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Transfusion of recently donated (fresh) red blood cells (RBCs) does not improve survival in comparison with current practice, while safety of the oldest stored units is yet to be established: a meta-analysis

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Abstract

Background and Objectives—Preclinical studies generated the hypothesis that older stored red blood cells (RBCs) can increase transfusion risks. To examine the most updated and complete clinical evidence and compare results between two trial designs, we assessed both observational studies and randomized controlled trials (RCTs) studying the effect of RBC storage age on mortality.

Materials and Methods—Five databases were searched through December 2014 for studies comparing mortality using transfused RBCs having longer and shorter storage times.

Results—Analysis of six RCTs found no significant differences in survival comparing current practice (average storage age of 2 to 3 weeks) to transfusion of 1- to 10-day-old RBCs (OR 0.91, 95% CI 0.77–1.07). RBC storage age was lower in RCTs vs. observational studies ($P=0.01$). The 31 observational studies found an increased risk of death (OR 1.13, 95% CI 1.03–1.24) ($P=0.01$) with increasing age of RBCs, a different mortality effect than RCTs ($P=0.02$).

Conclusion—RCTs established that transfusion of 1- to 10-day-old stored RBCs is not superior to current practice. The apparent discrepancy in mortality between analyses of RCTs and observational studies may in part relate to differences in hypotheses tested and ages of stored RBCs studied. Further trials investigating 1-to 10-day-old stored RBC benefits would seem of lower priority than studies to determine whether 4- to 6-week stored units have safety and efficacy equivalent to the 2- to 3-week-old stored RBCs commonly transfused today.

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Conflicts of interest

The authors declare no conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article: Data S1. Search Terms.

Keywords

blood safety; clinical trial; quality control; red cell components; transfusion medicine (in general); transfusion therapy

Introduction

Red blood cells (RBCs) stored for transfusion progressively undergo a series of metabolic and rheologic changes referred to as the 'storage lesion' [1]. Although some loss of efficacy likely occurs at the end of the 5- to 7-week storage period (depending on the country) [2], a decrease in safety is not expected. However, laboratory [1], preclinical animal [3] and clinical studies [4] suggest that transfusion of RBCs at the end of the storage period may increase morbidity and/or mortality. There is no standard definition for either 'old' or 'fresh' red cells, and the terms relate to arbitrary short and long refrigerated storage intervals.

In a prior analysis of primarily observational studies, transfusion of older, conventionally issued RBCs was reported to increase mortality [4]. The emphasis on observational studies was necessary because of the paucity of randomized controlled trials (RCTs), accounting only for 126 patients. Since the publication of this analysis in 2012, multiple large RCTs have been completed and published. These RCTs compared current practice, where transfused RBCs are stored on average for 2 to 3 weeks, to very fresh RBCs, transfused within the first 10 days after donation. The number of observational studies evaluating the effect of RBC storage on outcomes has also surged during this time. Observational studies compared two age groups of stored RBCs commonly found within current practice: the shortest to the longest transfused conventionally issued RBCs within usual care. These two types of studies addressed slightly different questions, respectively: whether 1- to 10-day-old stored RBCs should be transfused instead of current practice, and whether the acceptable RBC storage time should be decreased by excluding the oldest units currently licensed for transfusion. Therefore, to assess the most updated clinical evidence examining the effect of storage age of RBCs on mortality, we have reviewed the available data from recent RCTs and observational studies and compared results between the two trial designs.

Materials and methods

Data sources and study selection

Five databases (PubMed, EMBASE, Web of Science, Scopus and Cochrane library) were searched from May 2011 to 15 December 2014 for publications in English comparing mortality in patients transfused with shorter and longer stored RBCs (supplemental methods). Abstracts from transfusion medicine conferences and published systematic reviews were also reviewed to identify studies. Studies were excluded if they did not report mortality data or document the storage age of transfused RBCs. For clinical studies of storage age with outcomes other than mortality, the authors were queried about mortality rates and, if provided, included in the meta-analysis [5, 6].

