Original Investigation

Association of Blood Donor Age and Sex With Recipient Survival After Red Blood Cell Transfusion

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IMPORTANCE While red blood cells (RBCs) are administered to improve oxygen delivery and patient outcomes, they also have been associated with potential harm. Unlike solid organ transplantation, the clinical consequences of donor characteristics on recipients have not been evaluated in transfusion medicine.

OBJECTIVE To analyze the association of RBC donor age and sex with the survival of transfusion recipients.

DESIGN, SETTING, AND PARTICIPANTS We established a longitudinal cohort by linking data from a blood collection agency with clinical and administrative data at 4 academic hospitals.

MAIN OUTCOMES AND MEASURES Cox proportional hazards regression models were fitted to evaluate the risk of donor age and sex on transfusion recipient survival.

RESULTS Between October 25, 2006, and December 31, 2013, a total of 30 503 RBC transfusion recipients received 187 960 RBC transfusions from 80 755 unique blood donors. For recipients receiving an RBC unit from younger donors, the risk of death was increased compared with recipients receiving an RBC unit from a donor 40 to 49.9 years old (adjusted hazard ratio, 1.08; 95% CI, 1.06-1.10; $P < .001$ for donor age range 17-19.9 years and 1.06; 95% CI, 1.04-1.09; $P < .001$ for donor age range 20-29.9 years). Receiving an RBC transfusion from a female donor was associated with an 8% statistically significant increased risk of death compared with receiving an RBC transfusion from a male donor (adjusted hazard ratio, 1.08; 95% CI, 1.06-1.09; $P < .001$).

CONCLUSIONS AND RELEVANCE Red blood cell transfusions from younger donors and from female donors were statistically significantly associated with increased mortality. These findings suggest that donor characteristics may affect RBC transfusion outcomes.

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Invited Commentary

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Red blood cell (RBC) transfusion is the most common medical procedure in contemporary medicine.[1] In the United States, 7.6% of all hospitalized patients will receive at least 1 blood transfusion during their hospitalization, and its use has increased between 1997 and 2011 by 134%.[1] With the main objective to improve oxygen delivery to tissues,[2] RBC transfusion is used in a variety of medical situations, ranging from correction of chronic low-grade anemia to resuscitation of the massively bleeding patient.[2-5] When a decision to transfuse has been made, usual practice is to order 1 or more compatible RBC units from the blood bank. Limited characteristics of the RBC unit can be requested, such as cytomegalovirus (CMV) status, leukoreduction, or irradiation; however, evidence of clinical benefit with these specific characteristics is limited.[6]

There is growing preclinical and clinical evidence that blood donor characteristics may affect recipient outcomes. Erythropoiesis is altered by aging,[7] as are other characteristics related to blood, including immune tolerance, inflammation, oncogenicity, and premature cellular turnover.[8,9] Humans who live longer may also have different genetic factors affecting RBC characteristics.[10] Immunological phenomena related to donors, such as the antileukocyte antibodies (anti-HLA or antineutrophil antibodies) that occur after pregnancies (eg, sex effect on transfusion-related acute lung injury [TRALI]), have been shown to affect clinical outcomes.[11,12]

Transfusion of a blood component is analogous to solid organ transplantation because it involves the retrieval of an organ

(blood) from a donor, postdonation processing and storage, and "transplantation" (transfusion) into a recipient.[13] In the transplant literature, specific donor characteristics have been associated with adverse outcomes in recipients. For example, in heart, lung, liver, kidney, and stem cell transplantation, donor age has repeatedly been shown to be associated with transplantation outcome.[14-22] Female donor sex has also been suggested to be associated with poorer outcomes in stem cell transplantation,[21] as well as a cohort study[23] assessing outcomes after RBC transfusions in male recipients. Such characteristics have not been extensively evaluated for RBC transfusion.[24] Understanding that current evidence (although limited) suggests that blood donor characteristics may influence transfusion recipient outcomes, the 2015 National Heart, Lung, and Blood Institute State of the Science in Transfusion Medicine meeting identified donor factors, such as age and sex, as "compelling questions necessitating additional basic, translational or clinical research."[25] Based on the emerging evidence and a lack of robust studies assessing potential clinical effects of donor characteristics, we analyzed the effect of donor age and sex on the survival of RBC transfusion recipients.

