Background Among transfused patients, the effect of the duration of red blood cell storage on mortality remains unclear. This study aims to compare the mortality of patients who were transfused with fresher versus older red blood cells.

Methods We performed an updated systematic search in the CENTRAL, MEDLINE, EMBASE and CINAHL databases, from January 2015 to October 2016. RCTs of hospitalized patients of any age comparing transfusion of fresher versus older red blood cells were eligible. We used a random-effects model to calculate pooled risk ratios (RRs) with corresponding 95% confidence interval (CI).

Results We identified 14 randomized trials that enrolled 26 374 participants. All-cause mortality occurred in 1219 of 9531 (12.8%) patients who received a transfusion of fresher red blood cells and 1810 of 16 843 (10.7%) in those who received older red blood cells (RR: 1.04, 95% CI: 0.98–1.12, P = 0.90, I² = 0%, high certainty for ruling out benefit of fresh blood, moderate certainty for ruling out harm of fresh blood). In six studies, in-hospital death occurred in 691 of 7479 (9.2%) patients receiving fresher red cells and 1291 of 14 757 (8.8%) receiving older red cells (RR: 1.06, 95% CI: 0.97–1.15, P = 0.81, I² = 0%, high certainty for ruling out benefit of fresh blood, moderate certainty for ruling out harm of fresh blood).

Conclusion Transfusion of fresher red blood cells does not reduce overall or in-hospital mortality when compared with older red blood cells. Our results support the practice of transfusing patients with the oldest red blood cells available in the blood bank.

Key words: blood processing, clinical trial, red cell component, transfusion therapy.
Each year, approximately 85 million red blood cells are transfused worldwide [2].

Red blood cells are stored at a temperature of 4°C for up to 42 days [3]. Blood storage is associated with biochemical, structural and functional changes that may impair their ability to deliver oxygen to tissues [4–8]. The effect of prolonged red blood cell storage prior to transfusion on clinical outcomes remains controversial.

Many observational studies have suggested a survival benefit of fresher compared with older red blood cell transfusions [9–15]. Wang et al. [16] conducted a meta-analysis (18 observational studies and three randomized controlled trials) comparing between new blood and old blood (definitions of new and old blood were set by each study). This study concluded that older blood was associated with higher risk of mortality (odd ratio [OR]: 1.16, 95% confidence interval [CI]: 1.07–1.24 [16]). However, observational studies on the effects of red blood cell storage are subject to bias due to definition of storage time, number of transfused red blood cells, confounders and publication bias [17].

To solve the conflicting results of observational studies, randomized controlled trials were conducted. A meta-analysis of 12 randomized controlled trials involving 5229 transfused participants [18–29] reported no significant impact of fresher compared with older red blood cell transfusion on mortality (relative risk [RR]: 1.04, 95% CI: 0.94–1.14, P = 0.45) [30]. We recently reported the results of a large pragmatic randomized trial of more than 24 000 patients in which we found no difference in survival between patients receiving fresher versus older red blood cells [31].

The availability of new data from more than 20 000 patients provides an opportunity to further reduce residual uncertainty regarding the effect of transfusion of fresher compared with older red blood cell transfusion on mortality. Accordingly, we performed an updated systematic review and meta-analysis to obtain best estimates of the effect of red blood cell storage duration prior to transfusion on mortality.

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing fresher versus older red blood cell transfusion, adhering to standards of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [32].

Data source and search strategy

We performed a systematic search in the Cochrane Library Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL. The reference lists of included RCTs, systematic reviews and relevant reviews were searched to identify further relevant trials. We did not apply language restrictions. Our search strategy replicated a prior systematic review/meta-analysis [30]. The search was implemented from January 2015 to October 2016. The search used the following terms (appendix): blood or erythrocyte* or red cell*, red blood cell*, RBC or whole blood, transfuse*, infuse*, retransfus*, erythrocyte transfusion, age, aged, aging, fresh*, old, older, oldest, new, newer, newest, young, younger, youngest or store*, storage, storing, preserv*, MeSH term ‘blood transfusion’, ‘blood component transfusion’, ‘erythrocytes’, ‘*time factors’.

