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RESEARCH ARTICLE

The association of donor and recipient sex on sepsis rates and hemoglobin increment among critically ill patients receiving red cell transfusions in a retrospective study

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Abstract

Background: Existing research presents conflicting results on the influence of blood donor sex on hemoglobin (Hb) change and transfusion-associated infection and mortality in transfusion recipients.

Aim: This retrospective study explored the association between donor and recipient sex on hospital-onset sepsis (HO-sepsis) and Hb changes in critically ill patients receiving red blood cell (RBC) transfusions.

Methods: Data from 2010–2020 were extracted from an academic hospital's clinical database and a blood supplier's donor database. HO-sepsis was determined based on the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic codes without requiring a microbiology test within the first 48 h of admission. Hb increments were determined by comparing the last Hb result in the 24-h period prior to RBC unit issue and the first Hb result within 4–24 h after RBC unit issued for transfusion.

Results: 25,585 critically ill patients received one or more RBC transfusions; 3,410 were included in the HO-sepsis and 3,487 in the Hb increment analysis. There was no significant differences in the HO-sepsis rate among the four groups, but female recipients were more prone to HO-sepsis than males (OR 1.48, $p = 0.04$). Multivariate analysis found that the number of RBC unit transfused ($p = 0.001$) and recipient age ($p = 0.03$), but not recipient sex ($p = 0.63$), were significant contributors to HO-sepsis. Male blood was associated with higher Hb than female blood in female recipients ($p = 0.007$), but not in male recipients ($p = 0.75$). Variables such as donor Hb levels and recipient Hb level influenced Hb increments.

Conclusion: Blood donor sex was not associated with HO-sepsis in critically ill patients receiving RBC transfusion. Male to female transfusions were associated with a higher

Abbreviations: CBS, Canadian Blood Services; DAD, Discharge Abstract Database; Hb, hemoglobin; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; ICU, intensive care unit; IQR, interquartile ranges; LIS, Laboratory Information System; MRD, minimal residual disease; OR, odds ratio; RBCs, red blood cells; REB, research ethics board; SD, standard deviation; TRUST, Transfusion Research Utilization, Surveillance and Tracking; WB, whole blood.

Hb increment in recipients. Further exploration of the impact of sex mis-matched transfusion on recipient outcomes is warranted.

KEYWORDS
blood transfusion, hemoglobin increment, intensive care unit, sepsis

1 | INTRODUCTION

Among critically ill patients, red blood cell (RBC) transfusions are a common intervention for anemia [1], with approximately 30% undergoing this treatment to augment oxygen delivery to tissues [2]. While RBC transfusions can be lifesaving, they introduce potential risks, including heightened chances of infections [3–5] and, in some cases, increased mortality [5–7]. A growing body of evidence suggests that donor characteristics may affect hemoglobin (Hb) changes and mortality in recipients of red cell transfusion [6–11]. One observational study identified blood donor sex as a factor contributing to mortality in critically ill patients [12]. However, a randomized clinical trial reported that donor sex was not associated with mortality in all hospitalized patients [13]. Sepsis, a life-threatening condition, has been reported to significantly contribute to mortality in critically ill patients receiving RBC transfusion [12]. Previous studies may not have identified associations due to a broad examination of mortality. Our study focused on a specific patient group (excluding those with community-acquired sepsis) and targeted a detailed clinical outcome—hospital-onset sepsis (HO-sepsis).

In the specialized setting of intensive care units (ICU), critically ill patients often experience an Hb increment which falls short of the expected 10 g/L following an RBC transfusion [14]. Such suboptimal Hb recovery is concerning, especially given its reported association with heightened infection rates among transfused hospitalized patients [15]. Adding another layer of complexity, conflicting studies have reported that compared to male blood donors, blood from female donors can result in a smaller Hb increase in male recipients [16], yet donor sex did not affect Hb increment in patients in another study [17]. As male recipients have a larger body mass index compared to female recipients [16], this study explored the hypothesis that blood from female donors is associated with a lower Hb increment and higher HO-sepsis rate in critically ill male patients receiving RBC transfusions.