Key Points

Question What is the effect of red blood cell (RBC) donor age and sex on transfusion recipient survival?

Findings This longitudinal cohort study included 30 503 transfusion recipients who received 187 960 transfusions from 80 755 unique blood donors. Receipt of transfusions from female donors or donors younger than 30 years was associated with a statistically significant increased risk of death compared with receiving transfusions from male donors.

Meaning Donor characteristics may be associated with RBC transfusion outcomes and mortality.

Methods

Study Design and Setting

We conducted a longitudinal cohort study at 4 academic hospitals to investigate the association of donor age and sex with recipient survival after RBC transfusion. A detailed version of the study design and methods has been published.[13] Briefly, we obtained blood donor data prospectively collected at the time of blood donation from Canadian Blood Services (Edmonton, Alberta), the operator of the blood system in Canada in all provinces and territories except for Quebec; short-term descriptive and outcome data from hospital-based clinical and administrative databases; and long-term outcome data from population-based administrative data housed at the Institute for Clinical Evaluative Sciences (Toronto, Ontario, Canada). The 4 participating sites included the General, Riverside, and Civic campuses of The Ottawa Hospital and the University of Ottawa Heart Institute (all in Ottawa, Ontario, Canada). This study was approved by The Ottawa Hospital Research Ethics Board (protocol 20140111-01H) and Canadian Blood Services Research Ethics Board (protocol 2014.004). Informed consent was not required by the research ethics boards.

Recipient Population

We included all recipients regardless of age who received at least 1 RBC transfusion between October 25, 2006, and December 31, 2013, and had a mandatory valid health insurance number from the Canadian province of Ontario. The October 25, 2006, date was chosen because it represents the date when data on all blood products transfused were electronically stored at the included institutions. The recipients had to have a valid health insurance number for outcome data to be obtained from the provincial databases. We excluded recipients who received RBC units that could not be linked to Canadian Blood Services because they were produced by a different blood collection agency.

Donor Population

Donor information was obtained from Canadian Blood Services databases. Data collected included donor demographics (eg, age and sex), as well as blood product characteristics (blood group, CMV status, irradiation status, and additive solution) for each unit of blood collected.

Data Collection

We predefined exposures, covariates, and outcomes of interest in the published protocol.[13] We deterministically linked donor and blood product information for each RBC unit transfused at each study center. We then linked to hospital-based administrative data sets to determine recipient characteristics, including age, sex, transfusion history, and medical comorbidities. The resulting data set was then linked deterministically to the Ontario Registered Persons Database, which contains vital status information on all Ontario residents, to determine if and when recipients died. Therefore, the resulting data sets allowed the evaluation of the complete donor-to-recipient or vein-to-vein continuum.

Study Exposures

Our primary exposure of interest was donor age, and the secondary exposure was donor sex. This information was collected at the time of donation for each RBC unit transfused. We also collected the date of donation, donor ABO blood group, number of previous whole blood donations, and manufacturing methods (additive solution, filtration methods, CMV status, and irradiation status). All transfused RBC units were leukoreduced, and all donors were at least 17 years old as per Canadian Blood Services blood donation policies. Recipients could receive more than 1 RBC transfusion from more than 1 donor. For recipients, we collected the date and time of each RBC transfusion, whether they received any other blood products, hospital administrative information (admission and discharge dates and discharge disposition), age and sex, and ABO blood group. For inpatient transfusions, we collected the individual elements of the validated Charlson Comorbidity Index[26-28] to obtain the main comorbidities of each transfused recipient. This information was obtained from the Canadian Institute for Health

Information Discharge Abstract Database, which records detailed diagnostic and procedural information for all hospital admissions in Ontario. For outpatient transfusions, the elements of the Charlson Comorbidity Index were not available.

Study Outcome

Our primary study outcome was recipient survival, measured from the date of first RBC transfusion. Recipients who did not have a death record at the time of study completion were assumed to be alive and censored on December 31, 2013.

