Erythrocyte Storage Duration Is Not Associated with Increased Mortality in Noncardiac Surgical Patients

A Retrospective Analysis of 6,994 Patients

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ABSTRACT

Background: More than 5 million patients receive erythrocyte transfusions in the United States every year. Previous studies linked the storage duration of allogeneic erythrocytes to the risk of severe postoperative complications, especially after cardiac or trauma surgery. Limited data are available for noncardiac surgical patients. We therefore evaluated the association between storage duration of transfused erythrocytes and postoperative all-cause mortality among general surgery patients.

Methods: Perioperative data corresponding to 63,319 adult, general surgery patients were obtained from our registry and merged with blood product data. Patients receiving solely leukocyte-reduced, allogeneic erythrocyte transfusions were included. Multivariable Cox proportional hazards regression was used to characterize the relationship between median erythrocyte storage duration and postoperative mortality rate, adjusting for characteristics plausibly influencing the storage duration of erythrocytes.

Results: Of the 6,994 patients included in the final analysis, 23, 44, 11, 9, and 13% received 1, 2, 3, 4, and ≥5 erythrocyte units, respectively. The authors found no evidence that increasing median storage duration was associated with a difference in the risk of postoperative mortality (hazard ratio, 0.99 [0.94–1.04]; $P = 0.64$). Analyzing the mean storage duration of erythrocyte units as a function of year of transfusion, the authors demonstrate a relevant decrease in utilization of the oldest blood units, whereas young blood storage duration remains nearly unchanged.

Conclusion: The authors' study supports the recent literature in surgical and medical patients and underlines the importance of sufficiently powered randomized trials to finally resolve the erythrocyte storage duration debate.

What We Already Know about This Topic

- Transfusion of blood with a longer storage time has been associated with increased mortality in cardiac surgery patients, but studies outside this setting have been small and with mixed results

What This Article Tells Us That Is New

- In a study of nearly 7,000 patients receiving transfusions for noncardiac surgery, there was no relationship between median storage duration time and mortality

SINCE the discovery of circulation by Sir William Harvey, M.D. (Lumleian Lecturer, Royal College of Physicians and St. Bartholomew Hospital, London, England) (1578–1657) in the early 17th century, and the subsequent first successful intraoperative blood transfusion by George Washington Crile, M.D. (Professor of Clinical Surgery in the Western Reserve Medical College, Cleveland, OH) (1864–1943) at the Cleveland Clinic,[1,2] blood transfusions are important therapeutic agents. In the United States, more than 5 million patients receive erythrocytes every year.** Transfusions, specifically numbers of erythrocyte units, have been associated with severe adverse outcomes, including increased risk for infections,[3–5] pulmonary complications[6], and cancer recurrence,[7,8] and prolonged intensive care unit[4,5,9] and hospital length of stay.[5,9]

In recent years, the storage duration of allogeneic erythrocytes has been linked to the risk of severe postoperative complications, especially after cardiac surgery.[10,11] Time-dependent changes in the biochemical properties of stored erythrocytes collectively referred to as the "storage lesion,"

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have been proposed as the underlying mechanism.[12,13] These changes include alterations in the erythrocyte membrane and decreases in 2,3 diphosphoglycerate, nitric oxide, and intracellular potassium concentrations.[14] Storage lesion changes result in compromised *in vitro* erythrocyte function and viability.[12,15–17] However, the effect of these observed changes on clinical outcomes of transfused patients remains unclear.

Some studies show a significant association between storage duration of erythrocyte units and adverse outcomes, including mortality, hospital length of stay, intubation time, infectious complications, multiorgan failure, and composites of adverse events.[11,14,18,19] Other studies show no association or only minor associations that were largely attributed to increased baseline risk in transfused patients rather than to the effects of older transfused cells *per se*.[19–21] Interpretation of these studies is complicated by use of different methodological and analytical approaches, not all of which adequately adjust for confounding factors and disease severity. Most studies performed to date were in the cardiac surgery, intensive care, and trauma populations. Limited data are available for noncardiac surgical patients.[7,22,23] We thus sought to evaluate whether or not storage duration of transfused erythrocytes is associated with postoperative all-cause mortality among noncardiac surgery patients using data derived from the Cleveland Clinic Perioperative Health Documentation System registry.

