ORIGINAL ARTICLE

Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults

D. James Cooper, M.D., Zoe K. McQuilten, Ph.D., Alistair Nichol, Ph.D., Bridget Ady, M.Clin.Res.Meth., Cécile Aubron, Ph.D., Michael Bailey, Ph.D., Rinaldo Bellomo, M.D., Dashiell Gantner, M.B., B.S., David O. Irving, Ph.D., Kirsi-Maija Kaukonen, Ph.D., Colin McArthur, M.B., Ch.B., Lynne Murray, B.App.Sci., Ville Pettilä, Ph.D., and Craig French, M.B., B.S., for the TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

It is uncertain whether the duration of red-cell storage affects mortality after transfusion among critically ill adults.

METHODS

In an international, multicenter, randomized, double-blind trial, we assigned critically ill adults to receive either the freshest available, compatible, allogeneic red cells (short-term storage group) or standard-issue (oldest available), compatible, allogeneic red cells (long-term storage group). The primary outcome was 90-day mortality.

RESULTS

From November 2012 through December 2016, at 59 centers in five countries, 4994 patients underwent randomization and 4919 (98.5%) were included in the primary analysis. Among the 2457 patients in the short-term storage group, the mean storage duration was 11.8 days. Among the 2462 patients in the long-term storage group, the mean storage duration was 22.4 days. At 90 days, there were 610 deaths (24.8%) in the short-term storage group and 594 (24.1%) in the long-term storage group (absolute risk difference, 0.7 percentage points; 95% confidence interval [CI], –1.7 to 3.1; P=0.57). At 180 days, the absolute risk difference was 0.4 percentage points (95% CI, –2.1 to 3.0; P=0.75). Most of the prespecified secondary measures showed no significant between-group differences in outcome.

CONCLUSIONS

The age of transfused red cells did not affect 90-day mortality among critically ill adults. (Funded by the Australian National Health and Medical Research Council and others; TRANSFUSE Australian and New Zealand Clinical Trials Registry number, ACTRN12612000453886; ClinicalTrials.gov number, NCT01638416.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Cooper at the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, 553 St. Kilda Rd., Melbourne, VIC 3004, Australia, or at jamie.cooper@monash.edu.

*A complete list of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Cooper, McQuilten, and Nichol contributed equally to this article.

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Red-cell transfusions are common in critically ill patients,[1-3] and red cells may be stored for up to 42 days depending on manufacturing process, additive solution, and local policies or regulations.[4,5] During storage, red cells undergo structural, biochemical, and metabolic changes, known as the "storage lesion,"[5] and may cause harm.[6,7] However, usual practice is for blood banks to issue the oldest compatible red-cell units available.[8]

Transfusion of older red cells has been associated with increased morbidity and mortality among critically ill, surgical, and trauma patients.[6,7] Critically ill patients may be more sensitive than others to any adverse effects associated with red-cell storage.[6,9,10] The Age of Blood Evaluation (ABLE) trial[11] studied 2430 critically ill adults with a high risk of death, and the unblinded, randomized Informing Fresh versus Old Red Cell Management (INFORM) trial[12] involved unselected hospitalized adults, including 10,578 patients admitted to the intensive care unit (ICU). Both trials showed no significant differences in outcome between patients who received fresher red cells and those who received older red cells. In the ABLE trial, approximately 10 hours elapsed between randomization and first transfusion, which may have limited transfusion efficacy and decreased between-group differences. The mortality among the ICU patients in the INFORM trial was low, suggesting low illness severity. The smaller sample size of the ABLE trial and the limited outcome data in the INFORM trial reduced the capacity of these trials to detect small, important signals for harm, to evaluate key subgroups, and to rule out differences in nosocomial infections or transfusion reactions. Furthermore, a recent meta-analysis including these trials was unable to rule out harm from the transfusion of fresher red cells.[13]

We designed the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) trial to compare the effect of the freshest available red cells with that of standard-issue (oldest available) red cells, in 5000 high-risk critically ill patients. We hypothesized that administration of the freshest available red cells would result in lower 90-day all-cause mortality than administration of standard-issue red cells.