Statistical Analysis

The principal analysis was based on a Cox proportional hazards regression model that accounted for a recipient's cumulative RBC transfusion episodes over time.[29,30] Our model had to account for patients who received RBC transfusions from different donors with different donor characteristics (donor age and sex) (eAppendix in the Supplement). We considered the varying follow-up time of each recipient, with the start of follow-up defined as the time of first transfusion and the end of follow-up at either death or end of the study.

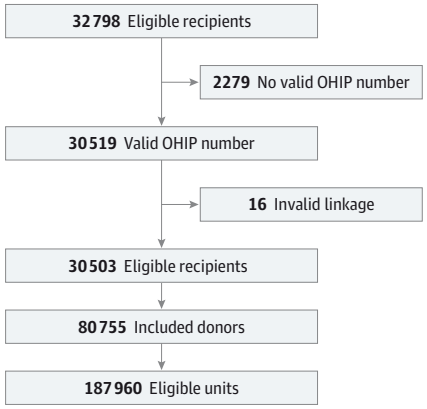
The exposure of interest was the cumulative number of units received with a feature of interest (ie, donor sex and donor age category), which was updated with each transfusion. We assumed that the effect of a previous transfusion would not stop at the moment of an additional RBC transfusion; therefore, the exposure of interest had to consider cumulative exposure over time. We calculated the risk (hazard) of receiving an RBC unit with a feature of interest compared with receiving an RBC unit from a fixed reference group (opposite sex and donor age group of 40-49.9 years), while adjusting for all other covariates, including the cumulative number of RBC units received. Donor age was categorized into groups of 10 years. All donors 70 years or older were considered in one group because of the limited number of donors older than 70 years. The exposure to RBCs from donors with one of the features of interest (donor age or donor sex) was allowed to be repeated over time and treated as time varying.

Our model adjusted for the cumulative mix of RBC donor exposures (ie, donor sex or donor age) and for the potential confounders of recipient age, sex, and comorbid illnesses. Confounding variables except recipient sex were treated as time-varying covariates. Comorbidity data were not collected for outpatient transfusions, coded as a dummy missing variable when occurring. Because outpatient comorbidity was missing not at random, multiple imputation strategies were deemed inappropriate.[31]

Planned subgroup analyses were based on the following: recipient sex, recipient age (<1, 1 to <18, 18 to <65, or ≥65 years), and comorbid illness (using the Charlson Comorbidity Index). To test the at-random distribution of the exposures, we also compared characteristics of recipients who received RBCs only from male or female donors or from young or older donors. The effect of exposures was also tested for proportionality over time. We tested visually any evidence of departure from proportionality by plotting Kaplan-Meier survival curves for patients who received only one unit of blood of each characteristic. To test whether the cumulative risk associated with one transfusion also respected the proportionality assumption, we introduced a time interaction term between the cumulative exposure covariates and the time each patient was exposed to each level of covariates in each model.

All tests of statistical inference reflect a 2-sided α = .05. Analyses were performed using statistical software (SAS, version 9.4; SAS Institute).

Figure 1. Flowchart of the Study Cohort



OHIP indicates Ontario Health Insurance Plan.

Results

Over the study period, 32 798 patients received at least 1 RBC transfusion. A total of 2279 (6.9%) recipients were excluded because they did not have a valid health insurance number, and 16 (0.1%) recipients were excluded because they could not be linked to the provincial databases. A further 133 RBC units were excluded because they were obtained from a different blood collection agency. Therefore, our cohort included 30 503 recipients, 80 755 unique blood donors, and 187 960 transfused RBC units (**Figure 1**) The mean (SD) recipient follow-up was 2.3 (2.1) years from the time of first transfusion, and maximum follow-up was 7.2 years. Death occurred in 13 118 (43.0%) of our cohort of recipients.

