Effect of storage time and donor sex of transfused red blood cells on 1-year survival in patients undergoing cardiac surgery: an observational study

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BACKGROUND: Red blood cell (RBC) storage lesions and RBCs from females transfused into male recipients may have adverse effects on transfusion recipients' survival. We hypothesized that the effect of donor sex and the effect of age of blood on mortality would be most apparent in cardiac surgery patients.

STUDY DESIGN AND METHODS: Using data from French Blood Services and two university hospitals, we conducted a retrospective cohort study on cardiac surgery patients whose first transfusion occurred between 2007 and 2011. The age of blood and donor sex effects on 1-year survival were studied using Cox regression modeling, with time-dependent stratification on the number of RBCs and adjustments for the type of surgery and other products transfused.

RESULTS: Among the 2715 cardiac surgery patients, 85.1% were alive after 1 year. Age of blood and donor sex were associated with survival before adjustments ($p < 0.0001$). However, the adjusted hazard ratios (HRs) for patients transfused with blood stored for 29 days or more versus 14 days or less were 0.97 (95% confidence interval [95% CI], 0.69-1.35; $p = 0.98$) and 1.22 (95% CI, 0.81-1.82) for patients who received only sex-mismatched RBCs versus all matched units ($p = 0.27$). For males transfused solely with female RBCs, the HR was 0.96 (95% CI, 0.57-1.61; $p = 0.69$); in females transfused only with male RBCs, it was 2.03 (95% CI, 0.87-4.73; $p = 0.17$).

CONCLUSIONS: In this first study of survival after transfusion in France, there was no significant effect for age of blood or donor sex. Contrary to previously reported data, female RBCs appear to be safe for male recipients.

Blood transfusion is a lifesaving therapy in situations of blood loss and severe anemia. During storage, red blood cells (RBCs) undergo changes collectively known as storage lesions.[1-3] Among other effects, RBCs undergo morphologic changes and display reduced deformability and a decreased capacity for oxygen transfer to tissues. They also shed procoagulant

ABBREVIATIONS: DA(s) = discharge abstract(s); DRG = diagnosis-related groups; EFS = Etablissement Français du Sang; HC = heart catheterization; HR(s) = hazard ratio(s); IQR(s) = interquartile range(s).

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microvesicles. Proinflammatory mediators are released in the storage solution and may also promote inflammation in the transfused recipient.[4] Thus, storage lesions may cause adverse effects in transfused patients.

Numerous studies have suggested that the risk of complications and mortality increase after transfusion with blood stored for long periods.[3,5-8] Several authors have focused their work on cardiovascular surgery patients. Such patients may be especially vulnerable to end-organ injury because of compromised cardiac output or the proinflammatory state that follows the surgery. The hypothesis for the effect of older RBCs is based on perturbations of microcirculation and their higher affinity for oxygen, thus increasing the risk of ischemia and multiorgan failure.[9,10] An immunomodulatory effect may also increase the risk of sepsis.[11]

More recently, a large observational study suggested a possible effect of the transfusion of RBCs from female donors on the survival of male recipients.[12] The effect was seen as early as 1 month after transfusion. However, the authors did not provide adjustments for the underlying illness in their analyses. Regarding donor sex, the current hypothesis is an immunomodulatory effect, possibly related to anti-HY antibodies in female RBC donors, which could increase the risk of sepsis and transfusion-related acute lung injury (TRALI).[12-14]

Although transfusion safety is at an all-time high,[15] French Blood Services remain highly conscious of transfusion recipient safety and are interested in a new hemovigilance tool based on available databases. Such a tool would allow the monitoring of known but also unknown transfusion-related incidents and adverse outcomes. No studies of survival after transfusion have been conducted in France. One aim of this pilot study was to create a database of transfused patients to investigate patient survival after transfusion and the safety of blood products with regard to certain characteristics.

It is thought that cardiac surgery provides more consistent results and may provide a more sensitive context to study the effects of transfusion because of the strong proinflammatory environment after surgery.[16] We hypothesized that if the donor sex effect were real, it would be maximal in cardiac surgery patients. Therefore, we investigated the effects of storage lesions and donor sex on short-term and long-term postoperative survival in cardiovascular surgery patients.

MATERIALS AND METHODS

Setting

Since 2000, a single institution has managed blood services in France: Etablissement Français du Sang (EFS). The EFS regional subdivision spans two administrative regions of eastern France (Franche-Comté and Burgundy). The population eligible for the study consisted of cardiovascular surgery patients transfused in the two university hospitals of the regions (located in Besançon and Dijon). Blood component preparation practices are similar in both centers. All RBC units transfused were leukoreduced before usage and suspended in SAGM. The maximum storage time for RBCs in France is 42 days.

