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Additive effects of blood donor smoking and gamma irradiation on outcome measures of red blood cell transfusion

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Abstract

BACKGROUND: Recent publications have reported conflicting results regarding the role of blood donor tobacco use on hemoglobin levels in patients following red blood cell (RBC) transfusion. We examined associations and interactions between donor, component, and recipient factors to better understand the impact of donor smoking on transfusion outcomes.

STUDY DESIGN AND METHODS: We linked blood donor and component manufacturing data, including self-reported cigarette smoking, with a cohort of patients transfused RBCs between 2013 and 2016. Using multivariable regression, we examined hemoglobin increments and subsequent transfusion requirements following single-unit RBC transfusion episodes, adjusting for donor, component, and recipient factors.

RESULTS: We linked data on 4,038 transfusion recipients who received one or more single-unit RBC transfusions (n=5,086 units) to donor demographic and component manufacturing characteristics. Among RBC units from smokers (n=326), hemoglobin increments were reduced following transfusion of gamma irradiated units (0.76 g/dL; p=0.033) but not unirradiated units (1.04 g/dL; p=0.54) compared to those from non-smokers (1.01 g/dL; n=4,760). In parallel with

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Study concept and design: All authors.

Acquisition of data: Roubinian, Busch, Plimier

Statistical analysis: Plimier, Lee, Roubinian

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changes in hemoglobin levels, donor smoking was associated with the receipt of additional RBC transfusions for irradiated (OR 2.49; p=0.01) but not unirradiated RBC units (OR 1.10; p=0.52).

CONCLUSION: Donor smoking was associated with reduced hemoglobin increments and the need for additional transfusions in recipients of gamma irradiated RBC units. Additional research is needed to better understand interactions between donor, component, and recipient factors on efficacy measures of RBC transfusion.

INTRODUCTION:

Understanding how blood donor, component manufacturing, and recipient characteristics interface with one another to impact patient outcomes is a topic of high interest in transfusion medicine.[1,2] Red blood cell (RBC) donors represent a heterogenous population for which biologic, genetic, and behavioral variables as well as manufacturing and storage conditions contribute to variation in the hemoglobin dose of packed RBC units and their capacity to withstand cold storage.[3–9]

However, the translation of findings from *in vitro* studies of blood donors and component manufacturing to outcomes in transfused patients has been challenging. Recently, a pilot study identified smaller hemoglobin increments in transfused patients who received RBC units which were cotinine-positive, a metabolite of nicotine correlated with tobacco use.[10] In this study, donor tobacco use, which has been associated with inflammation and increased rates of RBC hemolysis, was hypothesized to play a role in the muted response to transfusion. However, the pilot study was limited in sample size and conflicted with the results of a larger observational study which found that hemoglobin increments after RBC transfusion did not vary by self-reported donor smoking status.[11]

Neither of these two studies examined donor smoking in a multivariable analysis or assessed interactions between donor and component factors. Given known differences in storage hemolysis with donor sex and age, adjustment for donor demographic characteristics of smokers may be relevant.[3] In addition, all cotinine-positive RBC units were gamma irradiated in the pilot study, a factor known to increase susceptibility to *in vitro* hemolysis and recently shown to negatively impact hemoglobin increments in transfusion recipients.[11–13] Furthermore, combinations of factors individually associated with hemolysis, such as gamma irradiation or donor sex, may have additive effects when occurring concurrently.[8] In this study, we sought to examine associations and interactions between blood donor and component manufacturing characteristics, including donor smoking status, on hemoglobin increments and subsequent transfusion requirements following single-unit RBC transfusion episodes.

MATERIALS AND METHODS:

Study Design and Setting

We conducted a retrospective cohort study using electronic health record (EHR) donor data from Vitalant Incorporated linked to RBC transfusion recipients from Kaiser Permanente Northern California (KPNC) which uses a common EHR (Epic, Verona, WI) for both

inpatient and outpatient care. The KPNC and University of California, San Francisco Institutional Review Boards approved this study.