Methods

Trial Design

The TRANSFUSE trial was a multicenter, randomized, double-blind, parallel-group trial that compared the effect on mortality of the freshest available, compatible, allogeneic red cells with that of standard-issue red cells in critically ill patients who received a red-cell transfusion prescribed by their treating physician. We conducted the trial in 59 hospital ICUs in five countries: Australia (42 ICUs), New Zealand (8), Ireland (6), Finland (2), and Saudi Arabia (1).

Before enrollment was completed, we published the protocol and statistical analysis plan[14] (also available with the full text of this article at NEJM.org). Ethics committees at Monash University and each participating site approved the trial before patient enrollment. We applied waiver of consent, opt-out consent, or a deferred consent procedure, according to the requirements of the human research ethics committees at the participating institutions and local law. An independent data and safety monitoring committee oversaw the trial. The committee reviewed a planned interim analysis after 2500 patients had reached 90 days of follow-up.[14]

The Australian National Health and Medical Research Council, Australian Red Cross Blood Service, Health Research Council of New Zealand, and Irish Health Research Board funded the trial. The Australian and Finnish Red Cross Blood Services, New Zealand Blood Service, Irish Blood Transfusion Service, and the blood bank of King Abdulaziz Medical City, Riyadh, Saudi Arabia, provided support. No commercial entity supported this trial. The trial was designed by the authors, who vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. No one who is not an author or a member of the trial management committee contributed to the writing of the manuscript.

Patient Population

Patients 18 years of age or older who were admitted to a participating ICU, who had an anticipated ICU stay of at least 24 hours, and in whom the medical staff had decided to transfuse one

or more red-cell units were eligible for inclusion. Exclusion criteria were previous red-cell transfusion or cardiac surgery during the hospital admission, hematologic cancer, organ transplantation, pregnancy, expected death in less than 24 hours, objection to the administration of human blood products, participation in a competing study, and the opinion of the treating physician that randomization would not be in the best interest of the patient (lack of equipoise).

RANDOMIZATION

We concealed treatment-group assignments through a computer-generated schedule including variable-block randomization in a 1:1 ratio, with stratification according to center. To enroll patients, clinical ICU staff used a Web-based system that assigned a unique identification number. When provided with the identification number, hospital transfusion services assigned each patient to the appropriate treatment group according to the randomization schedule of the center, without the involvement of clinical staff.

We randomly assigned patients to receive either the freshest, compatible, allogeneic red-cell units available from the transfusion service (short-term storage group) or the oldest available, compatible, allogeneic red-cell units (long-term storage group). After discharge from the ICU, patients continued to receive red cells according to their assigned treatment group throughout their index hospital stay. Red cells were all leukoreduced before storage and resuspended in saline–adenine–glucose–mannitol additive solution with a 42-day shelf life (Australia and Saudi Arabia) or a 35-day shelf life (New Zealand, Finland, and Ireland). The treating physicians determined the indication for transfusion and the timing and number of red-cell units to be transfused.

Treatment-group assignments were concealed from treating medical and nursing staff, research staff, and statisticians. Two staff members who were not involved in the direct care of each trial patient checked the designated red-cell units for that patient and concealed the collection and expiration dates from clinical staff using a bag with opaque panels or (in New Zealand and Finland) an obscuring sticker. A previously published pilot study confirmed the effectiveness of this blinding method.[15] To ensure an adequate difference in the duration of red-cell storage between the two treatment groups, we assessed the storage duration at each site after 50 patients had received a transfusion, with a minimum difference of 7 days required for ongoing site participation.

OUTCOMES

The primary outcome was 90-day all-cause mortality. Secondary outcomes included 28-day mortality, persistent organ dysfunction or death at day 28, days alive and free of mechanical ventilation at day 28, days alive and free of renal-replacement therapy at day 28, new bloodstream infection in the ICU, febrile nonhemolytic transfusion reactions, length of stay in the hospital and in the ICU, and quality of life at day 180 after randomization. We followed patients until death or 180 days after randomization. We defined a febrile nonhemolytic transfusion reaction as occurring when a patient had an unexpected increase in temperature of 1°C or more within 4 hours after transfusion in the absence of other pyretic stimuli. Quality of life at day 180 after randomization is not reported here.