Data sources

Since 1992, the EFS regional center has maintained a register of all transfused blood units and transfusion recipients. Each transfused unit is identified through its blood donation number. It can be linked to the characteristics of the donor, including sex. Basic characteristics of the blood unit are also stored, including storage duration. We collected data on patients transfused for the first time in either hospital.

Since 1997, all French public and private hospitals gather health and administrative data on inpatients, in a manner inspired by the Medicare diagnosis-related groups (DRG) system. The system was initially created to analyze hospital activity and to help implement strategic health plans. From 2008 on, hospital budgets have been linked to activity through the DRG system. The administrative and medical data are summarized in discharge abstracts (DAs) and sent under strict patient anonymity to the social security health administration, where they are compiled at the national level. It is very difficult to obtain authorization to use the social security number to perform linkage in France. (This is not usually the case in Medicare database studies.)[17] DAs contain diagnoses identified during the hospital stay coded according to the 10th edition of the International Classification of Diseases (ICD-10); procedures performed are coded according to the French common classification for medical procedures (Classification commune des actes médicaux [CCAM]). After processing the diagnosis and procedures, each hospital stay is classified into a DRG.

The vital status of all persons born in the country and most permanent residents can be obtained from the national directory for the identification of natural persons (Répertoire national d'identification des personnes physiques [RNIPP]). The procedure requires the basic patient identification information (names, date, and place of birth).

Record linkage between the transfusion register and DAs was performed within the hospitals' medical information departments to collect the birthplace and basic clinical information of the patients. The linkage was based on a shared patient identification number when available and a probabilistic linkage method[18] using identification characteristics otherwise. Importantly, the data were then rendered anonymous before analysis to protect patients' privacy. The relevant local ethics committee (Comité de protection des personnes [CPP Est II]) and the national ethics committee on information and healthcare research

(Comité consultatif sur le traitement de l'information en matière de recherche en santé [CCTIRS]) approved the study. The French data protection agency (Commission nationale informatique et libertés [CNIL]) approved the data security and rights to privacy aspects.

Patients

In this retrospective cohort study, exposure to transfusion was defined by transfusion register data. The eligible patients consisted of all adult patients transfused for the first time (defined as patients with no known history of RBC unit use in the transfusion register), at the university hospitals of Besançon or Dijon, between January 2007 and December 2011. Among these patients, only those who underwent cardiovascular surgery were included. Selection was based on relevant DRG data for the hospital stay. Appendix S1 (available as supporting information in the online version of this paper) shows a list of the cardiovascular surgery DRGs found in the study.

Variables

Patients were described using their basic characteristics (sex and age in quartiles) and the type of surgery they underwent. The type of surgery was found in the DRG of the hospital stay. The duration of the hospital stay in days was also reported.

Regarding blood products transfused, the number of transfusion episodes (a transfusion episode was defined as consecutive RBC transfusions separated by 7 days or less[19,20]), number of RBC units received, and mean and maximum age of the RBC units received (in days) were calculated. Transfusion with plasma and platelets (PLTs) were treated as binary variables. In most analyses, the total number of RBC units was divided into three categories (1 or 2, 3 or 4, and 5 or more RBC units), and the age of the oldest RBC unit was categorized using quartiles as cut points. Donor sex was also treated as a categorical variable: 1) "full match," when all units transfused were from a donor of the same sex as the recipient; 2) "full mismatch," when all units transfused were from a donor of the opposite sex; and 3) "partial mismatch," for all situations in between. Only units transfused during the initial hospital stay were considered in our analyses, regardless of transfusion episodes.

Statistical analysis

The basic characteristics of the patients and transfusions were analyzed for all cardiovascular surgery patients and in groups according to the number of RBC units received. Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables as numbers and percentages of patients. Analysis of variance and chi-square tests were used to compare groups for continuous and categorical variables, respectively.

Patient survival was estimated using the Kaplan-Meier method with calculation of the short-term (30-day), but also 90-day and 1-year postoperative survival. The log-rank test was used to compare survival rates according to patients' characteristics (age, sex), type of surgery, and transfusion characteristics (number of RBC units, use of PLTs and plasma, storage of the oldest RBC unit in quartiles, donor sex).

In the bivariate and multivariate analysis, the relative risks of death within 1 year were estimated using Cox proportional hazard regression and expressed as hazard ratios (HRs). Baseline covariate included the age and sex of the patient, the type of surgery according to the hospital stay DRG, and transfusions with PLTs or plasma during the hospital stay. Age of blood and donor sex were time-dependent variables updated daily. Multivariate models were stratified in a time-dependent manner on the cumulative number of RBC units received, as previously described.[21] Model assessments were carried out to test the assumption of proportional hazards using Schoenfeld residuals. A center effect was included in the models when significant. Significance was set at $p < 0.05$. All record linkages, data management, and analysis were performed using computer software (SAS/STAT, Version 9.4 for Windows, SAS Institute, Inc., Cary, NC).