Blood donor and component characteristics

Information on blood donors, donations, and processing was obtained from databases of Vitalant Incorporated which supplies blood components to 9 KPNC medical centers. All blood products were leukocyte-depleted by pre-storage filtration, and all donors were at least 16 years old. Data collected included donor demographics (e.g., age, sex, ABO/Rh status), RBC collection date and method (whole blood or apheresis) as well as blood component characteristics (gamma irradiation status and additive solution) for each unit collected. Date and time of gamma irradiation, which occurred at the blood center prior to shipment to the receiving hospital, was included. Between 1/2013 and 12/2016, all donors at one collection center (Blood Centers of the Pacific) were surveyed regarding cigarette smoking at the time of blood donation using the following question: “During the past 30 days (including today), have you smoked part or all of a cigarette?”. Donors who answered affirmatively were also asked to self-report their average daily cigarette usage in the past 30 days, on a scale from 0 to 7 as follows: 0: Zero per day; 1: More than zero, but less than one cigarette per day; 2: 1 cigarette per day; 3: 2 to 5 cigarettes per day; 4: 6 to 15 cigarettes per day (about ½ pack); 5: 16 to 25 cigarettes per day (about 1 pack); 6: 26 to 35 cigarettes per day (about 1 ½ packs); 7: More than 35 cigarettes per day (about 2 packs or more).

Recipient cohort and characteristics

We included adult KPNC patients who received a single RBC unit during one or more transfusion episodes at 9 medical centers between January 1, 2013 and December 31, 2016. Recipient details included age, sex, body mass index (BMI), and tobacco use as well as the storage duration, transfusion date and time, and product identification numbers of transfused RBCs. Transfusion location was designated by inpatient or outpatient status. Hemoglobin levels were measured by the clinical laboratory prior to and following each RBC transfusion event. To assess the role of indication bias related to the transfusion of gamma irradiated RBC units, we grouped primary oncology diagnoses (e.g. leukemia, lymphoma, solid tumor, or receipt of chemotherapy) using International Classification of Diseases 9th and 10th Revision (ICD-9 & 10) diagnosis codes using Health Care Utilization Project (HCUP) Clinical Classifications Software categories.

Outcomes

The primary outcome was the hemoglobin increment following transfusion of a single RBC unit. Hemoglobin increments were calculated using the difference in hemoglobin levels prior to and following each transfusion episode. Transfusion episodes were excluded from analyses if the patient received multiple RBC transfusions during an episode or if there were no pre- or post-transfusion hemoglobin levels during the specified time periods. Pre-transfusion hemoglobin level was defined as the proximate hemoglobin level within 18 hours prior to RBC transfusion. To avoid bias related to ongoing bleeding, we limited our analyses to transfusion events without subsequent RBC transfusions in the following 24 hours, assessing hemoglobin levels occurring closest to 24 hours following transfusion, within a 12 to 36-hour window. As a secondary outcome and complementary

efficacy measure to hemoglobin increments, we examined the incidence of subsequent RBC transfusions occurring within 7 days of the index transfusion event.

Statistical Analysis

We linked donor, component, and transfusion recipient characteristics using product identification numbers for donations which included donor smoking data and then assessed donor, component, and recipient variables according to donor smoking status. Hemoglobin increments were examined by donor smoking status and stratified by donor sex, gamma irradiation status, and oncologic diagnosis. Donor, component, and recipient variables were then included in multivariable linear regression models to examine associations with hemoglobin increments following RBC transfusion. Intervals from the time of laboratory testing (pre- and post- transfusion hemoglobin levels) in relation to transfusion time as well as the year of transfusion were included in regression models. We also stratified by and examined interactions between individual variables to detect the presence of effect modification, including pre-specified interaction testing between donor smoking status with donor sex, unit gamma irradiation, and recipient oncologic diagnosis – all of which have been associated with differences in hemoglobin increments.[11,14] Time from collection to gamma irradiation and from gamma irradiation to transfusion in days were included as covariates in analyses of gamma irradiated RBC units. For the secondary outcome, multivariable logistic regression models were fit to evaluate the incidence of additional RBC transfusions occurring within 7 days of the index event, adjusting for the same donor, component, and recipient characteristics.