Our literature search yielded a total of 565 new publications since May 2011. After excluding those articles unrelated to RBC storage and those not in English ($n = 509$), 39

articles and one conference abstract were evaluated in detail. Studies that did not report mortality or storage age of transfused RBCs adequately were further excluded. Fifteen studies met inclusion criteria (Fig. 1, Tables 1, 2) and were added to the 21 trials from our previous meta-analysis. After completion of our search, another multicentre RCT was published [7] that enrolled more than double the sum of the patients in the previous five RCTs and was therefore included in a number of confirmatory analyses. RCTs and observational studies were analysed separately given their differences in study design, and hypothesis tested.

Data extraction

Two investigators (K.E.R and I.C.P.) independently reviewed each publication and extracted data on study design, patient characteristics, storage age of transfused RBCs and mortality rates (Tables 1, 2). A third reviewer resolved disagreements (C.N.).

Data synthesis and analysis

The odds ratio of death (OR) following transfusion of old versus fresh stored RBCs was estimated using a random-effects model. Each study was summarized consistent with our previous meta-analysis [4]. We considered statistical significance ($P < 0.05$) when the OR did not cross 1. When both count data (survivor or non-survivor) and adjusted results [hazard ratio (HR), odds ratio (OR) or relative risk (RR)] were provided, all analyses were performed using both the adjusted data and the counts. Heterogeneity among studies was assessed using the Q statistic and I^2 value. See supplemental methods for further details.

Results

Study characteristics

Tables 1, 2 summarize the characteristics of the included studies. Two RCTs [8, 9] and thirteen observational studies [5, 6, 10–20] published between 2011 and 2015 were added to the 21 studies (18 observational studies and 3 RCTs) included in our previous analysis (Fig. 1, Tables 1, 2) [21–38]. One RCT [39] was reported only in abstract form during our study enrolment period, but has subsequently been published in full [9].

Effect of old *versus* fresh transfused RBCs on mortality

Among the five RCTs [8, 9, 40–42], comparing 1- to 10-day-old stored RBC transfusion to usual care, heterogeneity was minimal ($I^2 = 0\%$, $P = 0.56$) and there was no significant effect on mortality [OR of death = 1.03, 95% confidence interval (CI) = 0.72–1.47, Fig. 2]. Including a large RCT in critically ill patients completed after the enrolment dates for studies in our meta-analysis [7], the effect of 1- to 10-day-old stored RBC transfusion on mortality compared to current practice among the six RCTs was similar, with minimal heterogeneity among the trials ($I^2 = 0\%$, $P = 0.61$), and a non-significant effect on mortality (OR = 0.91, 95% CI = 0.77–1.07). Based on the combined results of six RCTs, including 4031 patients, transfusion of recently donated RBCs offers no survival advantage in comparison with current practice.

In contrast, among the 31 observational studies evaluating current practice, there was moderate heterogeneity ($I^2 = 38.9\%$, $P = 0.02$), and overall, the OR of death with transfusion of older compared with fresher conventionally issued RBCs was significantly increased 1.13 (95% CI = 1.03–1.24) (Fig. 3). When the analysis was done using adjusted results instead of counts for those studies in which these data were available, heterogeneity among studies moderately increased ($I^2 = 59.4\%$) and the overall effect size was slightly greater (OR = 1.18, 95% CI = 1.01–1.36). We performed multiple subgroup analyses aiming at identifying potential sources of this increased heterogeneity (supplemental results). An overall increase in mortality with longer stored transfused RBCs was consistently found among different surgical patient populations, in both adult and paediatric studies regardless of the volume of RBCs transfused, the size of the study and the date of publication (Supplemental Figures 2–8). The results of these sensitivity analyses were essentially unchanged if counts alone were employed or if adjusted analyses were substituted for counts when available. However, in contrast to the lack of significant mortality differences found in the six RCTs, among the 31 observational studies there was a different effect on mortality ($P = 0.01$), with a significant increase during current practice in mortality with transfusion of older *versus* fresher conventionally issued RBC units.