Materials and Methods

With approval from the Cleveland Clinic Institutional Review Board (Cleveland, OH), perioperative data corresponding to 63,319 adult, American Society of Anesthesiologists Physical Classification I–V, general surgery patients treated at Cleveland Clinic between January 6, 2005, and June 30, 2009, were obtained from our Perioperative Health Documentation System registry. Erythrocyte transfusion and product data were obtained from the laboratory information system. Patients receiving leukocyte-reduced allogeneic erythrocyte transfusions between 2 days before the date of surgery and 7 days afterward were included in the study. Only the most recent operation for each patient was analyzed. Postoperative mortality information in our Perioperative Health Documentation System registry was obtained by combining data from both hospital records and the U.S. Social Security Administration's Death Master File. The U.S. Social Security Administration's Death Master File was queried on June 15, 2011, matching patients on their social security numbers. Patients for whom long-term death information was not available from the Death Master File were censored at hospital discharge.

Erythrocyte storage duration as an exposure is complicated because patients potentially receive multiple units and thus are exposed to multiple storage durations but can experience only one mortality outcome. Koch *et al.*,[11] in a study evaluating the association between storage duration and mortality among cardiac surgery patients, created two groups by splitting the overall distribution of erythrocyte storage duration at the observed median of 14 days. This approach is useful for studying whether or not there is evidence of an overall association but does not provide an assessment of dose–response. With this latter goal in mind, we characterized the storage duration exposure using the median storage duration of all erythrocyte units transfused to a patient. But to keep the groups homogeneous, we excluded patients for whom the range of storage duration among transfused units exceeded 5 days.

Statistical Methods

First, we grouped patients into three storage duration groups based on whether their median storage duration was ≤14 days, >14 days but ≤28 days, or >28 days. Kaplan–Meier survival density function estimates were then obtained and plotted for each of the three groups.[24] Although this analysis is useful for visualizing patterns of survival, it does not adjust for potential confounding factors. Therefore, no testing for differences was undertaken in this exploratory analysis.

For the primary hypothesis, multivariable Cox proportional hazards regression was used to characterize the relationship between median erythrocyte storage duration and postoperative mortality rate over time. We adjusted for any patient and surgical characteristic plausibly influencing the storage duration of erythrocytes. Previous studies have been criticized for inadequately considering baseline parameters such as patient comorbidities. We cannot plausibly postulate a mechanism that would explain how older blood might get assigned to particular subgroups of patients. Blood banks are typically unaware of patient characteristics, and standard operating procedures require using the oldest available matching. We did adjust for blood type of the patient, Rhesus factor of the patient, number of units transfused, range of storage duration among the transfused erythrocyte units within a patient, and date of surgery.[25]

First, we developed a Cox model whereby the relationship was modeled flexibly *via* a smoothing procedure (specifically, penalized *B*-spline smoothing).[26] Covariate-adjusted mortality incidence estimates (at several fixed postoperative times: up to 2 yr postoperatively) were then obtained and graphed as a function of patient-median erythrocyte storage duration using this model. Nonlinearity of the relationship (between patient-median erythrocyte storage duration and the logarithm of the hazard rate) was tested for significance using a Wald chi-squared test. If no significant evidence of nonlinearity was found, we used a simpler linear model to describe the relationship.

Adequacy of the assumption of proportional hazards across postoperative time for our final model was assessed using various graphical and analytic methods (*e.g.*, a plot of log-cumulative hazards against log-time, Schoenfeld residual plots, and chi-squared tests for consistency of Cox model coefficients over time).[27,28] R statistical software

version 2.1 2.1 for 64-bit Windows (The R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis. The Type I error rate for all hypotheses was fixed at 5%.

Results

Of the 63,319 surgical patients included in our study, 10,090 (15.9%) were transfused with allogeneic erythrocyte products. We removed 314 patients who received one or more autologous erythrocyte units and an additional 669 who received allogeneic erythrocyte units that were not leukocyte-reduced. Of the remaining 9,107 patients, 2,113 (23.2%) received multiple units with storage duration ranging greater than 5 days; removing these patients, we analyzed perioperative data on 19,462 allogeneic erythrocyte units transfused to 6,994 patients (fig. 1).