Eligibility criteria

RCTs of hospitalized patients of any ages comparing transfusion of fresher versus older red blood cells were eligible. We included studies investigating both surgical and nonsurgical participants. We applied no exclusion criterion based on the indications for the blood transfusion. Studies were excluded if they did not report mortality outcomes.

Study selection and data extraction

Two investigators (CC and PEA) independently screened the titles and abstracts and retrieved the full text of any articles that either reviewer deemed potentially eligible studies. The investigators resolved disagreements on full-text eligibility review through discussion. Two investigators (CC and PEA) independently performed data extraction including study design, setting, sample size, inclusion and exclusion criteria, patient characteristics, details of transfusion, age of transfused red blood cells, indication for transfusion and outcome measures including number of events in each treatment group.

End-point

The primary outcome of this study was all-cause mortality at any time-point. The secondary outcome was in-hospital mortality.

Risk of bias assessment

Two investigators (CC and PEA) independently assessed risk of bias using the Cochrane Collaboration’s tool for assessing risk of bias [33, 34]. We assessed risk of bias in nine domains: selection bias (random sequence generation and allocation), performance bias (blinding of participants and personnel), detection bias (blinding outcome assessors), attrition bias (incomplete outcome data), reporting
bias (selective outcome report), bias due to severe baseline imbalance, bias due to early stoppage or discontinuation, and other bias. Each domain was judged to be either ‘high risk of bias’, ‘probably high risk of bias’, ‘low risk of bias’ and ‘probably low risk of bias’ [35]. The reviewers resolved disagreements by discussion.

Statistical analysis

Primary analysis
We calculated the pooled estimate of the treatment effect using a random-effects model [DerSimonian and Laird random-effects methods] [36]. We present risk ratios (RRs) with their corresponding 95% confidence intervals (CIs), along with associated forest plots. P-values were calculated using a two-sided test with a threshold P-value of <0.05.

Heterogeneity was assessed using the $I^2$ statistic [37]. An $I^2$ of 0–40% indicated minor heterogeneity, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity [37].

We assessed publication bias by constructing a funnel plot of standard error of the effect estimate vs effect size and considered publication bias present if inspection of the funnel plot showed substantial asymmetry [38]. Statistical tests for publication bias used both Egger’s regression test [39] and Peters’ test [40]. The main analyses were conducted using Stata version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). The funnel plot was generated using Review Manager [(RevMan) version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014].

Subgroup analysis

We performed a priori subgroup analyses based on age of red blood cells in the old red cell group (<20 or ≥20 days) and study participants (paediatric or adult patients). Subgroup interactions were investigated using a chi-square statistic [37].

Certainty of evidence assessment

We assessed the certainty of evidence (also referred to as confidence or quality) for all-cause mortality and in-hospital mortality according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [41] evaluating the following domains: risk of bias, inconsistency of the results, indirectness of the evidence, publication bias, imprecision and other considerations. The certainty of the evidence was judged as 'high', 'moderate', 'low' or very low.

Results

Study selection

We screened 2220 citations from the updated search and 12 RCTs from a previous systematic review [30]. After screening of titles and abstracts, we retrieved 19 full-text articles for eligibility assessment. Of these, 14 RCTs proved eligible (Fig. 1) [18–29, 42]. Table 1 presents the characteristics of the included trials. Five trials [18, 25, 27, 28, 31, 42] investigated paediatric patients, eight trials investigated adult patients, [19–22, 24, 26, 29, 31], and one trial did not report the age of participants [23]. Seven studies [18, 20, 25–28, 42] enrolled patients in intensive care units (ICUs) or non-surgical units, four [19, 21, 23, 24] enrolled surgical patients, and three [22, 29, 31] enrolled those who had either medical or surgical conditions. The mean or median duration of storage of transfused red blood cells ranged from 1-6 to 13 days in patients who were allocated to receive fresher red blood cells and 9-0–32 days in patients allocated to receive older red blood cells.