Data are presented as counts and percentages, means with standard deviations (SD) or medians with interquartile ranges (IQRs). Accordingly, X^2 tests for equal proportion, t tests, or Wilcoxon rank sum tests were used to test differences. Linear regression results were reported as coefficients with 95% confidence intervals (CI) representing the mean hemoglobin increment following RBC transfusion for that variable. Logistic regression results were reported as odds ratios (OR) with 95% CI representing the incidence of subsequent RBC transfusion within 7 days of the index transfusion event. Two-sided p-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using Stata Version 14.1, StataCorp, College Station, TX and SAS version 9.4, SAS Institute, Cary, NC.

RESULTS:

We identified 4,038 patients who received 5,086 single-unit RBC transfusions for which donor smoking status and relevant donor, component, and recipient data were available (Table 1). RBC units from blood donors who reported active smoking (n=326) were more often from younger males than units from donors who did not smoke (n=4,760). Apheresis blood collections were more common in donations from smokers, while storage durations and proportions of gamma irradiated RBC units did not differ between donations from smokers and non-smokers. Amongst transfusion recipients, sex, age, BMI, oncologic diagnosis, self-reported smoking status, and pre-transfusion hemoglobin levels were similar between those who received donor smoker and non-smoker RBC units. Timing of pre- and

post-transfusion hemoglobin measurements also did not differ between recipients of smoker and non-smoker RBC units. Donor smokers quantified their average daily cigarette use in 228 (70%) of the 326 donations: 59 (25.9%) donors smoked less than one cigarette daily on average; 26 (11.4%) smoked one cigarette daily; 70 (30.7%) smoked 2-5 cigarettes daily; 58 (25.4%) smoked 6-15 cigarettes daily; and 15 (6.6%) smoked more than 15 cigarettes daily.

Hemoglobin increments were similar between recipients of smoker and non-smoker RBC units in univariate analyses (Table 1). Table 2 examines differences in unadjusted hemoglobin increments for combinations of donor smoking status with gamma irradiation or donor sex. Hemoglobin increments were reduced in recipients of gamma-irradiated RBC units from donor smokers compared to unirradiated RBC units from donor smokers [0.74 g/dL (SD 0.80) vs. 1.05 g/dL (SD 0.98); p=0.045]. In parallel, hemoglobin increments were reduced in recipients of gamma-irradiated RBC units from donor non-smokers compared to unirradiated RBC units from donor non-smokers [0.94 g/dL (SD 0.83) vs. 1.03 g/dL (SD 0.92); p=0.02]. There were no differences in hemoglobin increments between unirradiated RBC units from donor smokers and those from non-smokers [1.05 g/dL (SD 0.98) vs. 1.03 g/dL (SD 0.92); p=0.80]. Smaller hemoglobin increments for transfusion of gamma-irradiated RBC units from donor smokers [0.74 g/dL (SD 0.80); n=54] compared to irradiated units from non-smokers [0.94 g/dL (SD 0.83); n=903] were not statistically significant (p=0.074). Comparing RBC units from donor smokers and non-smokers, there were no differences in hemoglobin increments in subgroups of male (p=0.23) or female donors (p=0.14). In the subset of gamma irradiated RBCs, comparisons of donor, component, and recipient factors from smoking and non-smoking donors did not explain reduced hemoglobin increments seen after transfusion of units from smoking donors (Appendix Table 1). To assess for indication bias related to transfusion of gamma irradiated units to oncology patients, we examined hemoglobin increments in the subset of recipients without oncologic diagnoses (n=4,349). In non-oncologic patients, hemoglobin increments were reduced following transfusion of gamma-irradiated RBC units from donor smokers [0.71 g/dL (SD 0.93); n=35] compared to those of non-smokers [0.99 g/dL (SD 0.89); n=536]; while the effect size was similar to that in the full cohort, the difference in this subset of recipients was not statistically significant (p=0.078).