The advent of comprehensive databases like the Transfusion Research Utilization, Surveillance and Tracking (TRUST) database has facilitated exploratory research for hypothesis generation and hypothesis testing [18]. To understand the association of donor sex on transfusion outcomes, a retrospective study of adult patients admitted to the ICU was performed to explore changes in Hb and HO-sepsis after receiving RBC transfusions from exclusively male or female blood donors.

2 | METHOD AND MATERIALS

2.1 | Study design

This retrospective cohort study was conducted using electronic health records from TRUST and blood donor records from Canadian Blood Services (CBS). The Hamilton Integrated Research Ethics Board (HIREB-#14539-C), Canadian Blood Services Research Ethics Board (CBSREB #2022.015) and University of Alberta Institutional Review Board (Pro00119217) approved a waiver of consent for this study.

2.2 | Recipient population

All adults aged 18 years or older (at the time of hospital admission) admitted to the ICU at acute care hospitals within Hamilton Health Sciences (HHS; Hamilton, Canada) who received their first single allogeneic RBC transfusion in the ICU between January 1, 2010 and December 31, 2020 were included. Patients were excluded if they received: autologous or directed donations; RBCs from a donor of unknown sex or sex recorded other than male or female (ex. intersex); or RBCs from a blood supplier other than CBS. For the analysis focused on HO-sepsis, specific exclusion criteria were employed: patients with pre-existing sepsis prior to and within 48 h of admission (community-onset sepsis, determined using sepsis International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (Table S1) in conjunction with a documented microbiology test—commonly used to identify an infection-causing organism; patients who received RBCs from both female and male donors; and patients whose donor information was missing. For Hb increment analysis, patients were excluded if they received more than one unit of RBC in the first transfusion episodes or if they fell under the following categories: hema-oncology (purpura, with the exception of allergic purpura, and other hemorrhagic conditions; ICD-10 codes D691-D699); trauma (ICD-10 codes S00-T98); or hemolytic anemia (ICD-10 codes D55-D59). We also excluded any patients who did not have complete information about their blood donor information or their Hb levels. Patients' information was collected from TRUST, a comprehensive source of demographic, clinical transfusion, and laboratory test information on all transfusion patients within HHS. These data are updated monthly and sourced from the hospitals' Laboratory Information System (LIS) and Discharge Abstract Database (DAD). To ensure

data reliability, validation studies have been conducted to confirm the accuracy of the information, data encryption, and merging process [19–21].

2.3 | Donor information

Donor information was retrieved from the ePROGESA database (MAK System International Group, Paris, France), using the unique CBS RBC unit number and date of collection to link transfused product to donor. CBS supplies blood components to all Canadian provinces except Québec. All blood products were leukoreduced-depleted by pre-storage filtration and all donors were at least 17 years old at time of donation. Donor data collected on each transfused RBC included: demographic characteristics (sex, age, pre-donation hemoglobin), and blood component characteristics (ABO/Rh).

2.4 | Outcomes

The primary outcome focused on the rate of sepsis in hospital settings (non-community) among four distinct groups (female recipients who only received RBC units from female blood donors, male recipient who only received RBC units from male blood donors, female recipients who only received RBC units from male blood donors, and male recipients who only received RBC units from female blood donors). An interaction analysis was conducted to assess whether donor sex and recipient factors interacted with each other. The identification of a sepsis diagnosis was based on the ICD-10 codes (Table S1), which include validated codes for sepsis [22]. To better elucidate the relationship between the transfusion of RBCs and sepsis, we excluded cases of sepsis that had their onset in the community. Non-community onset sepsis, in contrast, is HO-sepsis. The secondary outcome was Hb increment of the first single unit transfusion determined by calculating the difference between Hb pre-transfusion (latest Hb result in the 24-h period before issue of RBC unit) and Hb post-transfusion (earliest Hb result within 4–24 h following issue of RBC unit without any other RBC unit(s) issued between first RBC unit and time of Hb test).