We next examined whether the different study designs employed and data sets obtained were associated with any divergence in the storage age of transfused RBCs. Among observational studies [6, 10–12, 14–18, 23, 24, 29, 30, 35, 38] and RCTs [7–9, 41, 42] reporting the median or mean storage age for the two transfused groups, we found that, although the degree of the differences in the storage age of transfused RBCs between the old and fresh RBC groups was similar for observational studies and RCTs ($P = 0.69$ for interaction), there was an overall significant downward shift of the median/mean storage age of transfused RBCs from the observational studies to the RCTs (main effect, $P = 0.01$) (Fig. 4). Thus, the median/mean storage age of transfused RBCs was significantly lower in both arms of the RCTs compared with both arms of the observational studies.

In the observational studies, a baseline difference in severity of illness of patients could underlie the ‘harmful’ effect of older RBCs. In 8 of 31 observational studies, the baseline severity of illness of patients in both study arms was described using a variety of scoring systems (Supplemental Figure 1) [10, 11, 14, 16–18, 25, 30]. In these studies with different severity of illness score balances between older and fresher RBC transfusion, there was no significant difference in treatment effect ($P = 0.66$ for interaction) and overall, among these eight studies, older RBC transfusion significantly increased the risk of death (OR = 1.46, 95% CI = 1.00–2.14, $P = 0.05$). Furthermore, five studies had identical baseline severity of illness scores in the two arms and also found an increased risk of death with transfusion of longer stored RBCs (OR = 1.65, 95% CI = 0.96–2.82, $P = 0.07$). These results are unchanged if we use count data alone for analysis or substitute adjusted values for counts when available. Examining the 10 observational studies with adjusted analysis and a low risk of bias, there was still an overall increase in the OR of death with transfusion of older *versus* fresher stored RBCs (OR = 1.12, 95% CI = 0.87–1.44) (Supplemental Figure 9). See supplemental results for details on the risk of bias within studies and publication bias.

Discussion

The six RCTs included in this analysis addressed the hypothesis that recently obtained RBCs, transfused 1–10 days after donation, are superior to the 2- to 3-week-old RBCs commonly transfused in standard practice. Ethical considerations prevented the six RCTs from intentionally ‘ageing’ RBCs and selecting the longest possible stored units to be randomized for human use. Therefore, these RCTs focused on evaluating the potential benefit of transfusing very recently donated RBCs, rather than on the potential risks associated with transfusing the longest possible stored units licensed for transfusion. These RCTs are appropriately assigned the highest level of evidence, and their combined analysis confirms that recently donated RBCs provide no survival advantage to current practice. This result was consistent across different clinical populations, including neonatal [8], cardiac surgery [9] and critically ill patients [7].

No similar body of high-quality evidence evaluating the risks of transfusing the oldest stored RBCs exists. The RCTs performed to date cannot exclude the possibility that RBCs stored for 4 to 6 weeks increase the risks of transfusion. The best available evidence evaluating the potential risks associated with transfusing these oldest RBCs is provided by a large number of observational analyses that studied significantly older RBC units than did the RCTs and were designed specifically to examine in usual practice the risk of the oldest donated RBCs. These observational studies suggest an overall increase in the OR of death with transfusion of longer stored conventional issue RBCs.

Evidence from non-randomized studies is not equivalent to evidence from RCTs. Lack of randomization and controls can subject observational studies to both recognized and unrecognized bias [43]. Even large observational studies are useful primarily for generating hypotheses. However, in our analysis, the adverse effect of longer stored RBC transfusion on survival rates was also present among those studies with a lower risk of bias that reported adjusted mortality data based on prognostic factors (Supplemental Figure 9). Even observational studies in which the baseline severity of illness score was identical for patients enrolled in the two arms found a significant increase in mortality risk with older stored transfused RBCs (Supplemental Figure 1). Consistent with observational studies, a large body of animal data [3, 44–46] suggests that transfused RBCs stored for more than 4 weeks can worsen outcomes, particularly in clinical settings such as infection in which the consequences of *in vivo* haemolysis, with iron and cell-free haemoglobin release, may increase risks.