Table 3 shows regression estimates from the multivariate model for the hemoglobin increments, estimating the mean hemoglobin increment after transfusion for each level change (for categorical variables) or unit increase (for continuous variables) of each predictor. In agreement with prior analyses, female donor sex, gamma irradiation, male recipient sex, younger recipient age, higher recipient body mass index, and higher pre-transfusion hemoglobin levels were significant predictors of reduced post-transfusion hemoglobin increments as was oncology diagnosis.[11] Donor and recipient smoking status were not significantly associated with hemoglobin increments. There were no interactions between donor smoking status and donor sex (p=0.34), gamma irradiation (p=0.27), or recipient oncologic status (p=0.28). Donor smoking status was not associated with differences in hemoglobin increments when stratified by donor sex (p=0.47) or by principal oncology diagnosis (p=0.28). Relative to hemoglobin increments in RBC units from non-smokers [1.01 g/dL (95% CI 0.99, 1.04); n=4,760], increments were reduced in RBC units from smokers which were gamma irradiated [0.76 g/dL (95% CI 0.53, 0.99); p=0.033; n=54]

but not from un-irradiated RBC units [1.04 g/dL (95% CI 0.95, 1.14); p=0.54; n=272]. Again, the effect size was similar though not statistically significant when examining only non-oncologic recipients of gamma irradiated RBC units from smokers [−0.24 g/dL (95% CI −0.56, 0.10); p=0.09; n=35]. Among gamma irradiated RBC units, increasing smoking intensity was associated with smaller hemoglobin increments (−0.15 g/dL for each level change of cigarette usage; p=0.02).

Comparing gamma irradiated RBC units from smokers and non-smokers, there were no differences between the median time from collection to irradiation [15 days (IQR 9-22) vs. 15 days (IQR 9-23); p=0.72], irradiation to transfusion [5 days (IQR 1-13) vs. 4 days (IQR 1-10); p=0.33] or overall storage duration [22.5 days (IQR 17-30.5) vs. 24 days (IQR 16-31); p=0.72], respectively. In multivariable analyses, there was no association between hemoglobin increments and the time from collection to gamma irradiation (−0.01 g/dL; p=0.18) or gamma irradiation to transfusion (−0.03 g/dL; p=0.65). Reduced hemoglobin increments in recipients of gamma irradiated RBC units from non-smokers did not vary by overall storage duration (−0.02 g/dL; p=0.49). However, storage duration greater than 28 days was associated with smaller hemoglobin increments (−0.54 g/dL; p=0.03) in recipients of gamma irradiated RBC units from smokers. Unadjusted comparisons of these transfusion events (gamma irradiated RBC units from smokers) also showed smaller hemoglobin increments for storage durations greater than 28 days compared to those with storage durations less than 28 days (0.6 g/dL; n=16 vs. 0.9 g/dL; n=38; p=0.03).

In univariate analysis, the rate of subsequent RBC transfusion within 7 days of the index transfusion event was similar between recipients of smoker and non-smoker RBC units (30.9% vs. 29.7%; p=0.69). In multivariable analysis, donor smoking status was not associated with the receipt of RBC transfusions within 7 days of the index episode [OR 1.17 (95% CI 0.90, 1.54); p=0.24], while female donor sex [OR 1.16 (95% CI 1.04, 1.30); p<0.01], donor age by year [OR 1.00 (95% CI 1.00, 1.01); p=0.04], gamma irradiation [OR 1.28 (95% CI 1.10, 1.48); p<0.01], and transfusion of Rh negative units [OR 1.24 (95% CI 1.03, 1.40) p=0.02] were significant.