STATISTICAL ANALYSIS

We conducted all analyses in accordance with a predefined analysis plan.[14] With 4664 patients, this trial had 90% power to detect an absolute difference of 4.2 percentage points (15% relative difference) in 90-day all-cause mortality from 28% with a two-sided P value of 0.05. We estimated the baseline mortality rate from an in-hospital mortality rate of 25% that was measured among patients who met the inclusion criteria for the TRANSFUSE trial in a previous observational study, and we conservatively estimated 90-day mortality to be 28%.[6] We increased our planned enrollment to 5000 patients to account for an estimated loss to follow-up (<5%) and for a single interim analysis.

We performed all analyses on an intention-to-treat basis unless otherwise indicated, and no assumptions were made for missing data. We compared the primary outcome of 90-day all-cause mortality using an unadjusted chi-square test for equal proportions, and we report frequency (percentage) per treatment group with a risk difference and 95% confidence interval and a corresponding odds ratio and 95% confidence interval. We conducted sensitivity analyses using hierarchical multiple logistic regression: first, we adjusted for the risk of death as assessed by means of the Acute Physiology and Chronic Health Evaluation

(APACHE) III model, hemoglobin level at randomization, and blood group, with patients nested within sites and site treated as a random effect, and then we adjusted for patient age, which was imbalanced between the treatment groups at baseline. We assessed the duration of patient survival using Cox proportional-hazards regression with data on patients censored at 180 days of follow-up or the last known point of contact. We visually assessed the proportional-hazards assumption across treatment groups using log-cumulative hazard plots. We present survival results as Kaplan–Meier survival curves with a corresponding log-rank test for equality of survivor functions across treatment groups.

Prespecified subgroups for the analysis of the primary outcome were type O or non–type O blood group, APACHE III risk of death below or above the median, and Sequential Organ Failure Assessment (SOFA)[16] score at baseline below or above the median. We determined heterogeneity between subgroups by fitting an interaction between treatment and subgroup with the use of logistic regression.

We undertook additional prespecified secondary analyses to further assess the effect of storage duration on mortality, by analyzing storage duration independently of treatment assignments in quartiles and as a continuous variable and by comparing outcomes of patients who received only the freshest red cells (<8 days old) with those of the other patients. No adjustments were made for multiple comparisons, and therefore P values for results other than the primary outcome should be interpreted as exploratory.

RESULTS

PATIENTS

From November 2012 through December 2016, we identified 6353 potentially eligible patients, and 4994 underwent randomization. Of the randomly assigned patients, 39 (0.8%) withdrew consent and 36 (0.7%) were lost to follow-up at 90 days, leaving 4919 (98.5%) included in the primary analysis: 2457 in the short-term storage group and 2462 in the long-term storage group (Fig. 1).

Patient characteristics at baseline were balanced between the two treatment groups, with the exception of age (mean [±SD] age, 62.5±16.8 years in the short-term storage group vs. 61.4±17.3 years in the long-term storage group; P=0.02) (Table 1). The mean hemoglobin level at randomization was 77.4±12.8 g per liter in the short-term storage group and 77.3±13.0 g per liter in the long-term storage group (Table 1).

TRIAL TREATMENT

Patients received a mean of 4.1±6.0 red-cell units in the short-term storage group and 4.0±6.2 red-cell units in the long-term storage group. The mean storage duration of transfused red cells was 11.8±5.3 days in the short-term storage group and 22.4±7.5 days in the long-term storage group (Table 2), for a mean difference of 10.6 days (95% confidence interval [CI], 10.3 to 11.0). The distribution of the duration of red-cell storage is shown in Figure S1 in the Supplementary Appendix, available at NEJM.org. The number of patients who received other blood products was similar in the two groups (Table 2). The median time from randomization to first red-cell transfusion was also similar in the two groups: 1.6 hours (interquartile range, 0.8 to 2.7) in the short-term storage group and 1.5 hours (interquartile range, 0.8 to 2.7) in the long-term storage group (Table 2).