Recipient and donor characteristics are summarized in **Table 1** and **Table 2**. There were no missing values for age and sex for either donors or recipients. The median recipient age was 69.0 years (interquartile range [IQR], 56.0-80.0 years), and 52.1% (n = 15 906) were female. The proportion of recipients with a Charlson Comorbidity Index of at least 5 was 20.7% (n = 6314). The median number of RBC units received was 3 (IQR, 2-6). The median donor age was 42.0 years (IQR, 27.0-52.0 years), and 48.7% (n = 39 328) were female. Donors had given a median of 5 (IQR, 1-17) whole blood donations.

Characteristics of the RBC units transfused are summarized in eTable 1 in the Supplement. A total of 32.1% (n = 60 334) of the units were produced using the buffy coat method. The

Table 1. Recipient Characteristics at the Time of First Transfusion

Variable	Value (n = 30 503)
Age, y	
Mean (SD)	66.2 (18.2)
Median (IQR)	69.0 (56.0-80.0)
Male age, y	
Mean (SD)	66.6 (17.2)
Median (IQR)	69.0 (58.0-79.0)
Female age, y	
Mean (SD)	65.8 (19.1)
Median (IQR)	69.0 (54.0-81.0)
Sex, No. (%)	
Male	14 597 (47.9)
Female	15 906 (52.1)
ABO blood group, No. (%)	
A negative	1943 (6.4)
A positive	9872 (32.4)
AB negative	202 (0.7)
AB positive	1037 (3.4)
B negative	497 (1.6)
B positive	3153 (10.3)
O negative	2207 (7.2)
O positive	11 450 (37.5)
No result available	16 (0.1)
Variable results	90 (0.3)
First available Charlson Comorbidity Index, No. (%)	
0	8812 (28.9)
1-2	8155 (26.7)
3-4	4436 (14.5)
≥5	6314 (20.7)
Not available	2786 (9.1)
Comorbid conditions, No./total No. (%)[a]	
Cardiac disease	2521/27 717 (9.1)
Congestive heart failure	3313/27 717 (12.0)
Peripheral vascular disease	2079/27 717 (7.5)
Cerebrovascular disease	818/27 717 (3.0)
Dementia	842/27 717 (3.0)
COPD	1820/27 717 (6.6)
Connective tissue disease	308/27 717 (1.1)
Peptic ulcer disease	1020/27 717 (3.7)
Mild liver disease	767/27 717 (2.8)
Moderate or severe liver disease	495/27 717 (1.8)
Diabetes with no organ damage	2448/27 717 (8.8)
Diabetes with organ damage	4830/27 717 (17.4)
Hemiplegia	400/27 717 (1.4)
Moderate or severe renal failure	2205/27 717 (8.0)
Cancer without metastases	7246/27 717 (26.1)
Cancer with metastases	3164/27 717 (11.4)
Human immunodeficiency virus	92/27 717 (0.3)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a] A total of 2786 patients had no comorbid conditions data collected.

Table 2. Donor Characteristics at the Time of First Donation

Variable	Value (n = 80 755)
Sex, No. (%)	
Male	41 427 (51.3)
Female	39 328 (48.7)
Age, y	
Mean (SD)	40.4 (14.5)
Median (IQR)	42.0 (27.0-52.0)
Age group, y, No. (%)	
17-19.9	8643 (10.7)
20-29.9	14 787 (18.3)
30-39.9	12 461 (15.4)
40-49.9	19 178 (23.8)
50-59.9	18 485 (22.9)
60-69.9	6903 (8.6)
≥70	298 (0.4)
No. of previous whole blood donations	
Mean (SD)	12.7 (19.0)
Median (IQR)	5 (1-17)
Donor ABO blood group, No./total No. (%)	
A negative	6258 (7.8)
A positive	23 782 (29.5)
AB negative	687 (0.9)
AB positive	1869 (2.3)
B negative	1683 (2.1)
B positive	6874 (8.5)
O negative	8584 (10.6)
O positive	31 018 (38.4)

Abbreviation: IQR, interquartile range.