Relative to RBC-units from non-smokers, donor smoking was associated with an increase in the receipt of additional RBC transfusions in the subset of irradiated [OR 2.49 (95% CI 1.22, 5.01); p=0.01] but not unirradiated RBC units [OR 1.10 (95% CI 0.82, 1.47), p=0.52]. The unadjusted mean and median number of additional RBC units transfused within 7 days was 1.28 (SD 16.3) and 1 (IQR 0-1.5) in recipients of gamma irradiated units from donor smokers and 0.44 (SD 0.82) and 0 (IQR 0-1) in recipients of unirradiated units from donor smokers, respectively. In a sensitivity analysis examining only irradiated RBC units (n=957), donor smoking status remained associated with subsequent transfusions [OR 2.15 (95% CI 1.03, 4.53), p=0.043]. In parallel to differences in hemoglobin increments, increased risk of subsequent transfusion occurred in irradiated RBC units with storage durations greater than 28 days [OR 8.7 relative to storage age ≤ 28 days (95% CI 0.87, 87.44); p=0.066]. Among gamma irradiated RBC units, increasing smoking intensity was associated with increased likelihood of subsequent transfusions [OR 2.05 (95% CI 1.33, 3.20); p=0.001].

DISCUSSION:

Using a multivariable regression approach, our current retrospective analysis is consistent with the findings of a pilot study showing reduced hemoglobin increments following transfusion of gamma irradiated RBC units donated by smokers. Smaller hemoglobin increments were only observed with transfusion of smoker RBC units when they were gamma irradiated, and this reduction was greater than the effect identified with gamma irradiation alone. Complementing this finding, recipients of gamma irradiated units donated by smokers were more likely to receive subsequent RBC transfusions compared to RBC units from non-smokers. Thus, RBCs donated by smokers may be more susceptible to irradiation-induced damage compared to nonsmokers.

It is recognized that cigarette smoking and gamma irradiation may negatively impact RBC structure and physiology. Cigarette smoking has been associated with significant changes in markers of inflammation, osmotic fragility, oxidative stress, programmed cell death, and hemolysis.[15–20] In addition, RBCs donated by chronic smokers have higher carboxyhemoglobin (COHb) content and greater levels of cadmium and lead compared to nonsmokers.[21,22] Despite these concerns, there are no available data showing donor tobacco use impacts transfusion recipient outcomes, and donor smoking habits are not routinely assessed before blood donation.

In parallel, gamma irradiation has been associated with irreversible changes to RBC morphology, oxidative injury, and increased *in vitro* hemolysis.[23,24] Disruption of the RBC membrane is thought to cause hemolysis with studies showing increased potassium and free hemoglobin in the supernatant of blood units and decreased recovery after transfusion.[12,13,25,26] While gamma irradiation of RBCs is indicated for patients with malignancy or transplants to prevent transfusion-associated graft-versus-host disease, receipt of these blood components has been associated with smaller hemoglobin increments, even when accounting for these patient comorbidities.[11] Timing of gamma irradiation and overall storage duration have been shown to impact rates of hemolysis and other measures of RBC quality.[8,27] In our study, reduced hemoglobin increments related to gamma irradiation did not vary by storage duration except for RBC units from smokers.

Our findings suggest complexity to donor, component, and recipient interactions on transfusion outcomes. We hypothesize that donor and component factors may have “multi-hit” effects on RBC quality; in this case, the first “hit” being blood donor smoking and the second “hit” being gamma irradiation. Furthermore, cigarette smoking may have additive detrimental consequences on RBC quality as a dose effect on hemoglobin increments was observed in RBC units from donors with increasing smoking intensity. Compounded sequelae of oxidative stress and hemolysis associated with prolonged storage may represent the mechanism of action for these observations. Prior studies have shown that manufacturing method and storage solution influence rates of hemolysis of irradiated RBCs.[9,28] The cumulative impact of donor and component exposures on RBC quality align with the concept that the “metabolic age” of RBCs may vary significantly from changes expected with chronological storage.[29] Other donor behaviors and habits may also contribute to a RBC component’s biologic age, potentially impacting its metabolism and storability.