Risk of bias assessment

Figure 1S appendix presents the risk of bias assessment. All of the studies except one [19] were judged to be 'low risk of bias'. Most of the included trials did not blind the outcome assessors; however, mortality can be ascertained without risk of bias. Trials demonstrated concealment of randomization was satisfactory and loss to follow-up was infrequent.

Main outcome

In the 14 eligible trials, 1219 of 9531 (12.79%) patients who received transfusion of fresher red blood cells died compared with 1810 of 16 843 (10.74%) of those who received older red blood cells (RR: 1.04, 95% CI: 0.98–1.12, $P = 0.90$, $I^2 = 0\%$, Fig. 2). P-values for the test of interaction for the two subgroup analyses did not approach statistical significance ($P = 0.77$ for duration of red blood cells storage, $P = 0.39$ for patient population, Appendix Figs S2, S3). Although the inspection of the funnel plot demonstrated minimally asymmetrical appearance (Fig. 3), the Egger’s and Peters’ tests did not suggest publication bias ($P$-value 0.49 and 0.27, respectively).

In six studies [26–29, 31, 42] that reported in-hospital mortality, death occurred in 691 of 7479 (9-24%) patients who received transfusion of fresher red blood cells and 1291 of 14 757 (8-75%) who received older red blood cells (RR: 1.06, 95% CI: 0.97–1.15, $P = 0.81$, $I^2 = 0\%$, Fig. 4). We did not assess publication bias for this
subgroup due to small number of included studies (less than 10) [43].

Certainty of evidence

With respect to ruling out the possibility of benefit from transfusion of fresher red blood cells, the certainty of the evidence was rated as ‘high’ for overall mortality and in-hospital mortality (Table 2). We judged all domains to have ‘no serious’ concerns.

With respect to ruling out the possibility of harm of fresh red blood cell transfusion, the certainty of the evidence was rated as ‘moderate’ for overall mortality and in-hospital mortality (Table 2). We judged all domains to have ‘not serious’ concerns except for imprecision. The confidence intervals of the pooled estimates in the primary analysis included both a potential for very small benefit and appreciable harm of fresher red blood cell transfusion. In a population with a risk of dying of over 10% (the average in the included studies), fresher blood could lead to as many as 13 deaths in 1000 patients (Table 2). We therefore rated down the certainty of evidence for imprecision.

Discussion

This systematic review/meta-analysis established that fresher red blood cell transfusions do not reduce overall mortality and in-hospital mortality when compared with transfusions of older red blood cells. The certainty of evidence was ‘high’ for ruling out benefit of fresher blood. The certainty of evidence was only moderate for ruling out the possibility of harm because the upper limits of the 95% confidence intervals suggested that mortality could be increased by as much as 12% with fresher red blood cells (RR: 1.04, 95% CI: 0.98–1.12). Heterogeneity was trivial, and subgroup analyses failed to support any effect modification.

