically ill patients, whose haemoglobin deficit is more than simply acute blood loss. Repeated phlebotomies, gastrointestinal blood loss, and invasive procedures significantly contribute to the development of anaemia in critical illness together with coagulopathies, pathogen-associated haemolysis, blunted erythropoietin production and erythropoietin response, abnormalities in iron metabolism, and nutritional deficiencies. In contrast, surgical blood loss and haemodilution are important determining factors in patients' intra- and postoperative haemoglobin concentration.[43–45] Anaemia in perioperative settings is often an acute event, while in critically ill patients it has chronic pattern in the majority of the patients. The ability to tolerate anaemia will depend in part on how quickly compensatory mechanisms develop.[43] Moreover, a surgical population does not typically have the same baseline extent of organ dysfunction.

Strengths and limitations

In few trials, mortality data were not properly reported (Supplementary Digital Content 1) and this led to their exclusion from the meta-analysis; nonetheless, we were able to include 27 trials with more than 11 000 patients and this is the largest meta-analysis on this topic performed to date. We combined data from trials performed in different clinical settings (e.g. cardiac surgery is different from orthopaedic surgery) and that varied in triggers for blood transfusion (in one study[12] the restrictive trigger was higher than the liberal trigger in other trials), but this is a bias that cannot be overcome[46] and that was present in previously published meta-analyses.[6 8]

There was incomplete blinding of the participants in the individual trials because of the nature of the intervention. Nonetheless, we assessed the most clinically relevant endpoint and we give physicians an important message. Future international guidelines should take into account the possibility that a restrictive transfusion strategy could have an opposite effect on survival in critically ill patients and in the perioperative period, as suggested by our findings (*P*=0.03 for mortality when comparing these two settings). A liberal transfusion strategy will probably be included among the few topics with randomized evidence of perioperative mortality reduction.[47]

In conclusion, the present meta-analysis of RCTs demonstrates the importance of the clinical setting when RBCs transfusion strategies are considered. Within a perioperative adult surgical population, a liberal blood transfusion strategy reduces all-cause mortality when compared with a restrictive strategy.

Authors' contributions

Study design/planning: E.F., A.P., F.M., A.M.S., A.K., R.R.B.G., L.A.H., A.Z., G.L.
Study conduct: E.F., A.P.
Data analysis: E.F., A.P., A.Z., G.L.
Writing paper: E.F., A.P., F.M., A.M.S., A.K., F.R.B.G., L.A.H., A.Z., G.L.
Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgements

We thank the authors of RCTs that provided further details on their trials: Drs. Kamilla Nielsen, Merete Gregersen, Babette Prick, and Claudia S. Robertson. The Authors of this article gratefully acknowledge the technical contribution of Teresa Greco. None received compensation.

Declaration of interest

None declared.

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Handling editor: J. G. Hardman