Despite being considered the highest level of evidence, RCTs are also subject to acknowledged limitations. RCTs represent a snapshot over a short period of time and may not be fully representative of the total target population and of actual usual care practices. Further, most of the RCTs included here had substantial overlap in the ages of RBCs transfused in both groups. Our meta-analysis did not evaluate the effects of different storage ages of transfused RBCs on outcomes other than mortality. However, recently published systematic reviews of exclusively RCTs have evaluated the effect of fresher RBCs compared to current practice on secondary outcomes and found minimal adverse effects [47, 48].

Multiple *in vitro* experiments [1, 49], studies conducted in human volunteers [50] and animal models [3, 44], have provided evidence that RBCs undergo a series of progressive changes during storage. With increasing storage age, haemolysis occurs both in the storage bag and *in vivo* after transfusion, with release of iron and cell-free haemoglobin (CFH) [3, 44, 46, 51]. Increases in iron and CFH with transfusion may increase risks by well-defined mechanisms. Transfusion of 42-day-old stored RBCs in human volunteers [50] and animal models [3, 44–46, 51] results in increased plasma levels of iron in the form of non-transferrin-bound iron (NTBI). Increases in plasma NTBI have been shown to worsen outcomes in the presence of established infection [3, 44–46, 51, 52]. Similarly, in populations at risk of infection, increasing volumes of older RBC transfusion appear to be associated with an increased risk of complicated sepsis [53]. Increased CFH levels can also worsen outcomes through the vascular effects of nitric oxide (NO) scavenging [54, 55]. Transfusion-related increases in CFH have been shown in canines to scavenge NO, producing significant vascular effects [3].

Whereas the UK, the Netherlands and several other countries have limited the storage period of RBCs to 35 days or less, longer stored RBCs are still transfused throughout the world. Few published data and statistics address distribution of transfused RBCs by storage age. The mean age of conventionally issued transfused RBCs in the USA is only 17.9 days [6]. However, unpublished data from major blood collectors in the USA indicate that thousands of units of RBCs aged 4 to 6 weeks are released from blood collectors each week, accounting for approximately 8–18% of all the released RBC units (HG Klein, personal communication). Many more fresher units released to hospitals likely reach the last 2 weeks of storage on the hospital shelf prior to transfusion. This is of more than academic interest. While RCTs have successfully addressed whether recently donated RBCs are safer to transfuse than current transfusion practice, the potentially harmful effects of the longest possible stored RBCs are still incompletely understood.

Moderately sized RCTs similar to the ones included in our analysis are unlikely to answer whether the longest possible stored RBCs are safe for transfusion. Such trials do not enrol a large enough group of patients transfused with RBCs at the end of the storage period for meaningful comparisons. Future directions should focus on alternative study designs such as multicentre RCTs in which patient enrolment is limited to days when stored RBCs available for transfusion are older than 4 weeks, or large ‘pragmatic’ multicentre RCTs such as the INFORM trial in Canada which has enrolled 31 497 patients across four countries [56]. Lastly, high-quality, prospective, observational studies with a careful adjustment for prognostic factors and an adequate sample size can provide relevant data to address this question. There remains a pressing need to establish the safety of RBCs transfused at the end of the licensed storage period worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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JS performed statistical analyses; JW performed the literature search; DW and SBS helped in manuscript preparation; KER, IC, HGK and CN participated in study design literature search, data extraction, data analysis/interpretation and manuscript preparation.

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Fig. 1.
Study selection.

Randomized controlled trials (RCTs)

(author/date published^{reference})

Fig. 2.

Mortality in randomized controlled trials (RCTs). Lacroix trial was published after are enrolment period closed and part of a post hoc analysis. The size of the data markers is proportional to the inverse variance of each point estimate.