Strengths and limitations

Strengths of this systematic review/meta-analysis include the comprehensive search including recently published RCTs, duplicate assessment of eligibility and risk of bias, and application of the GRADE approach to rating certainty of evidence. We determined no serious problems in risk of bias, consistency and directness and excluded publication bias based on inspection and statistical tests. Although findings were not definitive with regard to harm of fresher red blood cells, the confidence interval was sufficiently narrow to exclude all but the smallest of benefits. We included both paediatric and adult patients and found results consistent across these groups, testifying to the generalizability of the studies to patients who require a transfusion of red blood cells.
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Patient population</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention (n)</th>
<th>Age of blood (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss (1996) [25]</td>
<td>Single centre, US</td>
<td>Paediatric</td>
<td>Very low-birthweight infant in NICU (weighing 0.6–1.3 kg) received blood transfusion</td>
<td>Unlikely to survive (e.g. severe congenital anomalies)</td>
<td>≤7 days (21)</td>
<td>≤42 days (19)</td>
</tr>
<tr>
<td>Schulman (2002) [23]</td>
<td>Single centre, US</td>
<td>NR</td>
<td>All patients admitted to trauma centre</td>
<td>NR</td>
<td>&lt;11 days (8)</td>
<td>&gt;20 days (9)</td>
</tr>
<tr>
<td>Fernandes da Cunha (2005) [28]</td>
<td>Single centre, Brazil</td>
<td>Paediatric</td>
<td>Very low-birthweight infant receiving blood transfusion</td>
<td>rapid infusion of RBC for haemorrhage, required &gt;1 RBC transfusion within 24 h</td>
<td>≤3 days (26)</td>
<td>≤28 days (26)</td>
</tr>
<tr>
<td>Hebert (2005) [19]</td>
<td>Multicentre, Canada</td>
<td>Adult</td>
<td>Patients requiring RBC transfusion, undergoing cardiac surgery or admitted to ICU</td>
<td>&lt;16 years old, terminal illness, received blood transfusion in 6 months</td>
<td>&lt;8 days (26)</td>
<td>&lt;42 days (31)</td>
</tr>
<tr>
<td>Bennett-Guerrero (2009) [21]</td>
<td>Single centre, US</td>
<td>Adult</td>
<td>≥18 years old, high morbidity and mortality risk, undergoing CABG or heart valve surgery</td>
<td>Haemodialysis or peritoneal dialysis within 7 days, history of RBC disease, blood type O negative</td>
<td>7 ± 4 days (12)</td>
<td>21 ± 4 days (11)</td>
</tr>
<tr>
<td>Aubron (2012) [26]</td>
<td>Multicentre, Australia</td>
<td>Adult</td>
<td>≥18 years old, hospitalized in ICU requiring at least 1 RBC unit</td>
<td>Palliative care, history of organ transplantation, haematologic disease</td>
<td>Freshest blood (25)</td>
<td>Standard of care (26)</td>
</tr>
<tr>
<td>Fergusson (2012) [18]</td>
<td>Multicentre, Canada [27, 42]</td>
<td>Paediatric</td>
<td>Premature infant with a birthweight of less than 1250 g, requiring ≥1 RBC transfusion</td>
<td>Already received RBC transfusion, undergoing an exchange transfusion, rare blood types, moribund</td>
<td>≤7 days (188)</td>
<td>2–42 days (189)</td>
</tr>
<tr>
<td>Heddle (2012) [29]</td>
<td>Single centre, Canada</td>
<td>Adult</td>
<td>≥17 years old hospitalized patient who required a blood transfusion</td>
<td>Had a medical indication for fresh blood, scheduled for autologous donation, expected to receive massive blood transfusion or outpatient</td>
<td>Freshest blood (309)</td>
<td>Standard of care [oldest in the inventory] (601)</td>
</tr>
<tr>
<td>Kor (2012) [22]</td>
<td>Single centre, US</td>
<td>Adult</td>
<td>≥18 years old, admitted to medical and surgical ICU, endotracheally intubated, mechanically ventilated, required RBC transfusion</td>
<td>Concurrent transfusion with other blood product, emergency transfusion, hemodynamically instable</td>
<td>≤5 days (50)</td>
<td>Standard of care (50)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Patient population</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Intervention (n)</th>
<th>Age of blood (days)</th>
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</tr>
<tr>
<td>Dhabangi (2013) [27]</td>
<td>Single centre, Uganda</td>
<td>Paediatric</td>
<td>0–5–9 years old, positive blood smear for malaria, Hb ≤5 g/dl and blood lactate ≥5 mmol/l</td>
<td>Patients with current cardiac disease, undergoing transfusion with other blood products</td>
<td>1–10 days (37)</td>
<td>1–10 days (37) 21–35 days (37)</td>
</tr>
<tr>
<td>Dhabangi (2015) [42]</td>
<td>Single centre, Uganda</td>
<td>Paediatric</td>
<td>0–5–5 years old, Hb ≤5 g/dl and blood lactate ≥5 mmol/l</td>
<td>Severe acute malnutrition, cardiac disease, transfusion within 48 h</td>
<td>1–10 days (145)</td>
<td>25–35 days (145)</td>
</tr>
<tr>
<td>Lacroix (2015) [20]</td>
<td>Multicentre, Canada, UK, France,</td>
<td>Adult</td>
<td>≥18 years old, admitted to ICU, required RBC transfusion within 7 days after admission to ICU or expected to require invasive or non-invasive mechanical ventilation</td>
<td>Already received RBC transfusion, elective cardiac surgery, terminal illness, required ≥1 unit of packed RBC</td>
<td>&lt;8 days (1211)</td>
<td>Standard of care (1219)</td>
</tr>
<tr>
<td>Steiner (2015) [24]</td>
<td>Multicentre, US</td>
<td>Adult</td>
<td>≥12 years old, body weight ≥40 kg, scheduled for complex cardiac surgery with median sternotomy, score ≥3 on TRUST score, Planned to use autologous transfusion, severe renal dysfunction, use of intra-aortic balloon pump, previous RBC transfusion</td>
<td>≥10 days (538) ≥21 days (560)</td>
<td>Freshest RBCs (6937)</td>
<td>Oldest RBCs (13 922)</td>
</tr>
<tr>
<td>Heddle (2016) [31]</td>
<td>Multicentre, Canada, Australia, Israel and US</td>
<td>Adult</td>
<td>≥18 years old, RBC transfusion was requested, admission to hospital</td>
<td>Expected to received massive transfusion, required uncross-matched blood, required autologous or directed transfusions, had an indication for fresh RBC transfusion</td>
<td>Freshest RBCs (6937)</td>
<td>Oldest RBCs (13 922)</td>
</tr>
</tbody>
</table>