Several limitations should be emphasized. Although our sample size of 326 RBC units donated by smokers is larger than the previous pilot study, it is still relatively small. As in prior studies, the prevalence of cigarette smoking among blood donors in the United States appears to reflect regional population rates.[10,19] While self-reported smoking may underestimate its true prevalence, rates of smoking in donors (6.4%) paralleled those of transfused recipients in our study. However, this rate was lower than in prior studies, increasing the possibility of a chance result (Type I error) related to the study of infrequent events (the combination of donor smoking and gamma irradiation) on transfusion outcomes.[30] The small number of gamma irradiated RBC units from smokers (~1% of studied RBC transfusion events) may thus be prone to unmeasured confounding biasing our outcomes. While we did attempt to account for indication bias related to gamma irradiation by examining interactions with oncologic diagnoses, validation of our results in centers where irradiation is more common or utilized universally would provide a larger sample size and strengthen our conclusions. In addition, reduced hemoglobin increments for gamma irradiated units from donor smokers were associated with a small increase in the need for additional RBC units; however, this finding was limited to downstream analysis of single-RBC unit transfusion events. Potential effects may be greater when accounting for repeated transfusion exposures or settings where donor smoking (or other nicotine exposure) is more prevalent or gamma irradiation is universal.

Our findings not only require validation in other cohorts but also additional correlative studies to explore a mechanistic explanation. Corroboration and further elaboration could be accomplished through a prospective cohort or the analysis of the Recipient Epidemiology and Donor Evaluation-III (REDS-III) vein-to-vein database.[31] Work in progress to link this donor-component-recipient database, which includes information on donor smoking, to *in vitro* donor osmotic and oxidative hemolysis measures and metabolomic profiles, may advance our understanding of how donor smoking influences RBC quality. Future studies could directly measure rates of *in vitro* hemolysis and hemoglobin levels in gamma irradiated units from smokers. Additional “hits” on RBC quality may include other social behaviors or component modifications. In addition, donor genetic polymorphisms, such as glucose-6-phosphate dehydrogenase deficiency, may have potential deleterious effects in conjunction with donor smoking, gamma irradiation, or other factors. Lastly, in isolation X-ray irradiation has shown similar effects on RBC component quality as gamma irradiation,[13,32] but the combined effects of X-ray irradiation with other donor, recipient, and component factors have not been examined.

Our study suggests that qualitative assessment of donor smoking through a questionnaire could be useful in conjunction with cotinine testing in planning future work and evaluating blood donors. A prior study showed that 12-hour abstinence from smoking before blood donation and smoking less than 20 cigarettes per day were associated with lower levels of cotinine and COHb in donated units.[22] Future studies could address for critical thresholds of the number of cigarettes smoked per day, timing of smoking prior to donation, or serum cotinine levels associated with a detrimental effect on RBC quality and transfusion outcomes.

We examined hemoglobin increments and the need for additional RBC transfusions as direct and indirect efficacy measures of transfusion, respectively. Two studies to date have not identified adverse recipient outcomes related to donor tobacco use in adult patients.[10,30] Mechanistic studies examining measures of hemolysis (e.g. cell-free plasma hemoglobin, haptoglobin, indirect bilirubin) either in irradiated RBC units from smokers or in transfused recipients need to be correlated with findings of reduced hemoglobin increments.[33] Prospective studies could associate rates of post-transfusion hemolysis with measures of tissue oxygenation, utilizing technologies such as near-infrared spectroscopy or other transfusion efficacy outcomes in pediatric in addition to adult populations.[34]