OUTCOMES

At 90 days after randomization, death had occurred in 610 patients (24.8%) in the short-term storage group and in 594 (24.1%) in the long-term storage group (absolute risk difference, 0.7 percentage points [95% CI, –1.7 to 3.1]; unadjusted odds ratio, 1.04 [95% CI, 0.91 to 1.18]; P=0.57) (Fig. 2). Adjustment for the four predefined baseline variables did not substantially alter this result (adjusted odds ratio, 1.05; 95% CI, 0.92 to 1.21; P=0.46). Further adjustment for patient age in addition to the predefined variables also did not substantially alter the results (Table S5 in the Supplementary Appendix).

There were no significant between-group differences in 28-day mortality; the rates of persistent organ dysfunction or death at day 28, new bloodstream infections, mechanical ventilation, and renal-replacement therapy; or ICU length of stay (Fig. 2). Febrile nonhemolytic transfusion reactions occurred more frequently in the short-term storage group than in the long-term storage group (123 events [5.0%] vs. 88 events [3.6%]; absolute risk difference, 1.4 percentage points [95% CI, 0.3 to 2.6]; unadjusted odds ratio, 1.42 [95% CI, 1.07 to 1.88]; P=0.01) (Fig. 2). After adjustment, the results were similar (adjusted odds

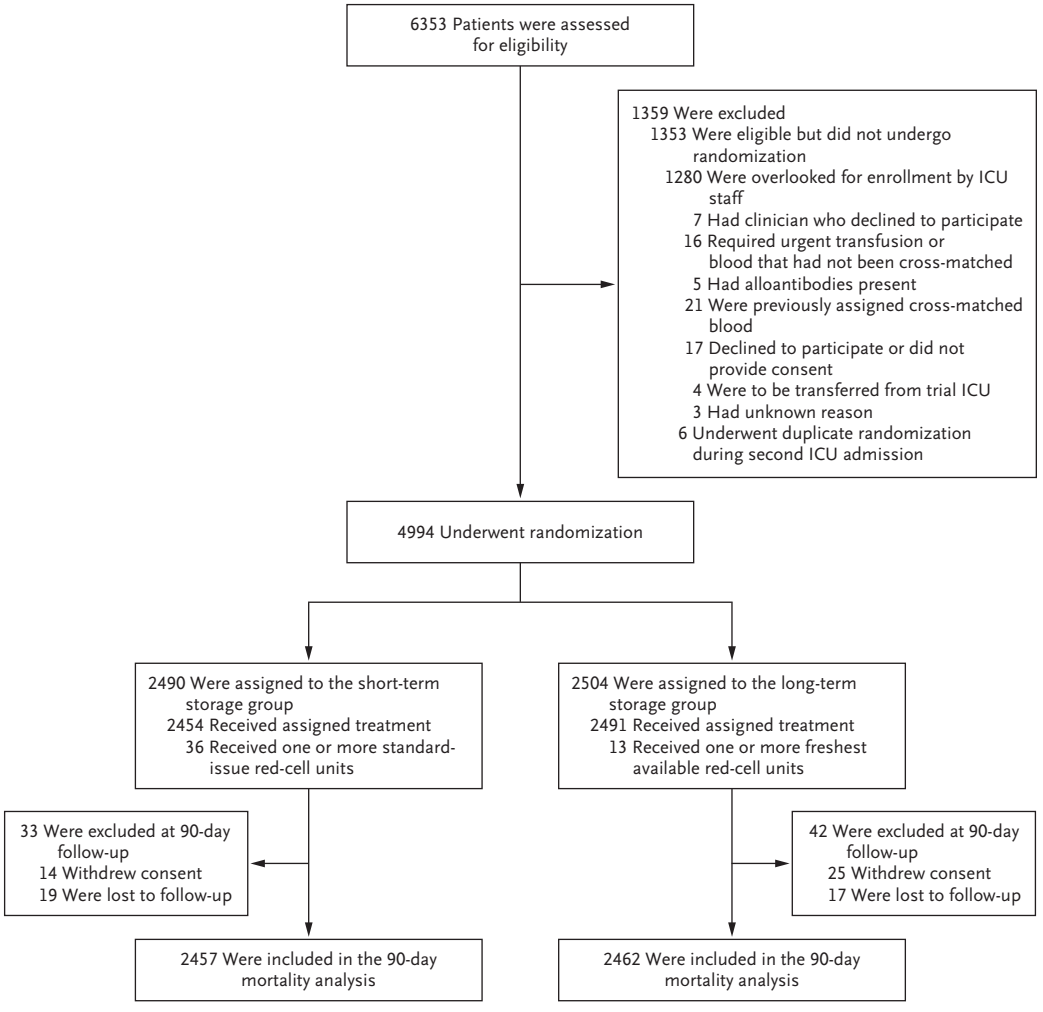


Figure 1. Randomization and Follow-up.
ICU denotes intensive care unit.