NICU, neonatal intensive care unit; NR, not reported; U, United States; UK, United Kingdom; SD, standard deviation; RBC, red blood cell; ICU, intensive care unit; CABG, coronary artery bypass graft; Q1, quartile 1; Q3, quartile 3.
Limitations of our review include the failure of included studies to specifically investigate red blood cells stored for 35–42 days. Goel et al. conducted a retrospective study using hospital billing database for patients discharged from John Hopkins Hospital. Although there was no significant difference among patients who received fresher red blood cells (storage ≤21 days) and older (either storage ≥28 days or ≥35 days), higher mortality was observed in subgroup of patients who were admitted in intensive care unit and who were transfused with older red blood cells (storage ≥35 days). It is important to note that patients who received older red blood cells in Goel et al.’s study were older and had more hypertension, renal disease and anaemia at baseline when compared to those who received fresher red blood cells. Prospective studies on the effect of oldest red blood cells (storage ≥35 days) on mortality are needed. Secondly, we did not investigate the impact of duration of red blood cell storage on nosocomial infections and other adverse effects due to the lack of reporting across included studies. Furthermore, there was variability of definitions of fresher and older blood, as well as the methods of blood processing and storage solution across the included studies.

Relation to prior work

Over the past 4 years, several meta-analyses have addressed the mortality impact of fresh versus older red blood cell transfusion [16, 30, 44]. In 2012, Wang et al.
[16] published a systematic review and meta-analysis that combined observational studies and randomized controlled trials. The main finding was that transfusion of older blood significantly increased the risk of death (odds ratio: 1·16, 95% CI: 1·07–1·24) when compared to fresher blood. A 2016 update of this meta-analysis analysed the reported data from RCTs and observational studies separately [44]. The 31 observational studies showed an increased risk of death when older blood was transfused (OR: 1·13, 95% CI: 1·03–1·24) (P = 0·01), whereas the results from six RCTs did not show a difference (OR: 0·91, 95% CI: 0·77–1·07) [44]. The results provide an example of how bias may influence results in observational studies compared to RCTs.

In 2016, our group published a systematic review of 12 RCTs comparing fresher versus older blood cell transfusion.[30] Mortality proved similar in fresher or older red blood cell transfusion, but the confidence interval was considerably wider than in the current review, still including possible benefit from fresher red blood cells (RR: 1·04, 95% CI: 0·94–1·14, P = 0·45, I² = 0%). The results of our updated review/meta-analysis are similar, but the narrower confidence interval excludes all but a trivial benefit from fresher red blood cells.