2.5 | Statistical analysis

Statistical analyses were performed using statistical software SAS (Version 9.4, USA). Continuous data were reported as means with standard deviations (SD) and/or medians with interquartile ranges (IQR). Categorical data were reported as proportions. Differences between study groups were assessed by a Chi-squared test or analysis of variance (ANOVA). Further regression modeling was conducted for HO-sepsis with a four-level exposure variable (female to female, male to male, male to female, and female to male) and adjusted for additional covariates, including recipient demographics (age, most responsible diagnosis, ABO group, pre-transfusion Hb), time interval between post-transfusion Hb and transfusion, and donor characteristics (donor age, pre-donation Hb). Variables that were significantly different among the four groups were further included in logistic regression analysis. When interpreting odds ratio (OR) = 1 indicates exposure does not affect odds of HO-sepsis, OR > 1 exposure indicates exposure is associated with higher odds of HO-sepsis, and OR < 1 exposure indicates exposure is associated with lower odds of HO-sepsis. A p-value < 0.05 was considered statistically significant difference.

3 | RESULTS

3.1 | Study population for hospital-onset-sepsis and Hb increment analysis

This research study encompassed a comprehensive review of 90,165 adult ICU patients from three HHS hospitals (Figure 1): 25,585 patients received RBC transfusions. The 10,307 patients that received their first RBC transfusion in the ICU were included in the HO-sepsis analysis. Various exclusion criteria were enforced, such as patients receiving autologous (n = 3) or non-CBS RBC transfusions (n = 7), patients who developed community-onset sepsis (n = 3,154, 30.5%), patients with missing donor information (n = 65), patients who received RBC transfusions from both sexes (mixed donor cases, n = 3,668). After the implementation of these exclusions, the study focused on a cohort of 3,410 patients who received multiple RBC transfusions from a single-sex donor group. In the cohort of 3,410 patients, 581 females received transfusions from female blood donors and 903 females from male blood donors, while 737 males received transfusions from female blood donors and 1,189 males from male blood donors. Donor information, transfusion records, and patient characteristics were summarized in Tables 1 and 2.

The Hb increment analysis started with a pool of 5,157 patients who received an initial transfusion of one unit of RBC with other two conditions including only one unit issued at the first transfusion of admission and no transfusion within 4 h post the first transfusion (Figure 1). Certain patients were excluded due to various factors. This included one patient who received deglycerolized RBCs, one patient with non-CBS RBCs, 194 hema-oncology patients, 873 trauma patients, and 2 patients with hemolytic anemia. Due to missing donor information and Hb increment data, we further excluded 29 and 570 patients, respectively. As a result, the final Hb analysis consisted of 3,487 patients. Donor information, transfusion records, and patient characteristics are summarized in Table S2.

3.2 | The impact of single-donor sex transfusion on hospital-onset-sepsis rate in critically ill patients receiving red blood cell transfusions

Notably, there were no statistically significant differences observed in the incidence of HO-sepsis among the four single-sex transfusion groups (Table 3). It was further confirmed in the bivariate analysis that female donors were not associated with an increased risk of developing