ratio, 1.45; 95% CI, 1.09 to 1.93; P=0.01). At 180 days after randomization, death had occurred in 687 of 2410 patients (28.5%) in the short-term storage group and in 678 of 2414 patients (28.1%) in the long-term storage group (absolute risk difference, 0.4 percentage points [95% CI, −2.1 to 3.0]; odds ratio, 1.02 [95% CI, 0.90 to 1.16]; P=0.75) (Fig. 2). Survival time according to treatment assignment is shown in Figure 3.

SUBGROUPS

The effect of red-cell storage duration on 90-day mortality differed significantly according to APACHE III risk of death (P=0.03 for heterogeneity). Patients who received the freshest available red cells had higher mortality in the subgroup with an APACHE III predicted risk of death at hospital discharge equal to or above the median of 21.5% (odds ratio, 1.18; 95% CI, 1.00 to 1.39; P=0.05) and lower mortality in the subgroup with a risk of death below the median (odds ratio, 0.86; 95% CI, 0.68 to 1.08; P=0.20). We observed no significant differences in the other subgroups (Fig. 2).

SECONDARY ANALYSES

The 90-day mortality in the quartile of all patients who received red cells with the oldest mean age did not differ significantly from that in the quartiles of patients who received fresher red cells. The mortality in each of the prespecified mean

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Short-Term Storage (N=2457)	Long-Term Storage (N=2462)	All Patients (N=4919)
Age — yr	62.5±16.8	61.4±17.3	62.0±17.1
Male sex — no. (%)	1311 (53.4)	1258 (51.1)	2569 (52.2)
Primary diagnosis — no. (%)†			
Cardiovascular condition	326 (13.3)	342 (13.9)	668 (13.6)
Respiratory condition	413 (16.8)	422 (17.1)	835 (17.0)
Gastrointestinal condition	551 (22.4)	514 (20.9)	1065 (21.7)
Neurologic condition	177 (7.2)	195 (7.9)	372 (7.6)
Sepsis	413 (16.8)	396 (16.1)	809 (16.4)
Trauma	240 (9.8)	262 (10.6)	502 (10.2)
Metabolic condition	68 (2.8)	71 (2.9)	139 (2.8)
Musculoskeletal condition	103 (4.2)	110 (4.5)	213 (4.3)
Renal condition	110 (4.5)	109 (4.4)	219 (4.5)
Other condition	51 (2.1)	35 (1.4)	86 (1.7)
Missing data	5 (0.2)	6 (0.2)	11 (0.2)
≥1 Coexisting condition — no. (%)‡	860 (35.0)	842 (34.2)	1702 (34.6)
APACHE III score§¶	72.6±29.2	73.2±29.6	72.9±29.4
APACHE III risk of death — %¶			
Median	20.9	22.0	21.5
IQR	8.5–46.0	8.7–46.7	8.6–46.5
SOFA score — median (IQR)¶‖	7 (4–10)	7 (5–10)	7 (5–10)
Organ support at randomization — no. (%)			
Invasive mechanical ventilation	1219 (49.6)	1267 (51.5)	2486 (50.5)
Renal-replacement therapy	342 (13.9)	360 (14.6)	702 (14.3)
ABO blood group — no. (%)			
Group A	928 (37.8)	961 (39.0)	1889 (38.4)
Group B	310 (12.6)	303 (12.3)	613 (12.5)
Group O	1126 (45.8)	1105 (44.9)	2231 (45.4)
Group AB	92 (3.7)	93 (3.8)	185 (3.8)
Missing data	1 (<0.1)	0	1 (<0.1)
Hemoglobin at ICU admission — g/liter	102±23.1	102±23.6	102±23.3
Hemoglobin at randomization — g/liter	77.4±12.8	77.3±13.0	77.3±12.9