As expected, patients included in the analysis were generally sick, with 80% being assigned an American Society of Anesthesiologists' Physical Classification of III or above (table 1). Patients received anywhere between 1 and 41 erythrocyte units; 23, 44, 11, 9, and 13% of patients received 1, 2, 3, 4, and ≥5 erythrocyte units, respectively. The patient-specific median erythrocyte storage duration was largely representative of the age of the individual units, with 94% of the units' storage duration being within ±2 days of the respective patient medians. Overall, there were 1,718 mortalities among the 6,994 patients analyzed (24.6%).

Estimated correlation (95% CI) between number of erythrocyte units transfused and median erythrocyte age was −0.10 (−0.13 to −0.08), indicating a slight relationship. Except for blood type and Rhesus factor—which are determinants of blood product supply—we found little evidence of relationship between patients' baseline characteristics and median erythrocyte storage duration. A summary of the top 15 principal procedures and diagnoses, as characterized by the U.S. Agency for Healthcare Research and Quality's single-level Clinical Classifications Software (Agency for Healthcare Research and Quality, Rockville, MD), is provided in table 2.

Two-year U.S. Social Security Administration's Death Master File data on mortality were available for 6,717 of 6,994 patients; the remaining 4% were censored at discharge. Kaplan–Meier survival density function estimates for three median erythrocyte storage duration groups are provided in figure 2; no appreciable differences between the three groups was evident. However, as stated in the Methods section, these results were not adjusted for potential confounders and were not compared statistically.

In our Cox regression modeling, we found no significant evidence of a nonlinear relationship between patient-median erythrocyte storage duration and mortality after adjusting for potential confounders (fig 3, in red; $P = 0.41$, Wald chi-squared test). A simpler model that characterized the relationship linearly revealed similar conclusions: we found no evidence that increasing median storage duration was associated with a difference in the risk of postoperative mortality ($P = 0.64$), and based on this model, the hazard ratio (95% CI) corresponding to a relative 1-week increase in median erythrocyte storage duration was 0.99 (0.94–1.04).

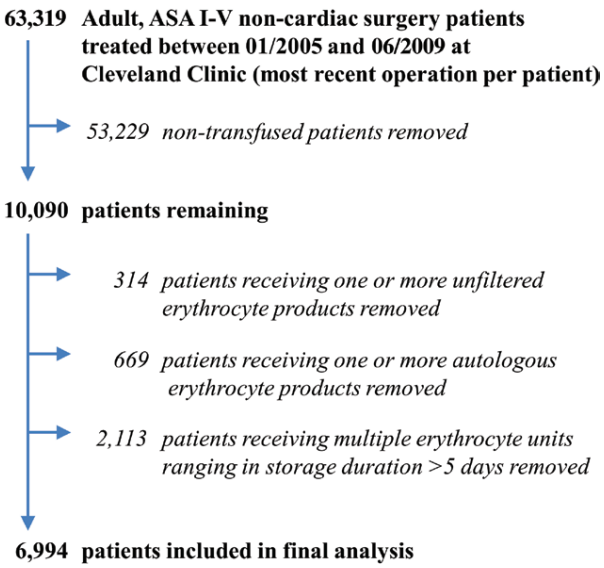

Fig. 1. Study flow diagram illustrating exclusion and inclusion of study population. ASA = American Society of Anesthesiologists.

No evidence against the assumption of proportionality of the erythrocyte storage duration effect over time was found in our modeling (diagnostic graphics and tests not reported).

To assess possible changes in blood product management over time, we analyzed the mean storage duration of erythrocyte units as a function of year of transfusion. Figure 4 shows a relevant decrease in utilization of the oldest blood units, whereas young blood storage duration remains nearly unchanged.

Discussion

Over the past 10 yr, investigators have considered whether prolonged storage duration of erythrocyte units may worsen patient outcomes in surgical and nonsurgical patients. Unfortunately, despite a large body of research, divergent results have so far not led to a conclusive answer, and no consensus has been reached. We thus used our Perioperative Health Documentation System to evaluate the relationship between erythrocyte storage duration and postoperative all-cause mortality in a cohort of 6,994 patients receiving 19,462 units of erythrocyte and undergoing general surgery. We did not find any association between erythrocyte storage duration and mortality and thus our study adds to the growing body of transfusion research, showing that erythrocyte age may not be associated with increased postoperative mortality or morbidity.