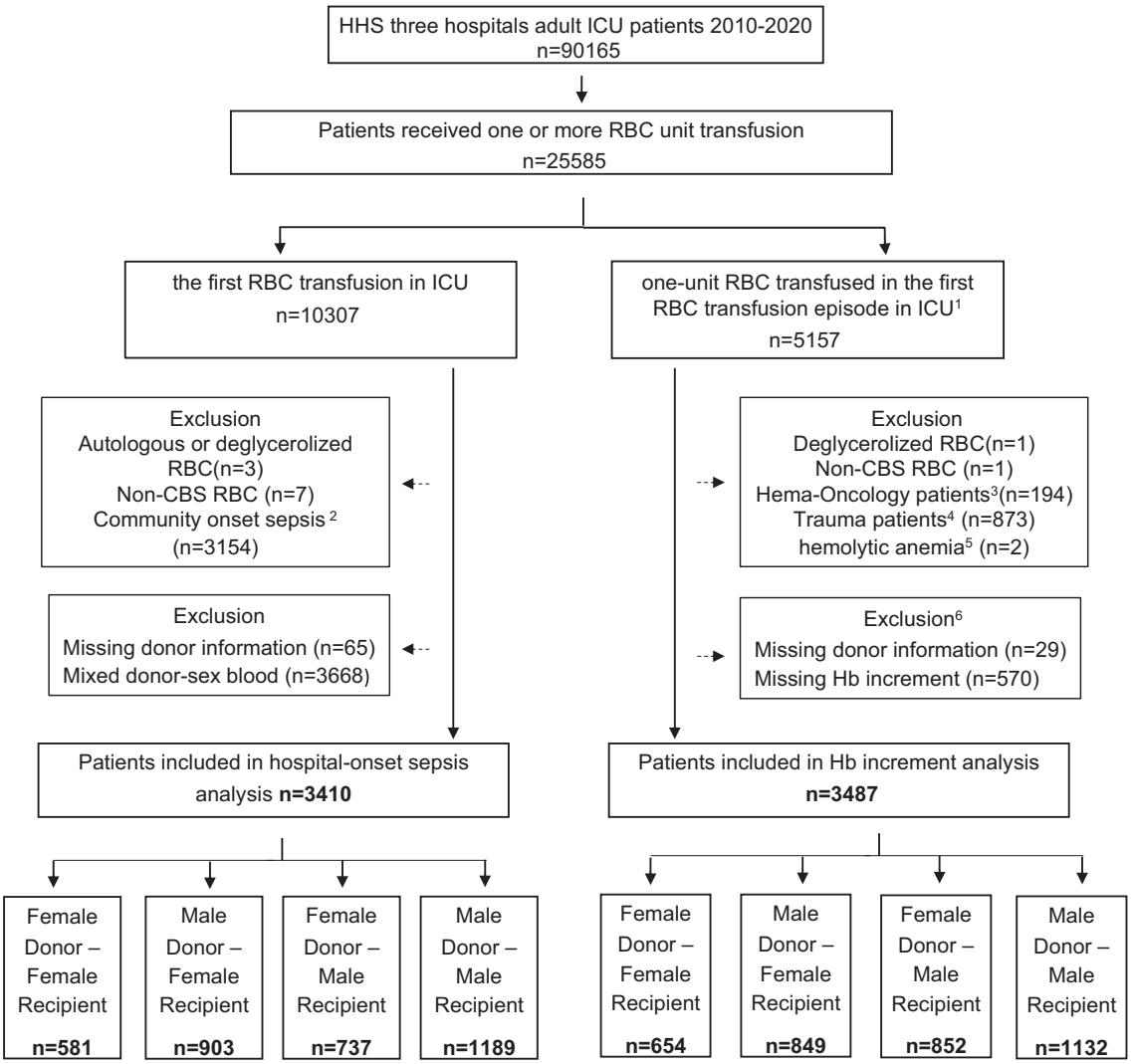

FIGURE 1 Study flow diagram for population selection of the hospital-onset sepsis and Hb increment analysis. 1. Three conditions: (a) only one unit issued at the first transfusion of admission; AND (b) first transfusion occurred during ICU admission; AND (3) no transfusion within 4 h post the first transfusion. 2. Community onset sepsis is defined as sepsis ICD 10 codes and had a microbiology test from 48 h before admission to 48 h post admission. Non-community onset sepsis (sepsis diagnosis ICD 10 codes) is hospital onset sepsis. 3. Any ICD 10 code D691- D699: Purpura (except for allergic purpura) and other hemorrhagic conditions. 4. MRD ICD 10 code S00-T98: Injury, poisoning and certain other consequences of external causes. 5. MRD ICD 10 code D55-D59: Hemolytic anemia. 6. Hemoglobin pre-transfusion was defined as the latest hemoglobin result within 24 h pre-issue of RBC unit. Hemoglobin post-transfusion was defined as the earliest Hemoglobin result within 4 –24 h post-issue of RBC unit without any other RBC unit(s) issued between issue of the RBC unit and time point of the hemoglobin test.

HO-sepsis compared to male donors, with an OR of 0.93 [95% confidence interval (CI), 0.63–1.35; $p = 0.69$; Figure 2]. Interestingly, it was discernible that female recipients exhibited a higher susceptibility to HO-sepsis compared to their male counterparts, with an OR of 1.48 (95% CI, 1.03–2.14; $p = 0.04$; Figure 2).

3.3 | The logistic model estimating hospital-onset-sepsis rate in critically ill patients receiving red blood cell transfusion

Multivariate logistic analysis revealed that the number of RBC units transfused, and the age of recipients are both significant predictors of the HO-sepsis rate. In contrast, donor sex, recipient sex, and whether the donor—recipient sex-matched or not did not significantly influence sepsis rates (Table 3). In the analysis where the number of RBC units transfused was treated as categorical data, the effects of receiving just one RBC unit compared to receiving more than 5 units were significantly different. Specifically, the OR of the latter was 5.5 (95% CI, 1.74–16.77; $p < 0.01$; Table 4), indicating an increased association of HO-sepsis rates. The effects of 3 and 4 units are slightly less definitive, with an OR of 2.19 (95% CI, 0.98–4.91; $p = 0.06$) and 2.58 (95% CI, 0.98–4.91; $p = 0.06$), respectively. When considering data as continuous, assuming the potential equivalence among RBC units, the number of RBC units transfused has a notable association on the likelihood of HO-sepsis, demonstrated by an OR of 1.37 (95% CI, 1.13–1.65;

TABLE 1 Description of participant demographics for hospital-onset sepsis analysis.