Observational studies(author/date published^{reference}) **Fig. 3.**

Mortality in observational studies. The overall summary of observational studies is provided using both counts for all studies and using adjusted results when available. The summary data show the RCTs had a significantly different effect on mortality than observational studies.

Fig. 4. Storage age of transfused red blood cells comparing observational studies and RCTs divided into older versus fresher blood groups.

Table 1

Characteristics of randomized controlled trials included in the meta-analysis

Author [Reference]	Years of Enrollment	Study Type	Study Population	No. of Patients in study	No. of Patients used in Meta-analysis	Mean volume of RBCs transfused (units of PRBC)	Age of stored blood compared ^a		Actual median age of stored blood		Blood storage solution ^b	Leucoreduced	Mortality	Risk of bias
							New blood (days)	Old blood (days)	New blood (days)	Old blood (days)				
Schulman 06/02	2000–2001	RCT	Trauma	17	17	New = 9.3 (1.9), Old = 10.6 (3.35) ^e	<11	>20	NR	NR	NR	Yes	Hospital mortality	Higher
Hebert 05/05	1999–2001	RCT	Cardiac surgery	57	57	New = 3 (2–5), Old = 2 (2–4) ^c	<8	15–42	4 ^d	19 ^d	CPD-2, AS-3	Yes	Hospital mortality	Lower
Fernandes da Cunha 12/05	2002–2003	RCT	Premature infant	52	52	New = 4.2 (3.1), Old = 4.4 (4.0) ^e	1–6	9	1–6 (0.6) ^e	9–0 (8.9) ^e	CPDA-1	Yes	Hospital mortality	Higher
Fergusson 10/12	2006–2011	RCT	NICU patient	377	377	New = 5.01 (4.00), Old = 4–94 (3.88) ^e	<7	2–42	5.1 (20) ^e	14.6 (8.3) ^e	CPD, SAGM, AS-3	Partially	90-day mortality	Lower
Steiner 09/14	2010–2014	RCT	Cardiac surgery	1481	1098	New = 3 (2.6), Old = 4 (2.6) ^c	<10	>21	7 (5–9) ^c	28 (24.33) ^c	AS-3	Yes	28-day mortality	Lower
Lacroix 03/15	2009–2014	RCT	ICU patient	2430	2430	New = 4.3 (5.2), old = 4.3 (5.5) ^h	<8	1–42	6.1 (4.9) ^e	22.0 (8.4) ^e	SAGM	Yes	90-day mortality	Lower

NR, not reported; OBR, observational retrospective study; OBP, observational prospective study; RCT, randomized controlled trial; ICU, intensive care unit; PICU, pediatric intensive care unit; PRBC, packed red blood cells.

^aWhen multiple ages of stored blood were presented only the extremes were analysed (see statistical method).

^bThe numbers and letters indicate the type of storage solution: C=citrate, A=adenine, P=phosphate, D=dextrose, S=sodium chloride, M=mannitol, G=glucose.

^cMedian (IQR).

	d_p	Median	e_p	Mean (SD)
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Table 2