Only few studies address the general surgical population and those are restricted to colon–rectal, prostate, and liver

Table 1. Summary of Baseline and Transfusion-related Patient Characteristics and Their Association with the Patient-median Erythrocyte Age Exposure of Interest (N = 6,994)

	Median (Quartiles)	Spearman Correlation Coefficient (95% CI) with Median Erythrocyte Storage Duration Exposure
Patient age, yr	66 (55–76)	0.01 (–0.01 to 0.03)
Body mass index, kg/m^2	27 (23–32)	–0.01 (–0.03 to 0.02)
Serum hematocrit, %	36 (31–41)	0.00 (–0.03 to 0.02)
Serum creatinine, mg/dl	0.9 (0.7–1.3)	–0.01 (–0.03 to 0.02)
Case duration, min	266 (180–383)	–0.04 (–0.06 to –0.02)
No. erythrocyte units transfused	2 (2–3)	–0.10 (–0.13 to –0.08)
Range of erythrocyte product storage duration, d	0 (0–2)	–0.02 (–0.04 to 0.00)
	% of Patients	Median (Quartiles) of Median Erythrocyte Storage Duration Exposure
Sex		
Male	46.0	15 (12–20)
Female	54.0	16 (12–21)
Race		
White	82.8	16 (12–21)
African American	14.2	16 (12–21)
Other	3.0	15 (11–19)
ASA physical status		
I	0.8	15 (12–19)
II	19.5	16 (12–21)
III	59.5	16 (12–21)
IV	19.7	15 (12–20)
V	0.5	14 (12–17)
Hypertension		
No	52.4	16 (12–20)
Yes	47.6	16 (12–21)
Chronic obstructive pulmonary disease		
No	86.3	16 (12–21)
Yes	13.7	15 (12–20)
History of tobacco use or dependence		
No	82.7	16 (12–21)
Yes	17.3	16 (12–21)
Diabetes mellitus		
No	82.1	16 (12–21)
Yes	17.9	16 (12–21)
History of stroke		
No	98.8	16 (12–21)
Yes	1.2	16 (13–20)
Peripheral vascular disease		
No	98.7	16 (12–21)
Yes	1.3	16 (11–23)
Patient disposition		
Elective	87.9	16 (12–21)
Emergent	12.1	16 (12–20)
Patient blood type		
A	41.0	18 (14–22)
B	11.2	21 (16–26)
O	44.1	13 (10–16)
AB	3.6	17 (14–22)
Patient Rhesus factor		
Positive	86.3	15 (12–20)
Negative	13.7	19 (14–24)

Comorbidity data in the Perioperative Health Documentation System (PHDS) is based on a combination of electronic medical record abstraction and billing data.

ASA = American Society of Anesthesiologists.

Table 2. Top 15 Principal Diagnoses and Procedures (Based on ICD Discharge Codes)

	N (%) of Patients
Top 15 Principal Diagnoses	
Osteoarthritis	704 (10.1)
Complication of device; implant or graft	604 (8.6)
Aortic; peripheral; visceral artery aneurysms	562 (8.0)
Complications of surgical procedures or medical care	245 (3.5)
Cancer of kidney and renal pelvis	244 (3.5)
Spondylosis; intervertebral disc disorders; other back problems	236 (3.4)
Secondary malignancies	224 (3.2)
Cancer of bladder	196 (2.8)
Other and unspecified benign neoplasm	160 (2.3)
Regional enteritis and ulcerative colitis	160 (2.3)
Other acquired deformities	147 (2.1)
Peripheral and visceral atherosclerosis	129 (1.8)
Cancer of colon	120 (1.7)
Other gastrointestinal disorders	116 (1.7)
Other bone disease and musculoskeletal deformities	111 (1.6)
Other diagnoses	3,036 (43.4)
Top 15 Principal Procedures	
Hip replacement; total and partial	641 (9.2)
Arthroplasty knee	544 (7.8)
Aortic resection; replacement or anastomosis	501 (7.2)
Colorectal resection	457 (6.5)
Spinal fusion	430 (6.1)
Nephrectomy; partial or complete	342 (4.9)
Other OR gastrointestinal therapeutic procedures	321 (4.6)
Other OR procedures on vessels other than head and neck	258 (3.7)
Other OR therapeutic procedures of urinary tract	237 (3.4)
Other organ transplantation	207 (3.0)
Hysterectomy; abdominal and vaginal	206 (2.9)
Other OR lower GI therapeutic procedures	184 (2.6)
Incision and excision of CNS	172 (2.5)
Open prostatectomy	141 (2.0)
Amputation of lower extremity	131 (1.9)
Other procedures	2,222 (31.8)