Characteristic	Female recipient		Male recipient		
	Female donor $n = 581$	Male donor $n = 903$	Female donor $n = 737$	Male donor $n = 1189$	*p*-Value
Age (years) mean ± SD; median (IQR)	66.4 ± 16.1; 69 (58–78)	66.3 ± 16.4; 69 (58–78)	67.8 ± 14.1; 70 (61–77)	66.6 ± 14.6; 68 (59–77)	0.2143
ABO blood group, number (%)					0.1355
A	246 (42.3)	360 (39.9)	299 (40.6)	457 (38.4)	
AB	20 (3.4)	42 (4.7)	22 (3.0)	64 (5.4)	
B	65 (11.2)	124 (13.7)	98 (13.3)	135 (11.4)	
O	249 (42.9)	377 (41.7)	318 (43.1)	533 (44.8)	
Most responsible diagnosis					<0.001
Circulatory diseases	259 (44.6)	392 (43.4)	471 (63.9)	745 (62.7)	
Trauma	116 (20.0)	176 (19.5)	111 (15.1)	193 (16.2)	
Neoplasms	56 (9.6)	64 (7.1)	26 (3.5)	55 (4.6)	
Digestive diseases	40 (6.9)	65 (7.2)	38 (5.2)	43 (3.6)	
Musculoskeletal disorder	28 (4.8)	47 (5.2)	15 (2.0)	26 (2.2)	
Respiratory diseases	17 (2.9)	35 (3.9)	23 (3.1)	40 (3.4)	
Endocrine disorders	12 (2.1)	20 (2.2)	11 (1.5)	20 (1.7)	
Pregnancy and childbirth	16 (2.8)	31 (3.4)	0 (0.0)	0 (0.0)	
Unclassified signs	3 (0.5)	13 (1.4)	11 (1.5)	19 (1.6)	
Nervous system disorder	6 (1.0)	19 (2.1)	6 (0.8)	11 (0.9)	
Genitourinary disorder	9 (1.5)	17 (1.9)	3 (0.4)	11 (0.9)	
Infectious diseases	8 (1.4)	1 (0.1)	7 (0.9)	4 (0.3)	
Hematologic diseases	4 (0.7)	5 (0.6)	5 (0.7)	5 (0.4)	
Health accessibility	2 (0.3)	9 (1.0)	2 (0.3)	3 (0.3)	
Mental disorders	1 (0.2)	2 (0.2)	2 (0.3)	8 (0.7)	
Skin disorders	2 (0.3)	5 (0.6)	2 (0.3)	4 (0.3)	
Congenital disorder	2 (0.3)	1 (0.1)	2 (0.3)	2 (0.2)	
Special purposes	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	
Ear disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	
Other transfusion					
Platelets	44 (7.6)	98 (10.9)	219 (29.7)	406 (34.1)	<0.0001
Plasma	50 (8.6)	113 (12.5)	150 (20.4)	295 (24.8)	<0.0001
Cryo	2 (0.3)	11 (1.2)	17 (2.3)	49 (4.1)	<0.0001
Other transfusion before RBC transfusion					
Platelets	29 (5.0)	72 (8.0)	205 (27.8)	347 (29.2)	
Plasma	37 (6.4)	74 (8.2)	121 (16.4)	221 (18.6)	
Cryo	1 (0.2)	6 (0.7)	9 (1.2)	21 (1.8)	

Abbreviations: IQR, Interquartile ranges; SD, standard deviation; RBC, red blood cells.

$p = 0.001$) (Table S3). Additionally, for every incremental year in patient age, there is a slight uptick in the risk for HO-sepsis, evidenced by an OR of 1.02 (95% CI, 1.00–1.03; $p = 0.03$; Table 4). Furthermore, having a trauma diagnosis heightened the likelihood of developing HO-sepsis development, marked by an OR of 2.28 (95% CI, 1.00–5.19; $p = 0.048$; Table 4).

3.4 | The impact of single-sex transfusion on Hb increment in critically ill patients receiving red blood cell transfusions

Female recipients exhibited lower average Hb increments from female donors (9.0 ± 10.2 g/L, $n = 654$) than from male donors (10.9 ± 10.3 g/L,

TABLE 2 Description of transfusion data for hospital-onset sepsis analysis.

Characteristic	Female recipient		Male recipient		*p*-Value
	Female donor *n* = 581	Male donor *n* = 903	Female donor *n* = 737	Male donor *n* = 1189	
Number of RBC unit transfused mean ± SD; median (IQR)	1.5 ± 0.8; 1 (1–2)	1.7 ± 0.9; 1 (1–2)	1.6 ± 0.8; 1 (1–2)	1.7 ± 1.0; 1 (1–2)	>0.09
Exposed to donors age > 50 years	285 (49.1)	501 (55.5)	359 (48.7)	629 (52.9)	0.0188
Number of units from donors age > 50 years					
1 unit	239 (83.9)	387 (77.2)	302 (84.1)	472 (75.0)	
2 units	44 (15.4)	95 (19.0)	53 (14.8)	123 (19.6)	
>3 units	2 (0.7)	19 (3.8)	4 (1.1)	34 (5.4)	
Exposed to donors age 18–50	418 (71.9)	635 (70.3)	535 (72.6)	859 (72.2)	0.7240
Number of units from donors age 18–50					
1 unit	311 (74.4)	436 (68.7)	383 (71.6)	565 (65.8)	
2 units	87 (20.8)	161 (25.4)	119 (22.2)	237 (27.6)	
>3 units	20 (4.8)	38 (6.0)	33 (6.2)	57 (6.6)	
Donor Hb pre-donation mean ± SD; median (IQR)	138.6 ± 8.2; 138 (133–144)	152.0 ± 10.2; 152 (145–158)	138.5 ± 8.5; 137 (133–144)	151.9 ± 10.9; 152 (145–159)	<0.0001
Recipient nadir Hb pre-transfusion Hb mean ± SD; median (IQR)	77.3 ± 13.0; 75 (70–82)	77.0 ± 13.2; 74 (69–81)	77.7 ± 12.2; 75 (70–82)	79.0 ± 13.9; 76 (70–84)	0.0031