**Implications**

Our results essentially exclude a benefit from transfusion of fresher compared with older red blood cells; however, they do not exclude the possibility that transfusion of fresh red blood cells is associated with an increase in mortality. This possibility is relevant for certain populations, such as neonates in the NICU and patients with inherited disorders of haemoglobin production requiring lifelong transfusion support, who often receive fresher blood. Fresh red blood cells can have higher concentrations of extracellular vesicles and cell-free DNA, possibly reflecting differences in the method of red cell collection (apheresis, whole blood) and the method by which whole blood is separated into a fresh red cell product [45]. Extracellular vesicles and cell-free DNA may play a role in inflammation, immune modulation and risk of thrombosis [46]. One large retrospective study has shown an association between the method of processing whole blood donations and in-hospital mortality in transfused adult patients [47].

The American Association of Blood Banks (AABB) has recommended in their revised red cell transfusion guidelines that patients ‘should receive red blood cell units selected at any point within their licensed dating period (standard issue) rather than limiting patients to transfusion of only fresh units’ [48]. Our results are consistent with this position and provide no support for the selective use of fresh red blood cells.

**Conclusion**

This systematic review and meta-analysis included the most recent randomized controlled trials and established that the transfusion of fresher red blood cell does not reduce mortality when compared with older red blood cells.
Table 2 GRADE evidence profile

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality outcome</td>
<td>14 RCTs</td>
<td>Not serious(^a)</td>
<td>Not serious(^b)</td>
<td>Not serious(^c)</td>
<td>Not serious(^d)</td>
<td>None(^e)</td>
<td>Fresher blood: 1219/9532 (12.8%)</td>
<td>RR 1.04 (0.98-1.12)</td>
<td>Five more deaths per 1000 (2 fewer deaths to 13 more per 1000)</td>
<td>⬠⬠⬠⬠ High(^f)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sample: n = 26377 events: n 3029</td>
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</tr>
<tr>
<td>In-hospital mortality outcome</td>
<td>6 RCTs</td>
<td>Not serious(^a)</td>
<td>Not serious(^b)</td>
<td>Not serious(^c)</td>
<td>Not serious(^d)</td>
<td>None(^e)</td>
<td>Fresher blood: 691/7479 (9.2%)</td>
<td>RR 1.06 (0.97-1.15)</td>
<td>Six more deaths per 1000 (2 fewer deaths to 14 more per 1000)</td>
<td>⬠⬠⬠⬠ High(^f)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sample: n = 22235 events: n 1982</td>
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</table>

CI, confidence interval; RR, risk ratio; RCT, randomized controlled trials.

\(^a\)Studies were at low risk of bias (Fig. S1).

\(^b\)For all outcomes, visual inspection of the forest plot, the test for heterogeneity (non-significant) and the \(I^2\) results of 0% all suggested consistent relative effects.

\(^c\)All studies enrolled relevant representative populations.

\(^d\)Confidence intervals demonstrate adequate precision.

\(^e\)We identified no reason to suspect publication bias or any other biases of material impact on the analysis.

\(^f\)High certainty for benefit and moderate certainty for harm of fresh red blood cells on mortality.
Role of the funding source

There was no funding source. CC and PEA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors

CC, NMH, MAC and PEA conceived designed. JWE and GG supervised the study. CC and PEA performed the analysis and drafted the report. GG and JWE supervised data interpretation. All authors critically revised the report.

Conflict of interests

MAC discloses having sat on advisory boards for Janssen, Leo Pharma, Portola and AKP America. MAC holds the Leo Pharma Chair in Thromboembolism Research at McMaster University. MAC’s institution has received funding for research projects from Leo Pharma and Bayer. MAC has received funding for presentations from Leo Pharma, Bayer, Celgene, Shire and CSL Behring. None of the other authors declares any competing interests.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig. S1 Summary of risk of bias assessment.

Fig. S2 Forest plot of overall mortality comparing fresh versus old red blood cells transfusion, subgroup analysis according to duration of red blood cells storage.

Fig. S3 Forest plot of overall mortality comparing fresh versus old red blood cells transfusion, subgroup analysis according to age of participants.