CNS = central nervous system; GI = gastrointestinal; ICD = International Classification of Diseases; OR = operating room.

transplant patients. For example, a study in 225 patients undergoing colon–rectal surgery showed that blood storage duration may, along with other risk factors, play a significant role in the development of postoperative infectious complications.[23] The same group demonstrated a decrease in the incidence of cancer recurrence in colon–rectal patients receiving younger blood.[7] On the other hand, our group found that storage duration did not affect the incidence of cancer recurrence in patients after prostate surgery.[22] In 405 patients receiving allogeneic transfusions, the biochemical recurrence–free survival rate at 5 yr was 74, 71, and 76% for those who received younger, middle, and older erythrocytes, respectively.[22] Recent data from 526 patients undergoing orthotopic liver transplantation do not show an association between erythrocyte age with infection, organ rejection, and death.[29]

Over the past 10 yr, storage duration has received most attention in patients undergoing cardiac surgery. In one of the largest retrospective studies, also performed at the Cleveland Clinic, Koch *et al.*[11] demonstrated an almost 60% percent increase in in-hospital mortality and significantly increased adverse events (cardiac, pulmonary, infectious, renal, and cerebrovascular) in patients receiving older blood. Andreasen *et al.*[10] investigated 1,748 patients undergoing coronary bypass graft surgery and found a significant relationship between blood product storage time and postoperative severe infections. More recent literature in the cardiac patient population could not identify any benefit of younger blood.[30,31]

Furthermore, in the largest study to date investigating storage duration in medical and surgical (cardiac and noncardiac) patients, Edgren *et al.*[20] found no association between storage duration and mortality in more than 400,000 transfused patients for any of the studied patient populations.

One problem with currently available literature in regards to erythrocyte duration is that almost all the studies

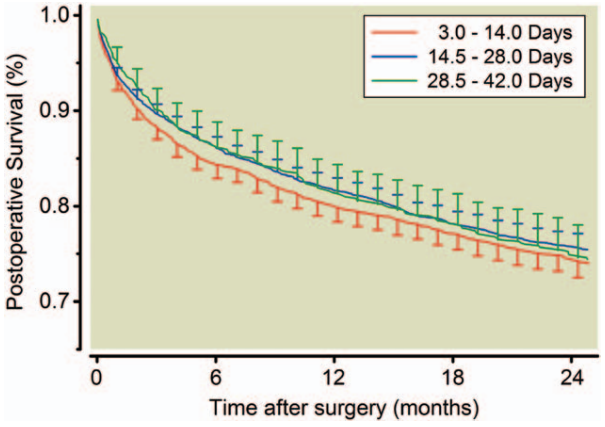

Fig. 2. Kaplan–Meier survival density function estimates of postoperative mortality (and associated pointwise 95% CI) for three groups characterizing patient-median erythrocyte storage duration.

published so far are retrospective studies. It is likely that different statistical approaches contributed to the divergent results. However, it is interesting to note, that most of the earlier research showed adverse effects of increased storage duration, whereas the newer studies do not see this association.