Notes: Unless explicitly stated, the data are represented as numerical values (percentage).

ǂpre-transfusion Hb was defined as the latest Hb result within 24 h pre-issue of RBC unit.

ǂǂHb post-transfusion was defined as the earliest Hb result within 4–24 h post-issue of RBC unit without any other RBC unit(s) issued between issue of the RBC unit and time of the Hb test. Abbreviations: IQR, Interquartile ranges; SD, standard deviation; RBC, red blood cells.

TABLE 3 The association of single-sex transfusion on HO-sepsis among critically ill patients.

Variable	Female recipient		Male recipient		*p*-Value
	Female donor *n* = 581	Male donor *n* = 903	Female donor *n* = 737	Male donor *n* = 1,189	
HO-sepsis,Yes #, (%)	25 (4.3)	38 (4.2)	19 (2.6)	37 (3.1)	0.17

Abbreviation: HO, Hospital-onset.

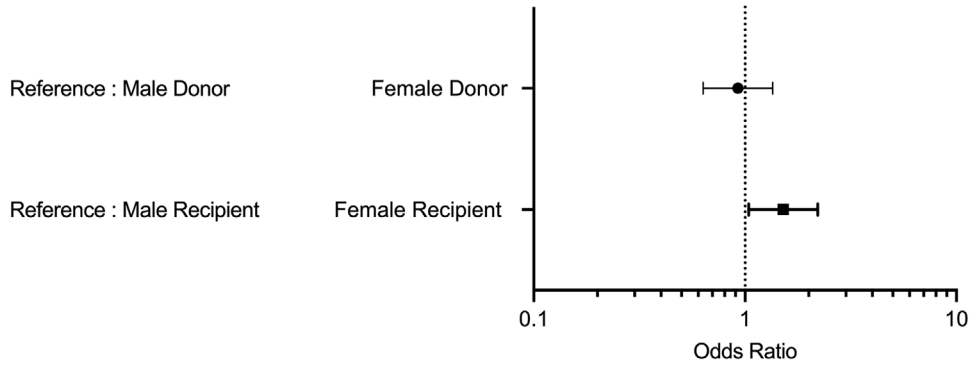

FIGURE 2 Forest plot depicting the odds ratios for the association between donor sex and hospital-onset sepsis. Female donor was not associated with increased risk to sepsis compared to male donor, with an OR of 0.93 (95% CI, 0.63–1.35; $p = 0.69$). Female recipients exhibited a higher susceptibility to sepsis compared to their male counterparts, with an OR of 1.48 (95% CI, 1.03–2.14; $p = 0.04$). OR, Odds ratios.

TABLE 4 Logistic regression analysis for HO-sepsis among critically ill patients.*