RESULTS

Record linkage and included patients

During the study period, 16,099 patients received at least 1 RBC unit for the first time in the Besançon or Dijon university hospitals. They received a total of 102,538 RBC units spread across 33,916 episodes. We were able to link 12,858 (79.9%) of the transfused patients. Vital status could not be obtained for 3007 patients (18.7%). The main reason why vital status could not be determined was that the birthplace of 2341 patients (14.5%) was not available in hospital records. When it was available, the success rate for record linkage was 95.1%, and 666 patients could not be linked to a single live or dead person in the RNIPP. Among the initial population, 2715 included patients were transfused during a hospital stay related to cardiovascular surgery (Fig. 1).

The main patient baseline characteristics are presented in Table 1. Most patients were men (63.1%). The median duration of hospital stay was 14 days (IQR, 10-23 days). The most common cardiovascular DRGs were related to valve replacement surgery (36.2%), followed by coronary bypass surgery (30.2%).

A total of 12,350 RBC units were transfused. The median number of units transfused per patient was 2 (IQR, 2-5; range, 1-111); the median age of transfused units was 18 days (IQR, 13-24 days). Among the 2715 patients, 185 (6.8%) were transfused during the year following the hospital stay. The median number of additional

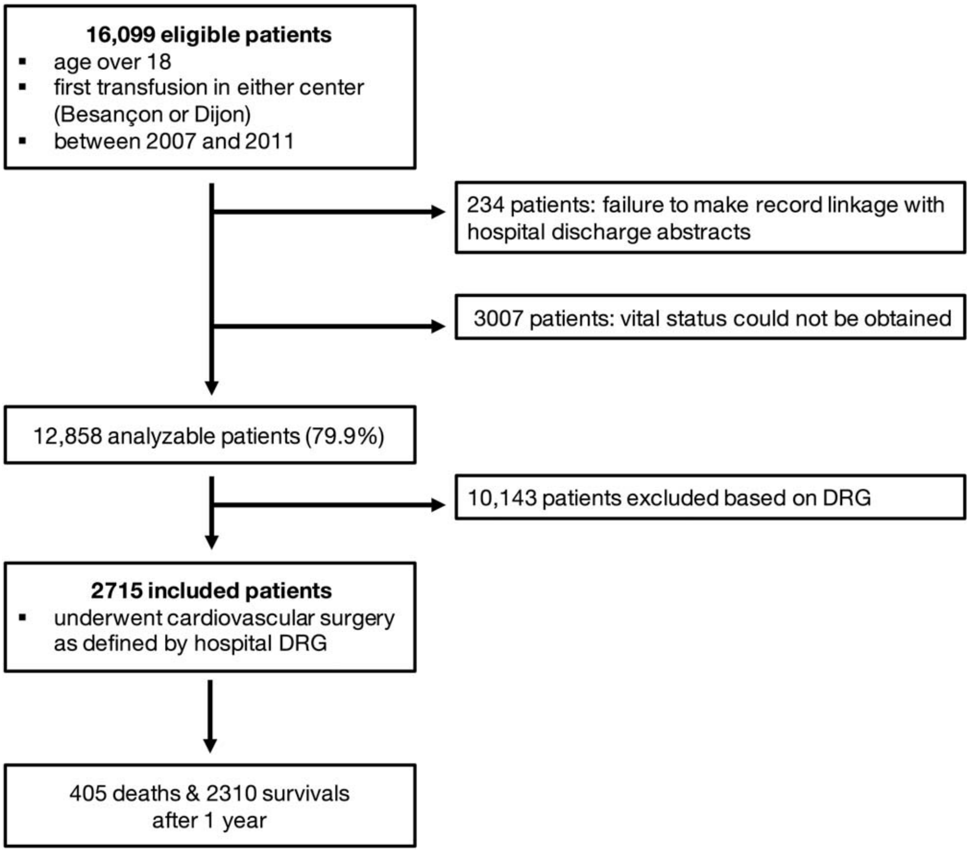

Fig. 1. Flow chart illustrating the number of eligible patients and patients included in the analysis. A total of 16,099 patients received a first transfusion in the university hospitals of Besançon or Dijon between 2007 and 2011. A total of 234 patients could not be linked with hospital records because of lacking or incorrect identification number. Vital status could not be obtained for 3007 patients because birthplace was not available in hospital records or because linkage with a living or dead person could not be made in the registry. A total of 10,143 patients were excluded because they did not undergo cardiovascular surgery based on the DRG of the DA.