* Plus–minus values are means ±SD. There were no significant differences between the two treatment groups in any baseline characteristic except age (P=0.02). Percentages may not sum to 100 because of rounding. ICU denotes intensive care unit, and IQR interquartile range.
† The primary diagnosis was classified according to the Acute Physiology and Chronic Health Evaluation (APACHE) III–J (Australian and New Zealand Intensive Care Society modified) diagnostic code.
‡ These conditions include a history of cardiac disease, an acute coronary syndrome, or an immunocompromised state during the index admission.
§ APACHE III scores range from 0 to 299, with higher scores indicating a higher probability of death.
¶ The APACHE III predicted risk of death at hospital discharge was calculated on the basis of variables measured in the first 24 hours of each hospital admission (before randomization).
‖ Sequential Organ Failure Assessment (SOFA) scores range from 0 to 24, with higher scores indicating a greater severity of organ dysfunction in critically ill patients.

Table 2. Transfusion Characteristics.*

Characteristic	Short-Term Storage (N=2457)	Long-Term Storage (N=2462)	P Value
Patients who received ≥1 red-cell unit — no. (%)	2395 (97.5)	2402 (97.6)	0.85
No. of red-cell units transfused per patient — median (IQR)	2 (1–4)	2 (1–4)	0.89
Pretransfusion hemoglobin — g/liter†	74.4±9.8	74.3±10.2	0.55
Duration of storage of red-cell units per patient — days‡			
Mean	11.8±5.3	22.4±7.5	<0.001
Median (IQR)	10.7 (8.3–14.1)	21.4 (16.7–27.4)	<0.001
Time from randomization to first red-cell transfusion — hr			
Median	1.6	1.5	0.38
IQR	0.8–2.7	0.8–2.7	
Patients receiving transfusion of other blood components — no. (%)			
Platelets	226 (9.2)	198 (8.0)	0.15
Fresh frozen plasma	292 (11.9)	257 (10.4)	0.11
Cryoprecipitate	91 (3.7)	70 (2.8)	0.09

* Plus–minus values are means ±SD.
† Shown is the mean hemoglobin level before all episodes of red-cell transfusion.
‡ The arithmetic mean of red-cell storage duration was calculated for each patient.

red-cell age quartiles was, from freshest to oldest, 22.9% (95% CI, 20.4 to 25.3), 24.9% (95% CI, 22.4 to 27.4), 25.3% (95% CI, 22.7 to 27.8), and 23.7% (95% CI, 21.2 to 26.1) (Table S6 in the Supplementary Appendix). Mortality did not differ significantly between patients who received only red cells less than 8 days old and other patients or between patients who received only red cells more than 35 days old and other patients (Tables S7 and S8 in the Supplementary Appendix). We also found no significant association between red-cell age (mean, minimum, or maximum) considered as a continuous variable and 90-day mortality (Table S9 in the Supplementary Appendix).

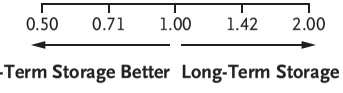
DISCUSSION

In our randomized trial involving 4994 critically ill adults undergoing transfusion, we found no significant difference in 90-day mortality according to the duration of red-cell storage. There was no benefit associated with the freshest available red cells with regard to the primary or secondary outcomes, either overall or in most subgroups. Among the many secondary outcomes tested, we noted a nominal difference in febrile nonhemolytic transfusion reactions that was small, and we are not sure of its clinical significance.