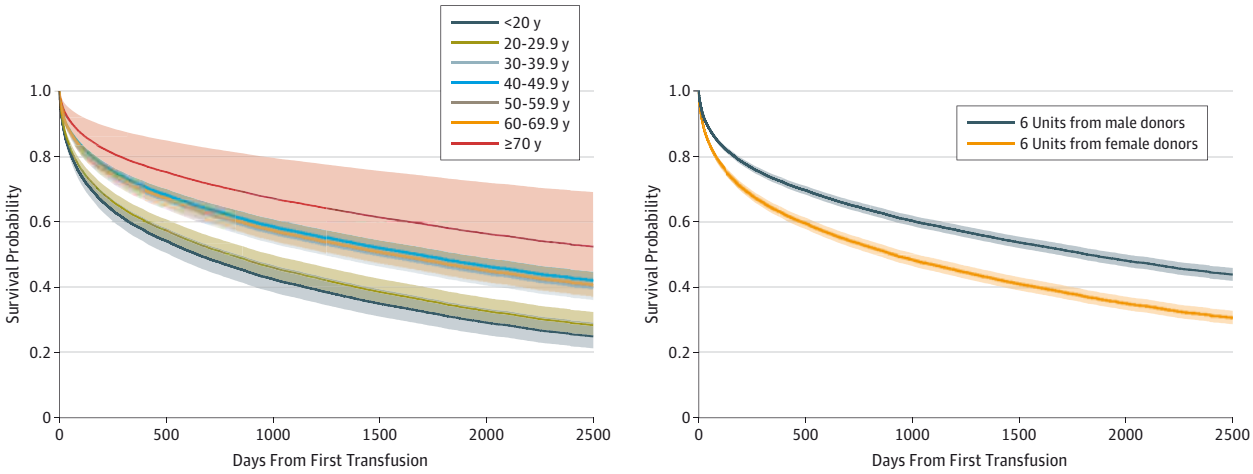
most commonly used additive solutions were saline-adenine-glucose-mannitol (73.6% [n = 138 328]) and AS-3 (25.7% [n = 48 314]). The median storage age of the transfused RBC units was 17 days (IQR, 13-23 days). A significant proportion of recipients (40.5% [n = 12 343]) also received other blood products (eTable 2 in the Supplement).

Primary Analysis

The risk of death was statistically significantly higher for recipients who received RBC transfusions from younger donors. For a recipient receiving an RBC unit from a donor 17 to 19.9 years old, the increased risk of death was 8% compared with a recipient receiving an RBC unit from a donor 40 to 49.9 years old (adjusted hazard ratio [HR], 1.08: 95% CI, 1.06-1.10 for each additional unit transfused; $P < .001$). For a recipient receiving a red blood cell unit from a donor aged 20-29.9 years, the increased risk of death was 6% compared with a recipient receiving an RBC unit from a donor aged 40-49.9 years (adjusted HR, 1.06; 95% CI 1.04 to 1.09; $P < .001$) (**Figure 2**, **Table 3**, and eFigure 1 in the Supplement).

Donor sex was associated with survival after RBC transfusion (Figure 2, Table 3, and eFigure 2 in the Supplement). The transfusion of each additional RBC unit from a female donor was associated with an increased risk of death of 8%

Figure 2. Patient Survival According to Donor Age and Sex Using a Base Case of 6 Total Transfusions (Study Mean) Over the Study Period Between 2006 and 2013



This figure represents the survival of a recipient of 6 units of only one donor characteristic vs the other at baseline at the study mean recipient age and median Charlson Score.

compared with receipt from a male donor (adjusted HR, 1.08; 95% CI, 1.06-1.09 for each additional unit transfused; $P < .001$).

Subgroup Analyses

Subgroup analyses (eTable 3 in the Supplement) suggested that young donor age was associated with reduced survival mainly in male recipients, with the greatest risk in male recipients receiving blood from the youngest donor strata (adjusted HR, 1.14; 95% CI, 1.11-1.17 for each additional unit transfused; $P < .001$). Female sex was associated with reduced survival in both male recipients (adjusted HR, 1.08; 95% CI, 1.07-1.10 for each additional unit transfused; $P < .001$) and female recipients (adjusted HR, 1.03; 95% CI, 1.02-1.05 for each additional unit transfused; $P < .001$).