Characteristics of observational studies included in the meta-analysis

Author (Reference)	Years of enrollment	Study type	Study population	No. of patients in study	No. of patients used in the meta- analysis ^a	Mean volume of RBCs transfused (units of PRBC)	Age of stored blood compared ^a		Actual median age of stored blood		Blood storage solution ^c	Leucoreduced	Mortality	Risk of bias
							New blood (days)	Old blood (days)	New blood (days)	Old blood (days)				
Mynster 07/01	1991–1993	OBP	Colorectal surgery	740	429	3 ^g	<21	>21	19 (3–35) ^b		SAGM	Yes	Long-term mortality	Higher
Murrell 09/05	2001–2002	OBR	Trauma	275	275	3 (2–6) ^a	NR	NR	NR	NR	NR	Yes	Hospital mortality	Higher
Van de Watering 10/06	1993–1999	OBR	Cardiac surgery	2732	1895	New = 4 (3–5), Old = 4 (3–5) ^a	<18	>18	13 (11–14) ^d	24 (21–27) ^d	SAGM	Yes	30-day mortality	Lower
Koch 03/08	1998–2006	OBR	Cardiac surgery	6002	6002	2 (2–4) ^a	<14	>14	11 (3–9) ^a	20 (17–25) ^a	NR	NR	Hospital mortality	Lower
Leal-Naval 04/08	2004–2006	OBP	Anemia	66	34	NR	<10	>19	16 (8–8) ^b		SAGM	Yes	ICU mortality	Higher
Weinberg 08/08	2000–2007	OBR	Trauma	1813	1169	4.95 (1–74) ^j	<14	>14	NR	NR	NR	Yes	Hospital mortality	Higher
Yap 08/08	2001–2007	OBR	Cardiac surgery	670	670	3 (2–5) ^a	<14	>14	8 &	19 &	NR	Partially	Hospital mortality	Lower
Weinberg 10/08	2000–2007	OBR	Trauma	430	430	3 (1–104) ^b	<14	>14	NR	NR	NR	Yes	Hospital mortality	Lower
Spinel la 09/09	2004–2007	OBR	Trauma	202	176	New = 9 (6–12.5), old = 9 (6–12) ^a	<21	>21	14 (11–17) ^a	20.5 (15.5–26) ^a	NR	Partially	Hospital mortality	Higher
Van Buskirk 09/09	NR	OBR	ICU patient	298	298	NR	<8	>14	NR	NR	NR	NR	Hospital mortality	Lower
Karam 04/10	2004–2005	OBP	PICU patient	296	296	New = 2.6 (3.6), old = 5.5 (5.7) ^h	<14	>14	14 ^c		NR	Partially	28-day mortality	Higher
Eikelboom 05/10	2002–2006	OBP	Cardiac disease	4933	4933	3 (2–5) ^a	<10	31–42	17 (13–22) ^a		AS-3	Yes	Hospital mortality	Lower
Robinson 05/10	1999–2005	OBR	Cardiac surgery	909	712	2 (1–21) ^b	<21	>21	25 (18–34) ^a		NR	Yes	30-day mortality	Higher
Edgren 06/10	1995–2002	OBR	Transfused at least one RBC unit	387 130	387 130	New = 2 (2.4), old = 2 (2–3) ^a	<9	>30	7 (5–8) ^a	34 (31–37) ^a	SAGM	NR	Short-term mortality (1 week)	Higher
Gauvin 09/10	2001–2005	OBP	PICU patient	455	224	New = 1.2 (0.5),	<7	>21	16.7 (10.3) ^b		NR	Yes	28-day mortality	Higher