In 14 previous randomized, controlled trials comparing outcomes of transfusion of red cells with different storage durations,[12,17,18] only 2 had large sample sizes and included critically ill patients. The INFORM trial showed no significant difference in in-hospital mortality among unselected hospitalized patients, and among the 10,578 patients admitted to the ICU, the 95% CI for the odds ratio for death in the hospital was 0.92 to 1.17.[12] The lower in-hospital mortality in the ICU subgroup in the INFORM trial (13.0%) than that observed in our trial at 90 days (24.5%) is consistent with lower illness severity in the INFORM patients. The ABLE trial involved 2430 critically ill patients and showed no significant between-group differences in 90-day mortality or secondary outcomes. In that trial, the age of red cells in the fresh-blood group was specified as less than 8 days. This requirement excluded 698 potentially eligible patients. Our trial avoided this limitation. Furthermore, in the ABLE trial, the mean time from randomization until the first red-cell transfusion was 10.3 hours in the fresh-blood group and 9.7 hours in the standard-blood group.[11] In the TRANSFUSE trial, these times

A Primary Outcome: Death at 90 Days

Subgroups	Short-Term Storage	Long-Term Storage	Odds Ratio (95% CI)	P Value	P Value for Heterogeneity
	no./total no. (%)				
All patients	610/2457 (24.8)	594/2462 (24.1)	1.04 (0.91–1.18)	0.57	
ABO blood group					0.60
Group O	264/1126 (23.4)	259/1105 (23.4)	1.00 (0.82–1.22)	1.00	
Non–group O	346/1330 (26.0)	335/1357 (24.7)	1.07 (0.90–1.28)	0.43	
APACHE III risk of death					0.03
<21.5%	152/1243 (12.2)	169/1209 (14.0)	0.86 (0.68–1.08)	0.20	
≥21.5%	457/1212 (37.7)	425/1251 (34.0)	1.18 (1.00–1.39)	0.05	
Baseline SOFA score					0.89
≤7	210/1317 (15.9)	191/1273 (15.0)	1.07 (0.87–1.33)	0.51	
>7	400/1140 (35.1)	403/1189 (33.9)	1.05 (0.89–1.25)	0.54	



B Secondary Outcomes

Outcome	Short-Term Storage (N=2457)	Long-Term Storage (N=2462)	Odds Ratio (95% CI)	P Value
Death at day 28 — no. (%)	476 (19.4)	463 (18.8)	1.04 (0.90–1.20)	0.61
Death at day 180 — no./total no. (%)	687/2410 (28.5)	678/2414 (28.1)	1.02 (0.90–1.16)	0.75
Persistent organ dysfunction or death at day 28 — no. (%)	573 (23.3)	549 (22.3)	1.06 (0.93–1.21)	0.39
New bloodstream infection in ICU — no. (%)	35 (1.4)	39 (1.6)	0.90 (0.57–1.42)	0.65
Febrile nonhemolytic transfusion reaction — no. (%)	123 (5.0)	88 (3.6)	1.42 (1.07–1.88)	0.01
Duration of stay — median (IQR)				
Days in ICU	4.2 (2.0–9.3)	4.2 (1.9–9.4)		0.86
Days in hospital	14.5 (7.4–27.5)	14.7 (7.4–28.3)		0.42
Use and duration of organ support				
Invasive mechanical ventilation — no. (%)	1441 (58.6)	1460 (59.3)	0.97 (0.87–1.09)	0.64
Days alive and free of invasive mechanical ventilation — median (IQR)	25 (11–28)	25 (13–28)		0.81
Renal-replacement therapy — no. (%)	342 (13.9)	360 (14.6)	0.94 (0.80–1.11)	0.48
Days alive and free of renal-replacement therapy — median (IQR)	28 (22–28)	22 (22–28)		0.97

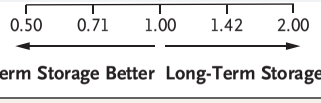


Figure 2. Forest Plot of Primary Outcome, According to Subgroups, and of Secondary Outcomes.

The risk of death was assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE) III model. Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater severity of organ dysfunction in critically ill patients. The divisions between the subgroups for APACHE III risk of death and baseline SOFA score were based on the median values. CI denotes confidence interval, and IQR interquartile range.

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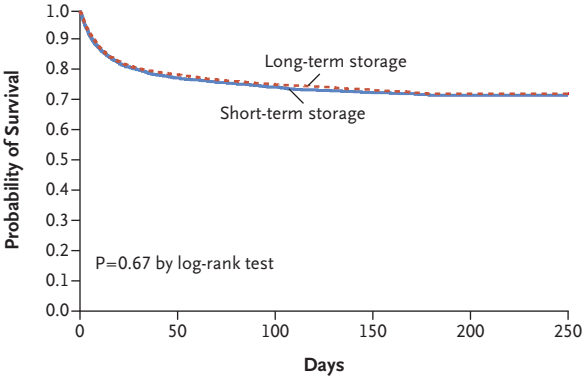
were much shorter (1.6 hours and 1.5 hours, respectively).