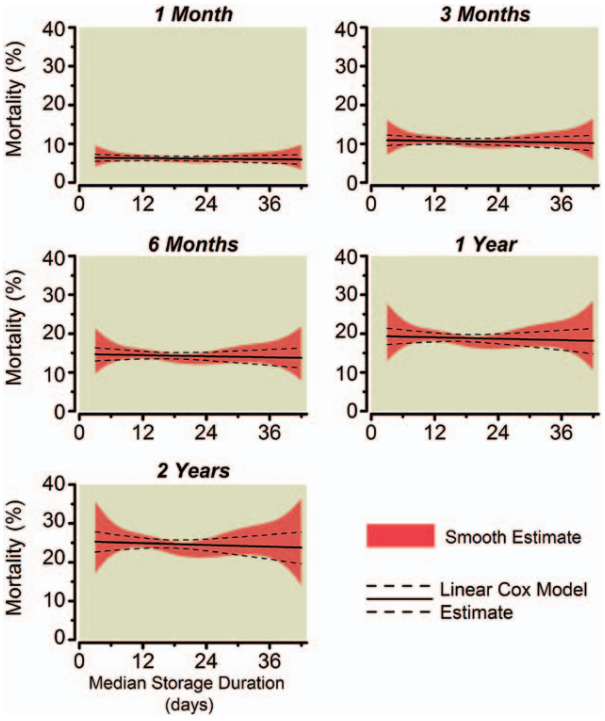

Fig. 3. Estimated incidence of mortality as a function of patient-median erythrocyte storage duration (in days) at various postoperative time points, up to 2 yr. In *red* is the pointwise 95% CI representing mortality incidence from a Cox regression model in which the structure relationship was relaxed by using smoothing, whereas a standard linear Cox model estimate (and pointwise 95% CI) is provided in *black*.

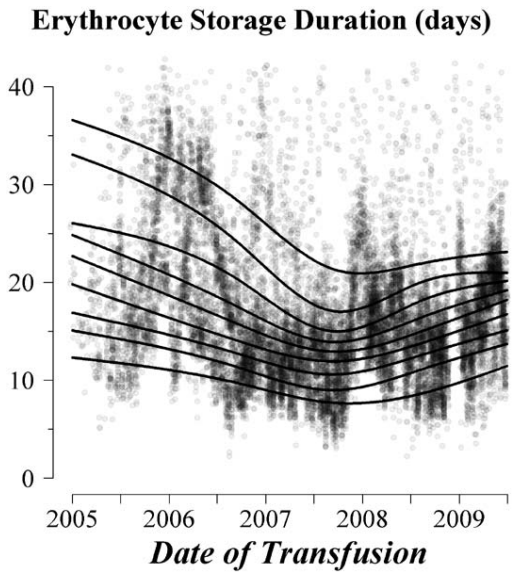

Fig. 4. Scatterplot of patient mean erythrocyte storage duration *versus* date of transfusion. Decile curves (estimated *via* quantile regression with a 4-degree-of-freedom natural cubic spline term for transfusion date) representing the distribution of storage duration over time are overlaid.

In our study, like others previously, we adjusted for year of surgery, ABO-type, and the number of erythrocyte units transfused because these are true confounding factors (*i.e.*, factors that might affect the likelihood of receiving older or younger blood). Other baseline characteristics, such as comorbidities and type of surgery, probably only influence the decision to transfuse *per se* rather than whether older or younger blood should be administered.

Our study, however, differs from previous ones, even from our own institution,[11,32] in several ways. One difference is that we calculated storage duration based on the age range of units a patient received and excluded patients with ranges greater than 5 days. This period was chosen to enforce a degree of measurement precision regarding the storage duration assigned to each patient. We thereby excluded 23% of otherwise eligible patients from the analysis but increased homogeneity of our study population. A grouping approach using predefined storage duration cutoffs would have eliminated a comparable number of patients.

A second difference is that we used storage duration as a continuous exposure rather than a dichotomous comparison for our primary analysis. This approach allowed us to address nonlinear time dependence. We found that postoperative mortality as a function of median storage duration for five specific snapshots in time (1, 3, and 6 months; 1 and 2 yr) does not change. It is thus not surprising that survival rates were similar when we divided our study population into three groups (patients receiving blood aged 3–14, 14.5–28, and 28.5–42 days) as a secondary survival analysis.

Since the first published reports on a possible association between storage duration and adverse outcomes, transfusion

practice might have changed. We therefore analyzed storage duration of erythrocytes as a function of the year of transfusion. Figure 4 demonstrates a clear decrease in storage duration for the oldest units, whereas ages of the youngest units seem unchanged over the study period from 2005 to 2009. Cleveland Clinic did not change policies for blood product selection and issue during this time period; therefore, the decrease in blood product age is most likely related to decreasing inventory levels combined with increasing or sustained blood product usage. Furthermore, studies showing adverse outcomes associated with transfusion might have led to decreased utilization of transfusions, thus leading blood banks to adjust the number of units ordered from blood suppliers and kept in store.