RBC units was 3 (IQR, 2-6). The distribution of patients according to the age of the oldest RBC unit transfused is shown in Fig. 2A. The mean storage duration was constant regardless of number of transfusions ($p = 0.34$). However, the median age of the oldest RBC rose with the number of total units transfused from 19 days in patients who received 1 or 2 units (IQR, 14-26 units) to 26 days in patients who received 4 units or more (IQR, 20-33 units; $p < 0.0001$). The proportion of patients who received blood stored for 29 days or longer was higher in the group that received 5 units or more than in the group that received 1 or 2 units (42.3% vs. 18.0%, $p < 0.0001$; Table 2).

Figure 2B shows the distribution of patients according to the percentage of units matched to their sex. While 17.8% of the patients received only units from a donor of the same sex (100% sex match), 17.9% received only units from donors of the opposite sex (0% sex match). The rest of the patients were included in the partial sex mismatch category. Interestingly, 27.3% of the patients received exactly half of the units matched for sex (50% sex match) while 37% received various percentages of sex-mismatched units. Males were more likely than females to receive sex-matched blood (21.2% vs. 12.4%). Because the odds of receiving blood from donors of the same sex decreased when the number of RBC units increased, the proportion of patients in the partial-sex-mismatch group was higher in patients who received 5 units or more than in patients transfused with 1 or 2 units (97.2% vs. 39.1%, $p < 0.0001$; Table 2). Patients who received 5 units or more were also more likely to be transfused with plasma (67.2% vs. 8.1%, $p < 0.0001$) and PLTs (60.1% vs. 9.0%, $p < 0.0001$; Table 2).

Patients' survival, storage duration, and donor sex

Patients' survival and unadjusted HR for the risk of death within 1 year after transfusion are presented in Table 3. Thirty-day survival for cardiovascular surgery patients was 92.2%. Ninety days after transfusion, survival was 89.1%, and after 1 year, 85.1% of the patients remained alive. Sex was not significantly associated with survival ($p = 0.11$). The patients with the best survival were those who underwent coronary bypass surgery without heart catheterization (HC; 30-day survival 97.2%; 1-year survival 92.9%). The data showed a strong association between the risk of death and the type of surgery before adjustments with HRs as high as 10.72 in the "other cardiothoracic surgery without cardiopulmonary bypass" group (95% confidence interval [CI], 6.74-17.02; p < 0.0001) compared with patients who had coronary bypass surgery without HC. The risk of death increased with the number of RBC units transfused: patients who received 1 or 2 RBC units had a 30-day survival of 96.8% (1-year survival 92.3%) while only 82.1% of those transfused with 5 units or more were alive 30 days after transfusion (1-year survival 69.6%; HR, 6.17; 95% CI, 4.87-7.83; p < 0.0001). Transfusion with plasma or PLTs was also associated with significantly lower survival rates (RBCs plus plasma—30-day survival 81.5% vs. 96.3%, 1-year survival 72.6% vs. 89.8%, p < 0.0001; RBCs plus PLTs—30-day survival 83.0% vs. 95.3%, 1-year survival 73.8% vs. 88.8%, p < 0.0001). Our main variables of interest, storage duration and donor sex, were also associated with the risk of death in bivariate analysis. Transfusion with blood stored for 21 to 28 days was associated with a HR of 1.52 (95% CI, 1.11-2.07). For those transfused with blood stored for 29 days or more, the HR was 2.07 (95% CI, 1.54-2.79). Patients transfused with sex-mismatched RBC units also appeared at risk with an HR of 2.28 (95% CI, 1.67-3.12), compared with patients transfused only with units from a donor of the same sex. The effect appeared more intense in female recipients (HR, 3.31; 95% CI, 1.54-7.12).

TABLE 1. Characteristics of patients and surgery

Characteristic	Number (%) of patients or median (IQR), n = 2715
Age (years)	72 (63-78)
Sex	
Male	1712 (63.1)
Female	1003 (36.9)
Duration of hospital stay (days)	14 (10-23)
Type of surgery	
Valve replacement surgery	
With CPB and HC	118 (4.3)
With CPB without HC	867 (31.9)
Coronary bypass surgery	
With HC	241 (8.9)
Without HC	578 (21.3)
Other cardiothoracic or vascular surgery	
With CPB	251 (9.2)
Without CPB	62 (2.3)
Major revascularization surgery	425 (15.7)
Other vascular surgery	116 (4.3)
Pacemaker or ICD implantation	30 (1.1)
Other procedures on the circulatory system	27 (1.0)

CPB = cardiopulmonary bypass; ICD = implantable cardioverter-defibrillator.