The point estimates for mortality in previous randomized trials have actually favored longer durations of storage.[13] The findings in our trial were similar. We found no significant between-group difference in rates of new bloodstream infections. Among patients who were more severely ill (with an APACHE III risk of death equal to or above the median), those who received the freshest available red cells had a higher mortality than those who received standard-issue red cells. Among all patients, the rate of febrile nonhemolytic transfusion reactions was higher in the short-term storage group than in the long-term storage group. However, these should be considered exploratory findings. A potential mechanism for the higher rate of febrile nonhemolytic transfusion reactions is damage-associated molecular patterns, including those involving mitochondrial DNA, which accumulate early during red-cell storage (within 1 to 2 weeks).[19] These have been associated with febrile nonhemolytic transfusion reactions[20,21] and the acute respiratory distress syndrome after transfusion.[22] Our findings reinforce the need for further investigation into factors that affect red-cell quality.

The trial included a generalizable patient population from 59 sites in five countries. The pragmatic feature of using the available red-cell inventory resulted in a substantial difference in storage duration of 10.6 days between the two treatment groups and a short time from randomization to transfusion. Pretransfusion hemoglobin levels closely approximated those in international guidelines, suggesting that transfusion practice was similar across the different sites and countries. Only 1% of our patients did not receive their assigned red-cell transfusion, as compared with approximately 12% in the fresh-blood group of the ABLE trial.[11] Our observed mortality rate was close to expected and, combined with the large sample size, ensured 90% power to detect a difference of 4.2 percentage points in 90-day mortality. We minimized bias through a blinding procedure that involved patients, clinical staff, and outcome assessors and through concealment of the assigned treatments at randomization. There was a low rate of loss to follow-up (<1%) and a high ratio of randomly assigned patients to eligible patients (0.79:1).

Our design had some limitations. The red-cell age in each treatment group was not prespecified but was determined by the blood-bank inventory at each institution. We did not design the trial to assign red cells toward the end of their shelf life (35 to 42 days). Although our prespecified secondary analysis showed no effect on mortality in patients who received the oldest red-cell quartile or those who received only red cells older than 35 days, there were relatively few patients who received red cells older than 35 days.



No. at Risk						
Long-term storage	2504	1939	1825	1767	425	83
Short-term storage	2490	1911	1802	1745	419	95

Figure 3. Kaplan–Meier Survival Analysis of Time to Death.

Our trial provides strong evidence that transfusion of the freshest available red cells as compared with standard-issue (oldest available) red cells provides no clinically meaningful benefits in critically ill patients. Our results support the current international usual practice of transfusing patients with the oldest red cells available.

In conclusion, we found no significant difference in the rate of death among critically ill patients who received transfusion of the freshest available red cells and those who received standard-issue, oldest available red cells.

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APPENDIX

The authors' affiliations are as follows: the Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University (D.J.C., Z.K.M., A.N., B.A., C.A., M.B., R.B., D.G., K.-M.K., L.M., C.F.), the Department of Intensive Care, Alfred Hospital (D.J.C., A.N., D.G.), the Department of Haematology, Monash Health (Z.K.M.), the Department of Intensive Care, Austin Hospital (R.B.), the University of Melbourne (R.B., C.F.), Research and Development, Australian Red Cross Blood Service (D.O.I.), and the Department of Intensive Care, Western Health (C.F.) — all in Melbourne, VIC, Australia; Irish Critical Care Clinical Trials Network, University College Dublin Clinical Research Centre at St. Vincent's University Hospital, Dublin (A.N.); the Département de Médecine Intensive Réanimation, Brest University Hospital, Brest, France (C.A.); the Department of Anesthesiology (K.-M.K.) and the Division of Intensive Care, Department of Anesthesiology (V.P.), Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki; and the Medical Research Institute of New Zealand and the Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand (C.M.).

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