Beyond RBC transfusion, the effects of donor smoking on platelets and recipient outcomes, such as bleeding, thrombosis, and corrected count increments, also warrant investigation, as smoking has been associated with increased platelet adhesiveness, aggregation, and platelet-dependent thrombin generation.[35,36] In addition, adverse effects of e-cigarette use, or “vaping”, are increasingly recognized and poorly understood, and their impact on RBC component quality and recipient transfusion outcomes are unexplored.[37] Lastly, use of other forms of nicotine administration (patches, gum) merit qualitative and quantitative assessment in blood donors in the development of future vein-to-vein databases and as part of mechanistic studies.

In conclusion, we describe an association of combined blood donor smoking and RBC component gamma irradiation on reduced hemoglobin increments and increased likelihood of subsequent RBC transfusion events in multivariable regression analyses. These findings suggest complex interactions between donor, component, and recipient factors on RBC quality. Further investigations may impact the donor health questionnaire and blood component modifications in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Donor, component, and recipient characteristics by donor smoking status

N (episodes)	Smoking Donor (n=326)	Non-smoking Donor (n=4,760)	
Blood Donor Characteristics			
Sex (% male)	70.0	63.2	0.01
Age in years (median, (IQR))	34 (25-53)	47 (28-60)	<0.001
(+) Rh status (%)	81.7	82.2	0.50
ABO status (%)			0.09
A	41.9	35.9	
B	1.2	2.1	
AB	11.4	14.4	
O	45.5	47.6	
Hemoglobin level (mean, (SD))	14.7 (1.27)	14.5 (1.23)	0.09
Blood Component Characteristics			
Apheresis-derived (%)	36.5	30.6	0.03
Gamma irradiated (%)	16.6	19.0	0.28
RBC storage duration in days (median, (IQR))	26 (18-32)	24 (18-31)	0.08
Storage solution (%)			0.09
AS-1	24.5	19.0	
AS-3	73.9	78.3	
CPDA	1.6	2.8	
Transfusion Recipient Characteristics			
Sex (% male)	48.3	49.5	0.85
Age (median, (IQR))	70 (60-82)	71 (61-81)	0.94
Body mass index (median, (IQR))	26.0 (22.4-30.5)	26.0 (22.8-30.6)	0.22
(+) Rh status (%)	91.7	88.7	0.02
ABO status (%)			0.39
A	40.4	36.0	
B	5.3	4.3	
AB	14.5	16.9	
O	39.8	42.7	
Current tobacco smoker (%)	7.4	5.8	0.24
Outpatient transfusion (%)	26.2	26.8	0.81
Oncology diagnosis (%)	12.0	14.7	0.18
Pre-transfusion Hb in g/dL (mean, (SD))	7.67 (0.80)	7.62 (0.75)	0.47
Post-transfusion Hb in g/dL (mean, (SD))	8.70 (1.12)	8.66 (1.03)	0.27
Hemoglobin increment in g/dL (mean, SD))	1.03 (0.93)	1.04 (0.88)	0.72
Time in hours between pre-transfusion Hb and transfusion (median, (IQR))	5.1 (2.9-8.2)	5.3 (2.9-8.4)	0.60
Time in hours between transfusion and post-transfusion Hb (median, (IQR))	19.9 (16.6-25.1)	19.5 (16.1-24.9)	0.24

IQR=interquartile range; SD=standard deviation

Table 2:

Hemoglobin increments after RBC transfusion by smoking status for gamma irradiation and donor sex