Multivariate models used the maximum age of RBC units, with adjustments on the patients' age and type of surgery, and were stratified by the number of RBC units received. In these models, the patients' age and type of surgery remained significant in the models. However, the use of PLTs and/or plasma, the age of blood, and donor sex effects were no longer significant. When considering the age of blood as a continuous variable, the relative risk of death was 1.00 (95% CI, 0.99-1.01; p = 0.95). The relative risk of death was not affected significantly by increasing quartiles of maximum age of blood: patients with the highest quartile (29-42 days) had a relative risk of 0.97 (95% CI, 0.69-1.35; see Table 4). Global tests of the proportional hazards assumption did not suggest any evidence against the models. We did not find evidence of an association between the daily maximum age of RBCs and survival (data not shown). There was no significant center

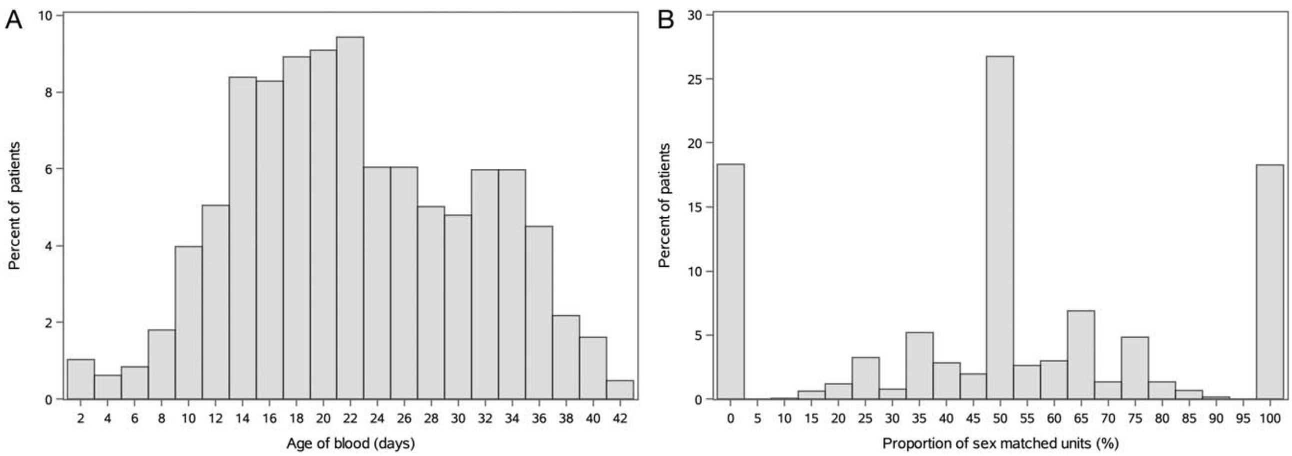

Fig. 2. Age and donor sex distributions. Patient distribution according to the storage time of the oldest RBC unit transfused (n = 2715; A). Patient distribution according to the proportion of sex-matched RBC units (n = 2714; B).

TABLE 2. Characteristics of transfusions

	All patients (n = 2715)	Number of RBC units transfused 1-2	3-4	5+	p value
Number of transfusion episodes	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-2)	
Number of RBC units transfused	2 (2-5)	2 (2-2)	4 (3-4)	7 (6-12)	
Mean age of RBC units (days)	18.0 (13.0-23.5)	18.0 (13.0-24.0)	18.0 (12.7-23.7)	18.2 (14.1-22.7)	0.34
Age of oldest RBC unit (days)	21 (15-29)	19 (14-26)	21 (16-28)	26 (20-33)	<0.0001
Age of oldest RBC unit (days)					<0.0001
0-14	581 (21.4)	376 (27.7)	139 (20.8)	66 (9.6)	
15-20	711 (26.2)	383 (28.2)	188 (28.1)	140 (20.3)	
21-28	721 (26.6)	354 (26.1)	176 (26.3)	191 (27.8)	
29-42	702 (25.9)	245 (18.0)	166 (24.8)	291 (42.3)	
Donor sex*					<0.0001
Full mismatch	484 (17.8)	414 (30.5)	62 (9.3)	8 (1.2)	
Partial mismatch	1743 (64.2)	531 (39.1)	544 (81.3)	668 (97.2)	
Full match	487 (17.9)	413 (30.4)	63 (9.4)	11 (1.6)	
Donor sex (male recipients†)					<0.0001
Full mismatch	237 (13.9)	206 (23.9)	28 (7.1)	3 (0.7)	
Partial mismatch	1111 (64.9)	351 (40.8)	318 (80.5)	442 (97.1)	
Full match	363 (21.2)	304 (35.3)	49 (12.4)	10 (2.2)	
Donor sex (female recipients‡)					<0.0001
Full mismatch	247 (24.6)	208 (41.9)	34 (12.4)	5 (2.2)	
Partial mismatch	632 (63.0)	180 (36.2)	226 (82.5)	226 (97.4)	
Full match	124 (12.4)	109 (21.9)	14 (5.1)	1 (0.4)	
Plasma transfusion	741 (27.3)	110 (8.1)	169 (25.3)	462 (67.2)	<0.0001
PLT transfusion	675 (24.8)	122 (9.0)	139 (20.8)	414 (60.1)	<0.0001