Few deaths occurred in the youngest recipient age groups (64 deaths among those <1 year and 19 deaths among those 1-18 years). Each additional RBC transfusion from any donor age or sex increased the risk of death except for the older donors (≥60 years) and male donors for recipients between 1 and 18 years old. Subgroup analyses of recipients between 18 and 64 years old or 65 years or older produced results similar to those of our main analysis, and female donor sex and younger donor age were associated with poorer survival.

An association between young donor age and survival was observed among recipients with a Charlson Comorbidity Index less than 3. For donor sex, the observed decreased survival associated with RBC units from female donors was consistent across Charlson Comorbidity Index subgroups.

Discussion

In our large cohort study, we found a statistically significant increase in the risk of death for recipients of RBC transfusions from young donors and female donors. The findings were observed across recipient subgroups of age, sex, and comorbidities. Because more than 100 million RBC units are collected and transfused worldwide every year,[32] an increased risk of death of 8% for each additional transfusion could have a significant mortality effect in absolute terms. For example, the observed 1-year mortality rate of 36.4% in recipients of 6 female donor units transfused (study mean) would decrease to 27.1% (absolute risk reduction, 9.3%; 95% CI, 8.3%-10.4%) compared with recipients of male-only transfusions. This observation translates to a number needed to treat of 11.

The fact that young donor age was associated with survival was unexpected. The results of animal investigations have suggested improved cognitive function and synaptic plasticity in mice that were transfused with young blood.[33] In a different study in mice, Loffredo et al[34] showed that shared blood circulation (parabiosis, not transfusion) between young and old mice may reverse age-related cardiac hypertrophy. However, we are unaware of any human studies that support such an association.[24] Five studies[35-39] involving a total of 586 recipients have assessed the association between RBC donor age and clinical outcomes. None directly assessed the risk of death. Four studies[35,36,38,39] reported no association with the outcomes of TRALI or risk of human immunodeficiency virus and human T-lymphotropic virus transmission. One study[37] evaluated the risk of death, but in patients receiving plasma. A recent matched cohort study[40] from the Scandinavian Donations and Transfusions 2 (SCANDAT2) database reported no association between donor age and survival after RBC transfusion. However, the transfusion exposure was restricted to 7 days after the first transfusion, and the authors excluded patients who received units from donors in more than 1 age category. Therefore, the median number of transfusions was low (1 transfusion), and it is likely that the transfusion

Table 3. Unadjusted and Adjusted Patient Survival According to Donor Age and Sex, per Additional Unit Transfused

	HR (95% CI)	
Variable	Unadjusted	Adjusted[a]
Donor age, y		
17-19.9	1.14 (1.12-1.16)	1.08 (1.06-1.10)
20-29.9	1.06 (1.04-1.08)	1.06 (1.04-1.09)
30-39.9	1.01 (0.99-1.03)	1.01 (0.99-1.03)
40-49.9	1 [Reference]	1 [Reference]
50-59.9	1.00 (0.99-1.02)	1.01 (0.99-1.02)
60-69.9	1.02 (1.00-1.03)	1.01 (0.99-1.03)
≥70.0	0.89 (0.83-0.95)	0.96 (0.89-1.03)
Donor sex		
Male	1 [Reference]	1 [Reference]
Female	1.08 (1.07-1.09)	1.08 (1.06-1.09)

Abbreviation: HR, hazard ratio.

[a] Adjusted for recipient age, recipient sex, and Charlson Comorbidity Index.

recipients received transfusions after the 7-day exposure windows, thus diluting the observed effect. In our study, we did not restrict the exposure period to RBC transfusions, we accounted for patients who received transfusions from donors of different age groups, we have a longer follow-up time, and patients received a larger RBC dose.

One potential explanation for our findings may be related to the healthy donor phenomenon.[41] This phenomenon is related to the fact that one must be in a good state of health to proceed with blood donation. Potential blood donors undergo a screening questionnaire that can lead to donation deferral if the provided responses are deemed inappropriate. Also, patients who are unhealthy are less likely to give blood, thus excluding the sickest patients from donating blood. It has also been shown that long-term blood donors are healthier than short-career donors.[41] Therefore, it is possible that our observation is related to a healthy donor effect, such that young donors may not be aware of an ongoing medical condition that may affect recipients, whereas the development of medical illnesses with age may lead donors to be excluded or to exclude themselves, leaving a more healthy older donor pool.