	Unirradiated RBC* **(n=4,129)**	**Irradiated RBC*** **(n=957)**	**Female Donor†** **(n=1,852)**	**Male Donor†** **(n=3,234)**
Non-smoker RBC units (n=4,760)	n=3,857	n=903	n=1,755	n=3,005
Pre-TX hemoglobin level (SD)	7.71 (0.82)	7.49 (0.73)	7.67 (0.81)	7.68 (0.81)
Post-TX hemoglobin level (SD)	8.74 (1.06)	8.43 (1.01)	8.64 (1.06)	8.72 (1.06)
Hemoglobin Increment (SD)	**1.03 (0.92)**	**0.94 (0.83)**	**0.97 (0.92)**	**1.05 (0.90)**
Smoker RBC units (n=326)	n=272	n=54	n=97	n=229
Pre-TX hemoglobin level (SD)	7.78 (0.90)	7.57 (0.72)	7.72 (0.93)	7.76 (0.86)
Post-TX hemoglobin level (SD)	8.83 (1.17)	8.30 (1.07)	8.83 (1.19)	8.74 (1.17)
Hemoglobin Increment (SD)	**1.05 (0.98)**	**0.74 (0.80)**	**1.11 (0.96)**	**0.98 (0.95)**

RBC=red blood cell; TX=transfusion

*P-values for t-test comparing hemoglobin increments for transfusion of gamma-irradiated RBC units from donor smokers to those for unirradiated RBC units from smokers (p=0.045), gamma-irradiated RBC units from donor non-smokers to those for unirradiated RBC units from non-smokers (p=0.02), unirradiated RBC units from donor smokers and non-smokers (p=0.80), and irradiated RBC units from donor smokers and non-smokers (p=.074).

†Hemoglobin increments did not differ between donor smokers and non-smokers when examining subgroups of RBC units donated by male and female donors (p=0.23 and 0.14, respectively).

Table 3:

Regression estimates for hemoglobin increments following single-unit RBC transfusion (n=5,086)*

Characteristic	Hemoglobin increment in g/dL (95% CI)	p-value
Male donor	0.09 (0.03, 0.14)	<.001
Donor age (ref: <20 years)		
20-45	0.001 (−0.08, 0.08)	0.93
45-70	0.002 (−0.08, 0.07)	0.92
>70+	−0.04 (−0.15, 0.08)	0.52
Donor Rh positive status	−0.04 (−0.14, 0.06)	0.48
Donor ABO status (ref: non-O)		
Blood type O	−0.01 (−0.07, 0.04)	0.65
Donor hemoglobin	0.00 (−0.04, 0.03)	0.91
Donor smoking	−0.02 (−0.12, 0.08)	0.72
Whole blood collection	0.08 (−0.01, 0.16)	0.07
RBC additive solution (ref: AS-1)		
AS-3	−0.04 (−0.13, 0.06)	0.47
Gamma irradiation	−0.10 (−0.18, −0.03)	<0.01
Storage duration (ref: 1-21 days)		
22-28	0.01 (−0.05, 0.07)	0.69
29-35	0.02 (−0.05, 0.08)	0.65
36-42	0.01 (−0.07, 0.08)	0.89
Female recipient	0.23 (0.18, 0.28)	<0.001
Recipient age†	0.04 (0.02, 0.06)	<0.001
Recipient body mass index	−0.02 (−0.02, −0.01)	<0.001
Recipient Rh positive status	0.03 (−0.08, 0.15)	0.59
Recipient ABO status (ref: non-O)		
Blood type O	0.01 (−0.06, 0.08)	0.87
Recipient smoking	0.02 (−0.09, 0.12)	0.72
Oncology diagnosis	−0.09 (−0.17, −0.02)	0.02
Pre-transfusion Hb level	−0.26 (−0.29, −0.22)	<.001
Hours between pre-Tx measurement and Tx	0.01 (0.01, 0.01)	<.001
Hours between Tx and post-Tx measurement	0.01 (0.01, 0.01)	<.001
Transfusion year	−0.05 (−0.08, −0.03)	<.001

RBC=red blood cell; Hb=hemoglobin level (g/dL); Tx=transfusion

*Pre-transfusion hemoglobin level within 18-hours of transfusion and hemoglobin increment for 24-hour window after transfusion

†Coefficient for recipient age correspond to change in mean outcome associated with 10-year increase.