Data are reported as median (IQR) or number (%).
* n = 2714, donor sex missing for 1 RBC unit.
† n = 1711.
‡ n = 1003.

effect in the bivariate or multivariate analysis (data not shown); final models were not adjusted or stratified on the center. There was no significant interaction between age of blood and donor sex in our models (data not shown). Because previous work showed a possible effect of female RBC units in male recipients, we carried out subgroup analyses by sex. There was no significant effect of donor sex in male patients ($p = 0.69$). The effect appeared more pronounced in female patients with a relative risk of death of 2.03 when transfused solely with RBCs from male donors but did not reach significance (95% CI, 0.87-4.73; $p = 0.17$) (Table 4).

DISCUSSION

This report is the first study of survival after transfusion in France. We report short-term (30-day, 90-day) and 1-year survival in cardiovascular surgery patients who had never before been transfused. We studied the effect of RBC storage and donor sex on the risk of death within 1 year. The number of RBC units transfused is a major confounding factor in this type of study.[22] The statistical analysis presented accounts for the number of units transfused: models were stratified on the number of units in a time-dependent fashion. Patients were considered at risk of death after the first transfusion in the first stratum and changed stratum with each daily transfusions. Using this method, the effects of age of blood and donor sex are average effects across all strata. After adjustments, the data showed no significant effect of RBC storage duration or donor sex. These results suggest that current blood management practices in terms of sex matching and RBC storage are safe for patients undergoing cardiovascular surgery.

In our analyses, we used the DRGs to adjust for the type of surgery. To our knowledge, DRGs have not been used in this way before. Although DRGs are meant as a resource management and billing method, we believe that they provide an effective way to stratify patients into groups with closely related mortality risks. This is particularly effective in the study of surgery, since DRGs are defined by the type of surgery performed and coding quality of procedures is higher than that of diagnoses[23-25] (see Appendix S1 for the list of DRGs used in this study and their clinical definitions).

Our study is one of the few that have studied medium-term postoperative mortality in transfused patients. Edgren and colleagues[20] showed a 5% increase in 2-year mortality when patients were transfused with blood stored for 30 days or more. The authors concluded that this small effect may not be clinically relevant since it may be the result of remaining confounding. Our study focused on cardiac surgery patients with adjustment for the type of surgery. We believe that this greatly reduced

TABLE 3. Patients' survival and 1-year risk of death according to types of surgery and transfusion characteristics