We found that the transfusion of a cumulative number of female donor units was also associated with worse survival. In normal physiological conditions, male and female RBCs are comparable regarding their oxygen delivery capacity, deformability, and composition.[42,43] However, sex differences exist when erythrocytes are exposed to adrenaline. It has been shown that the enzymatic activity (acetylcholinesterase) decreases, and there is increased RBC membrane rigidity and decreased affinity to oxygen in women but not men exposed to adrenaline.[42] These perturbations at the cellular level may explain the different tissue responses to stress between the sexes.[42] Blood composition is also affected by sex. Female donor plasma has been associated with TRALI. In a recent systematic review,[24] low-risk TRALI donor strategies, which included male plasma donors only, were associated with a reduced odds of TRALI (odds ratio, 0.61; 95% CI, 0.29-0.90). Female sex, history of pregnancy, and presence of human leucocyte antibodies in the donor have been associated with TRALI outcomes. These mechanisms may contribute to the increased risk of death in recipients of female blood but are unlikely to be the only factors because RBC products contain only a minimal amount of plasma. However, this residual amount of plasma may contain other circulating factors that could potentially affect recipient outcomes.

Effect on survival was observed early during follow-up and was maintained over time. Although we do not have a definitive explanation, transfusion of RBC units is associated with numerous immunomodulatory effects.[3,44,45] Those effects could differ depending on the donor characteristics. Immunomodulatory effects may be associated with an increased risk of infections and cancer recurrence over time, hence the lag in mortality. Because of the observational nature of our study, our findings are not evidence that young donor age is causal in the survival pathway of transfusion recipients. However, our results suggest that currently unknown biological or environmental factors affecting young donors may influence the RBC products transfused. The resulting association with mortality may not be due to young age but rather due to factors associated with young age. Once identified, removing donors with these adverse biological or environmental factors could mitigate the association with survival. Current blood screening and distribution procedures do not include considerations of potential associations between donor characteristics, such as age and sex, on posttransfusion survival. Our observation that blood from young donors, on average, may in fact be associated with increased mortality in transfusion recipients does not support the use of young blood for its therapeutic effects and warrants further epidemiological study to elucidate potential mechanisms.

Our study has some limitations. First, its observational design is subject to unmeasured confounding factors. However, because of the current practices in blood collection, distribution, and transfusion, we believe that unmeasured confounders will tend to be evenly distributed between groups. Indeed, the current model for allogeneic blood donation ensures that all donor characteristics are always strictly concealed from prescribing physicians and that blood is distributed in a random manner across and within hospitals. Therefore, our exposures of interest are randomly distributed among recipients. Because of the masking of donor characteristics, our study has similarities with features associated with randomized clinical trials, such as allocation concealment and double-blinding.[46,47] Furthermore, our statistical adjustments for recipient characteristics and comorbidities did not alter our effect estimates (although the selected covariates were strongly associated with outcome), suggesting a random distribution of donor characteristics (eTable 4 in the Supplement). Another limitation of the study is that it was impossible for us to further detail donor factors that may explain our findings. Our initial hypothesis focused on donor age and sex, and we did not design our study to examine other donor characteristics

that may provide further insight into our findings. However, our framework will enable such exploratory analyses in the future. Meanwhile, even without definitive mechanistic explanation, we believe that the strength of our findings, reproducibility across subgroups, and sensitivity analyses suggest that the observed associations are likely not due to chance alone or only to unmeasured confounders and further emphasize the need for more investigation.

Conclusions

Cumulative RBC transfusions from young donors and from female donors were statistically significantly associated with an increased risk of death in a large cohort of transfused recipients. These findings suggest that blood donor characteristics may affect transfusion recipient outcome, and clinical trials are warranted.

ARTICLE INFORMATION

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