Because of the retrospective nature of our study, we were limited to investigate only the association between storage duration and mortality. It is important to note that there is a time lag between the date of death for an individual patient and when that fact is entered into the U.S. Social Security Administration's Death Master File database. This delay at worst affected only a small portion of our sample and therefore has limited clinical relevance for our results. Currently, a number of prospective randomized trials investigating the relationship between storage duration and outcomes are underway, and results are anxiously awaited (ClinicalTrials.gov Identifier NCT00991341; NCT00458783).[33]

Our results might be influenced by center-specific characteristics, because data were collected at one site only. On the other hand, we included a fairly large number of patients with a broad spread of comorbidities who had a variety of surgical procedures. As is common in clinical practice, most of our patients were given a fairly small number of transfusions. It is possible that many of our transfused patients did not have a true oxygen carrying or oxygen delivery deficiency. Because poor outcome associated with storage lesion is thought to originate from impaired erythrocyte function or its effect on perfusion/oxygenation, it might not matter in patients with adequate oxygen delivery. It is thus possible that our results would differ in even sicker patients receiving larger numbers of erythrocytes. A possible effect in these specific patients could be postulated from studies in trauma patients showing a benefit from transfusion of younger erythrocytes.[34] Unfortunately, our sample size was not large enough to perform a sensitivity analysis restricted to massive transfusions.

Another limitation of our study might be that we only evaluated mortality but not postoperative morbidity. Mortality is a crude outcome, and it is most certainly possible that more intermediate outcomes might be more sensitive and benefit from younger blood. Subcutaneous tissue oxygen tension and wound infection could function as intermediate and clinical outcomes to demonstrate a storage age–related difference in oxygen delivery to tissues. Natural killer cell function might be used to assess possible impairing effects of storage duration on the patient's immune function. We chose a 2-yr mortality outcome because of emerging literature suggesting long-term effects of intraoperative interventions on postoperative outcomes. However, it is feasible that our 2-yr outcome is affected by other events occurring between transfusion and the mortality ascertainment.

In summary, in our large retrospective study in adult general surgical patients, we did not find an association between storage duration of erythrocytes and 2-yr mortality. This is in support of the majority of the most recent literature in surgical and medical patients. Our results represent yet another piece in a large puzzle and underline the importance of sufficiently powered randomized trials to finally resolve the erythrocyte storage duration debate.

References

1. Crile G: I. The Technique of Direct Transfusion of Blood. Ann Surg 1907; 46:329–32
2. Grunfeld GB: George Crile performs the first direct blood transfusion. In: Great Events from History: Science and Technology II, edited by Magill FN, Pasadena, CA, Salem Press, 1991, pp. 275–9
3. Chelemer SB, Prato BS, Cox PM Jr, O'Connor GT, Morton JR: Association of bacterial infection and red blood cell transfusion after coronary artery bypass surgery. Ann Thorac Surg 2002; 73:138–42
4. Leal-Noval SR, Rincón-Ferrari MD, García-Curiel A, Herruzo-Avilés A, Camacho-Laraña P, Garnacho-Montero J, Amaya-Villar R: Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. Chest 2001; 119:1461–8
5. Taylor RW, Manganaro L, O'Brien J, Trottier SJ, Parkar N, Veremakis C: Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. Crit Care Med 2002; 30:2249–54
6. Vamvakas EC, Carven JH: Allogeneic blood transfusion and postoperative duration of mechanical ventilation: Effects of red cell supernatant, platelet supernatant, plasma components and total transfused fluid. Vox Sang 2002; 82:141–9
7. Mynster T, Nielsen HJ; Danish RANX05 Colorectal Cancer Study Group: Storage time of transfused blood and disease recurrence after colorectal cancer surgery. Dis Colon Rectum 2001; 44:955–64
8. Makino Y, Yamanoi A, Kimoto T, El-Assal ON, Kohno H, Nagasue N: The influence of perioperative blood transfusion on intrahepatic recurrence after curative resection of hepatocellular carcinoma. Am J Gastroenterol 2000; 95:1294–300
9. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM: Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma 2003; 54:898–905; discussion 905–7
10. Andreasen JJ, Dethlefsen C, Modrau IS, Baech J, Schonheyder HC, Moeller JK, Johnsen SP; North-West Denmark Transfusion Study Group: Storage time of allogeneic red blood cells is associated with risk of severe postoperative infection after coronary artery bypass grafting. Eur J Cardiothorac Surg 2011; 39:329–34
11. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH: Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358:1229–39
12. Tinmouth A, Fergusson D, Yee IC, Hébert PC; ABLE Investigators; Canadian Critical Care Trials Group: Clinical consequences of red cell storage in the critically ill. Transfusion 2006; 46:2014–27
13. Zimrin AB, Hess JR: Current issues relating to the transfusion of stored red blood cells. Vox Sang 2009; 96:93–103
14. van de Watering L: Red cell storage and prognosis. Vox Sang 2011; 100:36–45