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Author (Reference)	Years of enrollment	Study type	Study population	No. of patients in study	No. of patients used in the meta- analysis ^d	Mean volume of RBCs transfused (units of PRBC)	Age of stored blood compared ^a		Actual median age of stored blood		Blood storage solution ^c	Leucoreduced	Mortality	Risk of bias
							New blood (days)	Old blood (days)	New blood (days)	Old blood (days)				
Weinberg 12/10	2000–2009	OBR	Trauma	1647	1647	New = 2.9, old = 3.4	<14	>14	NR	NR	NR	Yes	Hospital mortality	Higher
Van Straten 01/11	1998–2007	OBR	Cardiac surgery	3,597	3,141	New = 2.6 (1.5), old = 2.4 (1.4) ^b	<14	>14	NR	NR	SAGM	Yes	30-day mortality	Lower
Petti la 04/11	2008	OBR	CU patient (55% surgical, 45% non-surgical)	757	379	2 (1–4) ^a	<11	>28	7.7 (2–11) ^b	34.4 (28–42) ^b	NR	Partially	Hospital mortality	Lower
Mc Kenny 05/11	2002–2007	OBR	Cardiac surgery	1153	972	New = 2.4 (1.5), Old = 4.6 (3.9) ^b	<14	>14	10.8 (2.6) ^b	25.4 (4.8) ^b	NR	Yes	30-day or hospital mortality	Lower
Sanders 11/11	2005–2007	OBR	Cardiac surgery	176	142	2 (1–2) ^a	<14	>14	9 (2–12) ^a	20 (16–23) ^b	NR	Yes	Hospital mortality ^d	Higher
Phelan 02/12	NR	OBR	Trauma	153	153	9.9 (9.0) ^b	<14	>14	NR	NR	NR	Yes		Higher
Dunn 04/12	2000–2010	OBR	Orthotopic liver transplantation	509	509	10 (5–18) ^a			11.8 &	20 &	NR	NR	2-y mortality	Lower
Middelburg 01/13	2005–2009	OBR	Adult patients	4549	947	New = 2 (2–3), Old = 2 (2.3) ^a	<10	>24	NR	NR	SAGM	Yes	1-y mortality	Higher
Kadar 06/13	2007–2010	OBR	Hip fracture surgery	1381	663	New = 1.36, old = 1.33	<14	>14	9.1 ⁱ	22.3 ^j	NR	NR	1-year mortality	Higher
Kaukonen 10/13	2011	OBR	ICU patient	652	652	3 (2–6) ^b			12 (10–13) ^a	21 (16, 27) ^a	SAGM	Yes	Hospital mortality	Lower
Cywinski 11/13	2001–2011	OBR	Orthotopic liver transplantation	820	637	New = 6 (3–9), Old = 6 (3–10) ^e	<15	>15	12 (9–13) ^a	19 (18–22) ^a	NR	NR	ICU mortality	Higher
Cartotto 03/14	2000–2010	OBR	Burns > 20% TBSA	127	127	11 (1–40) ^b	<28	>28	22.2 (10.3–28) ^b	31.5 (28.3–41) ^b	AS-3, SAGM	Yes	ICU mortality	Higher
Aubron 06/14	2001–2011	OBR	ICU patient	8416	8416	4 (2–7) ^a	<21	>21	13 (9–17) ^a	27 (24–31) ^a	NR	Partially	Hospital mortality	Lower
Baltsavias 06/14	2006–2010	OBR	Pediatric cardiac surgery	570	570	New = 1.11, Old = 1.16	<7	>7	6 (5–7) ^a	14 (11–19) ^a	SAGM	No	ICU mortality	Higher
Min 10/14	2005–2012	OBR	Cardiac surgery	1072	1072	7(8) ^b	<14	>14	11.7 (5.2) ^b		CPDA-1	No	Hospital mortality	Lower

Author (Reference)	Years of enrollment	Study type	Study population	No. of patients in study	No. of patients used in the meta- analysis ^d	Mean volume of RBCs transfused (units of PRBC)	Age of stored blood compared ^a		Actual median age of stored blood		Blood storage solution ^c	Leucoreduced	Mortality	Risk of bias
							New blood (days)	Old blood (days)	New blood (days)	Old blood (days)				
Heddle 02/15	2006–2011	OBR	Cardiac disease	4594	4594	3 (2–5) ^a	<14	>35	18 (14–24) ^{a,b}		AS-3	Yes	Hospital mortality	Lower

NR not reported; OBR, observational retrospective study; OBP, observational prospective study; RCT, randomized controlled trial; ICU, intensive care unit; PICU, pediatric intensive care unit; PRBC, packed red blood cells.

^aWhen multiple ages of stored blood were presented, only the extremes were analysed (see statistical method).

^bSee statistical method for how stored blood groups were determined for comparison. For Pettila, Table 2 data was used. For Heddle, Table 3 results for week 6 vs. weeks 1–2 were used.

^cThe numbers and letters indicate the type of storage solution: C = citrate, A = adenine, P = phosphate, D = dextrose, S = sodium chloride, M = mannitol, G = glucose.

^dRaw mortality data was obtained directly from the authors.

^eMedian (IQR).

^fMedian (range).

^gMedian.

^hMean (SD).

ⁱMean (range).