	Patients' survival, % (SE)				
Exposure variable	30 days	90 days	365 days	HR (95% CI)*	p value†
All patients	92.2 (0.51)	89.1 (0.60)	85.1 (0.68)		
Age (years)					<0.0001
18-57	91.9 (1.38)	90.6 (1.47)	88.3 (1.62)	1.00 (reference)	
58-71	94.4 (0.76)	92.0 (0.90)	88.8 (1.04)	0.93 (0.66-1.32)	
72-80	92.1 (0.87)	89.0 (1.01)	83.9 (1.19)	1.39 (1.00-1.93)	
81+	88.4 (1.52)	81.9 (1.84)	76.9 (2.01)	2.12 (1.50-3.00)	
Sex					0.11
Male	91.8 (0.66)	88.5 (0.77)	84.2 (0.88)	1.00 (reference)	
Female	92.9 (0.81)	90.0 (0.95)	86.5 (1.08)	0.85 (0.69-1.04)	
Type of surgery					<0.0001
Valve replacement surgery					
With CPB and HC	86.4 (0.31)	82.2 (0.35)	77.1 (0.39)	3.56 (2.19-5.79)	
With CPB without HC	93.7 (0.83)	91.0 (0.97)	87.8 (1.11)	1.78 (1.24-2.55)	
Coronary bypass surgery					
With HC	90.5 (1.89)	87.6 (2.13)	84.6 (2.32)	2.30 (1.47-3.58)	
Without HC	97.2 (0.68)	95.2 (0.89)	92.9 (1.07)	1.00 (reference)	
Other cardiothoracic or vascular surgery					
With CPB	92.4 (1.67)	91.6 (1.75)	88.8 (1.99)	1.62 (1.00-2.63)	
Without CPB	59.7 (6.23)	56.5 (6.30)	48.4 (6.35)	10.72 (6.74-17.02)	
Major revascularization surgery	91.3 (1.37)	85.9 (1.69)	79.8 (1.95)	3.06 (2.11-4.43)	
Other vascular surgery	90.5 (2.72)	81.9 (3.58)	71.6 (4.19)	4.44 (2.81-7.02)	
Pacemaker or ICD implantation	86.7 (6.21)	86.7 (6.21)	76.7 (7.72)	3.53 (1.58-7.87)	
Other procedures on the circulatory system	81.5 (0.75)	74.1 (0.84)	70.4 (0.88)	4.96 (2.32-10.58)	
Number RBC units transfused					<0.0001
1-2	96.8 (0.48)	95.6 (0.56)	92.3 (0.72)	1.00 (reference)	
3-4	93.3 (0.97)	90.6 (1.13)	86.2 (1.33)	2.10 (1.59-2.79)	
5+	82.1 (1.46)	74.7 (1.66)	69.6 (1.75)	6.17 (4.87-7.83)	
Plasma transfusion					<0.0001
No	96.3 (0.43)	93.7 (0.55)	89.8 (0.68)	1.00 (reference)	
Yes	81.5 (1.43)	76.8 (1.55)	72.6 (1.64)	3.09 (2.54-3.76)	
PLT transfusion					<0.0001
No	95.3 (0.47)	92.7 (0.67)	88.8 (0.70)	1.00 (reference)	
Yes	83.0 (1.45)	77.9 (1.60)	73.8 (1.69)	2.64 (2.18-3.22)	
Age of oldest RBC unit transfused (days)					0.0002
0-14	94.3 (0.96)	91.9 (1.13)	89.2 (1.29)	1.00 (reference)	
15-20	92.8 (0.97)	90.0 (1.12)	86.6 (1.28)	1.28 (0.93-1.76)	
21-28	91.4 (1.04)	88.5 (1.19)	84.7 (1.34)	1.52 (1.11-2.07)	
29-42	90.7 (1.09)	86.3 (1.30)	80.5 (1.50)	2.07 (1.54-2.79)	
Donor sex					<0.0001
Complete sex match	95.9 (0.90)	95.1 (0.98)	90.8 (1.31)	1.00 (reference)	
Partial sex mismatch	90.4 (0.71)	86.3 (0.82)	82.4 (0.91)	2.28 (1.67-3.12)	
Complete sex mismatch	95.0 (0.99)	92.8 (1.18)	89.3 (1.41)	1.18 (0.79-1.75)	
Donor sex (male recipients‡)					<0.0001
Complete sex match	95.6 (1.08)	94.5 (1.20)	89.5 (1.61)	1.00 (reference)	
Partial sex mismatch	89.7 (0.91)	85.4 (1.06)	81.4 (1.17)	2.14 (1.52-3.03)	
Complete sex mismatch	95.8 (1.31)	93.7 (1.58)	89.9 (1.96)	0.98 (0.59-1.63)	
Donor sex (female recipients§)					0.005
Complete sex match	96.8 (1.59)	96.8 (1.59)	94.4 (2.07)	1.00 (reference)	
Partial sex mismatch	91.6 (1.10)	88.0 (1.29)	84.2 (1.45)	3.31 (1.54-7.12)	
Complete sex mismatch	94.3 (1.47)	91.9 (1.74)	88.7 (2.02)	2.02 (0.88-4.63)	

* HR for 1-year risk of death estimated by unadjusted Cox proportional hazard regression.
† Log-rank test.
‡ n = 1711.
§ n = 1003.
CPB = cardiopulmonary bypass; ICD = implantable cardioverter-defibrillator; SE = standard error.

the amount of confounding. In this setting, we found that the age of the blood had no effect on survival, thus suggesting the safety of transfusion with older blood even when survival in the longer term is considered.

The transfusion of young versus older RBCs has been the focus of numerous studies. Previous observational studies in various clinical settings reported conflicting results.[3,5-8] This situation called for large randomized clinical trials to clarify the conclusions. To date, two trials have reported results,[10,26] including one in cardiac surgery patients (the RECESS trial). Neither found a significant impact of the transfusion of older RBCs on various

TABLE 4. Relative risk of death after RBC blood transfusion in relation to storage age of transfused RBC and donor sex*