15. Berezina TL, Zaets SB, Morgan C, Spillert CR, Kamiyama M, Spolarics Z, Deitch EA, Machiedo GW: Influence of storage on red blood cell rheological properties. J Surg Res 2002; 102:6–12
16. Kirkpatrick UJ, Adams RA, Lardi A, McCollum CN: Rheological properties and function of blood cells in stored bank blood and salvaged blood. Br J Haematol 1998; 101:364–8
17. Wolfe LC: Oxidative injuries to the red cell membrane during conventional blood preservation. Semin Hematol 1989; 26:307–12
18. Eikelboom JW, Cook RJ, Liu Y, Heddle NM: Duration of red cell storage before transfusion and in-hospital mortality. Am Heart J 2010; 159:737–743.e1
19. Gauvin F, Spinella PC, Lacroix J, Choker G, Ducruet T, Karam O, Hébert PC, Hutchison JS, Hume HA, Tucci M; Canadian Critical Care Trials Group and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients. Transfusion 2010; 50:1902–13
20. Edgren G, Kamper-Jørgensen M, Eloranta S, Rostgaard K, Custer B, Ullum H, Murphy EL, Busch MP, Reilly M, Melbye M, Hjalgrim H, Nyrén O: Duration of red blood cell storage and survival of transfused patients (CME). Transfusion 2010; 50:1185–95
21. Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yii M: Age of transfused red cells and early outcomes after cardiac surgery. Ann Thorac Surg 2008; 86:554–9
22. Cata JP, Klein EA, Hoeltge GA, Dalton JE, Mascha E, O'Hara J, Russell A, Kurz A, Ben-Elihayhu S, Sessler DI: Blood storage duration and biochemical recurrence of cancer after radical prostatectomy. Mayo Clin Proc 2011; 86:120–7
23. Mynster T, Nielsen HJ: The impact of storage time of transfused blood on postoperative infectious complications in rectal cancer surgery. Danish RANX05 Colorectal Cancer Study Group. Scand J Gastroenterol 2000; 35:212–7
24. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–81
25. Cox DR: Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972; 34:187–220
26. Eilers PHC, Marx BD: Flexible smoothing with B-splines and penalties. Stat Sci 1996; 11:89–102
27. Schoenfeld D: Partial residuals for the proportional hazards regression model. Biometrika 1982; 69:239–241
28. Therneau TM, Grambsch PM: Modeling Survival Data, 1st edition. New York, Springer, 2000
29. Dunn LK, Thiele RH, Sawyer RS, Nemergut EC: Duration of red cell storage and outcome following orthotopic liver transplant. Presented at the Annual Meeting of American Society of Anesthesiologists, October 17, 2011; A884
30. McKenny M, Ryan T, Tate H, Graham B, Young VK, Dowd N: Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth 2011; 106:643–9
31. van Straten AH, Soliman Hamad MA, van Zundert AA, Martens EJ, ter Woorst JF, de Wolf AM, Scharnhorst V: Effect of duration of red blood cell storage on early and late mortality after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2011; 141:231–7
32. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH: Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006; 34:1608–16
33. Steiner ME, Assmann SF, Levy JH, Marshall J, Pulkrabek S, Sloan SR, Triulzi D, Stowell CP: Addressing the question of the effect of RBC storage on clinical outcomes: The Red Cell Storage Duration Study (RECESS) (Section 7). Transfus Apher Sci 2010; 43:107–16
34. Weinberg JA, McGwin G Jr, Vandromme MJ, Marques MB, Melton SM, Reiff DA, Kerby JD, Rue LW III: Duration of red cell storage influences mortality after trauma. J Trauma 2010; 69:1427–31; discussion 1431–2