	All patients (n = 2714)		Male recipients (n = 1711)		Female recipients (n = 1003)	
Exposure variable	HR (95% CI)*	p value	HR (95% CI)*	p value	HR (95% CI)*	p value
Age (years)		<0.0001		<0.0001		0.02
18-57	1.00 (reference)		1.00 (reference)		1.00 (reference)	
58-71	1.27 (0.84-1.90)		1.51 (0.92-2.49)		0.65 (0.44-2.03)	
72-80	2.41 (1.64-3.56)		2.84 (1.74-4.66)		1.91 (0.96-3.78)	
81+	3.20 (2.13-4.81)		3.93 (2.32-6.65)		2.02 (1.02-4.00)	
Female sex	0.83 (0.66-1.05)	0.12				
Type of surgery		<0.0001		<0.0001		<0.0001
Valve replacement surgery						
With CPB and HC	1.68 (0.98-2.88)		1.06 (0.50-2.23)		3.52 (1.34-9.25)	
With CPB without HC	1.24 (0.85-1.82)		1.12 (0.71-1.77)		1.82 (0.80-4.10)	
Coronary bypass surgery						
With HC	1.84 (1.15-2.94)		2.13 (1.25-3.63)		1.71 (0.61-4.85)	
Without HC	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Other cardiothoracic or vascular surgery						
With CPB	1.00 (0.59-1.69)		0.96 (0.51-1.80)		1.62 (0.55-4.75)	
Without CPB	6.40 (3.74-10.94)		8.70 (4.54-16.65)		4.53 (1.44-14.24)	
Major revascularization surgery	2.27 (1.53-3.37)		1.89 (1.21-2.97)		4.76 (1.95-11.66)	
Other vascular surgery	3.64 (2.24-5.90)		2.90 (1.60-5.27)		7.73 (2.97-20.11)	
ICD and Pacemaker implantation	3.33 (1.43-7.71)		4.91 (2.11-11.43)		Not calculable†	
Other procedures on the circulatory system	1.98 (0.85-4.59)		2.30 (0.72-7.29)		4.69 (1.23-17.92)	
Plasma transfusion	1.20 (0.88-1.65)	0.26	1.13 (0.76-1.69)	0.55	1.20 (0.67-2.14)	0.55
PLT transfusion	0.79 (0.57-1.09)	0.16	0.81 (0.54-1.20)	0.30	0.77 (0.42-1.43)	0.41
Age of oldest unit (days)		0.98		0.50		0.30
0-14	1.00 (reference)		1.00 (reference)		1.00 (reference)	
15-20	0.94 (0.67-1.31)		0.78 (0.52-1.19)		1.29 (0.71-2.34)	
21-28	0.99 (0.72-1.38)		0.93 (0.63-1.39)		1.25 (0.68-2.30)	
29-42	0.97 (0.69-1.35)		1.03 (0.69-1.53)		0.82 (0.42-1.58)	
Donor sex		0.27		0.69		0.17
Complete match	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Partial mismatch	0.89 (0.61-1.31)		0.83 (0.54-1.28)		1.40 (0.57-3.49)	
Complete mismatch	1.22 (0.81-1.82)		0.96 (0.57-1.61)		2.03 (0.87-4.73)	

* All analyses were stratified by number of RBC units transfused.
† No event in this group.

outcomes, including short-term mortality. Before these, other trials studied the effects of stored RBCs on pulmonary function and several cytokine levels, but found no significant differences when compared to fresh RBCs.[27,28] The results presented here are in agreement with regard to short-term postoperative mortality.

Contrary to a previous study, our study found no significant effect of RBC transfusion from donors of the opposite sex. In their work, Middelburg and coworkers concluded that male recipients transfused with RBCs from female donors may be at an increased risk of death.[12] They hypothesized an immunomodulatory effect in males transfused with RBCs from female donors alloimmunized against male-specific minor histocompatibility (HY) antigens that could lead to a susceptibility to infection and/or TRALI. Indeed, HY antigens are expressed by a wide range of tissues, including white blood cells.[13] HY antibodies are present in about 30% of women.[29] HY alloimmunization is known to induce transplant rejection[30] and is associated with graft-versus-host disease after stem cell transplantation.[29]

Because there was no adjustment for underlying illness, Middelburg and colleagues also suggested the possibility of an association between donor sex and death by chance only. To remove any such possibility, we investigated the effect in a focused clinical setting and could not reproduce the findings. Interestingly, our data suggested an opposite effect. In our models, females transfused with RBCs from male donors were at an increased risk of death compared to men transfused with female RBCs (HR, 2.03 vs 0.96). However, the effect did not reach significance. It may be necessary to study patients in other clinical settings, or patients who receive repeated transfusions, where an HY-related immunomodulatory effect may be more pronounced. Nevertheless, our admittedly observational findings suggest that RBC transfusion across sex is a safe practice, particularly in cardiac surgery.

One limitation of our study is related to the linkage between the transfusion register and the hospital DAs. We were only able to link about 80% of the initial population of transfusion recipients. This introduces a significant risk of selection bias in our study. Another limitation is related to the use of DRGs to describe the clinical context of the patients. DRGs were not designed to perform epidemiology studies, but to describe the use of hospital resources for billing purposes. They provide a rather imprecise description of the clinical setting and the patients' underlying illness and comorbidities.

In conclusion, the results presented here illustrate the potential of databases in the field of hemovigilance. Such a tool may provide a precise description of transfusion recipients and important information on their clinical follow-up. Expansion of the database to multiple centers across the country would provide a powerful hypothesis-generating tool.

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CONFLICT OF INTEREST

PT and LB are employees of Établissement Français du Sang. All other authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. List of cardiovascular surgery diagnosis-related groups (DRG) in the French discharge abstract database used to select the patients for inclusion.