	Model with interaction				Model with main effect			
	p-Value	OR	95%	CI	*p*-Value	OR	95%	CI
Recipient age (one year older)	0.05	1.02	1.00	1.03	0.05	1.02	1.00	1.03
ABO group	0.72				0.72			
A vs. O	0.32	1.30	0.78	2.17	0.32	1.30	0.78	2.17
AB vs. O	0.88	1.09	0.37	3.22	0.90	1.07	0.36	3.16
B vs. O	0.37	1.39	0.68	2.84	0.37	1.39	0.68	2.85
Most responsible diagnosis	0.08				0.08			
Circulatory diseases vs. other	0.96	0.98	0.43	2.22	0.97	0.98	0.43	2.22
Digestive diseases vs. other	0.61	1.35	0.43	4.26	0.60	1.36	0.43	4.28
Musculoskeletal disorders vs. other	0.54	1.54	0.39	6.12	0.55	1.53	0.39	6.05
Neoplasms vs. other	0.25	1.86	0.65	5.33	0.25	1.86	0.65	5.31
Trauma vs. other	0.05	2.28	1.00	5.19	0.05	2.29	1.00	5.21
Number of RBC unit transfused	0.01				0.08			
2 units vs. 1 unit	0.54	1.18	0.69	2.01	0.56	1.17	0.69	1.99
3 units vs. 1 unit	0.06	2.19	0.98	4.91	0.06	2.17	0.97	4.86
4 units vs. 1 unit	0.06	2.58	0.96	6.96	0.06	2.55	0.95	6.85
5 or more units vs. 1 unit	0.004	5.40	1.74	16.77	0.00	5.37	1.73	16.69
Other transfusion before RBC transfusion								
Platelets (yes vs. no)	0.31	0.64	0.27	1.51	0.31	0.64	0.27	1.51
Plasma (yes vs. no)	0.85	0.92	0.38	2.21	0.85	0.92	0.38	2.21
Mean donor pre-donation Hb	0.72				0.82			
136–145 vs. 120–135	0.52	1.29	0.59	2.82	0.59	1.24	0.57	2.67
146–155 vs. 120–135	0.28	1.59	0.69	3.68	0.37	1.41	0.66	3.00
>155 vs. 120–135	0.31	1.61	0.65	4.01	0.42	1.38	0.63	3.04
Recipient pre-transfusion nadir Hb	0.06				0.06			
0–70 vs. > 85	0.47	0.75	0.34	1.64	0.47	0.75	0.34	1.64
71–75 vs. > 85	0.23	1.57	0.75	3.26	0.23	1.57	0.75	3.26
76–85 vs. > 85	0.16	1.67	0.82	3.39	0.15	1.68	0.83	3.40
Recipient sex and donor sex								
Female: female blood vs. male blood	0.99	1.01	0.47	2.14				
Male: female blood vs. male blood	0.32	1.47	0.69	3.13				
Female recipient vs. male recipient					0.53	1.17	0.72	1.93
Sex mismatch vs. sex match					0.45	1.21	0.75	1.96

*Hemoglobin level and the number of RBC unit transfused were analyzed as categorical data.
Abbreviations: OR, Odds ratio; CI, confidence interval; HO, Hospital-onset; RBC, red blood cell.

$n = 849$; $p = 0.0022$; Figure 3A). The median Hb increment in female recipients also mirrored this trend, showing a lower median increment from female donors than from male donors, as detailed in Table S6. In contrast, male recipients showed no significant difference in Hb increments when receiving blood from female (6.2 ± 9.7 g/L, $n = 852$) or male donors (6.8 ± 10.0 g / L, $n = 1132$; $p = 0.58$; Figure 3A). Supporting these findings, the multivariate linear regression analysis further elucidated, in the model with main effect, that recipient sex was a decisive factor in Hb increments ($p < 0.0001$, Table 5). Concurrently, donor sex, although less definitive, presented a potential influence on the Hb increments ($p = 0.06$, Table 5). In initial bivariate analysis, recipients receiving blood from male donors experienced an Hb increment that was, on average, 1.2 g/L higher than those receiving blood from female donors ($p < 0.001$, Tables S4 and S5). When stratified by recipient using an interaction model analysis, male recipients' Hb increments remained unaffected by donor sex ($p = 0.75$, Table 5). Conversely, female recipients still experienced significant Hb increment variations contingent on donor sex ($p = 0.007$, Table 5).

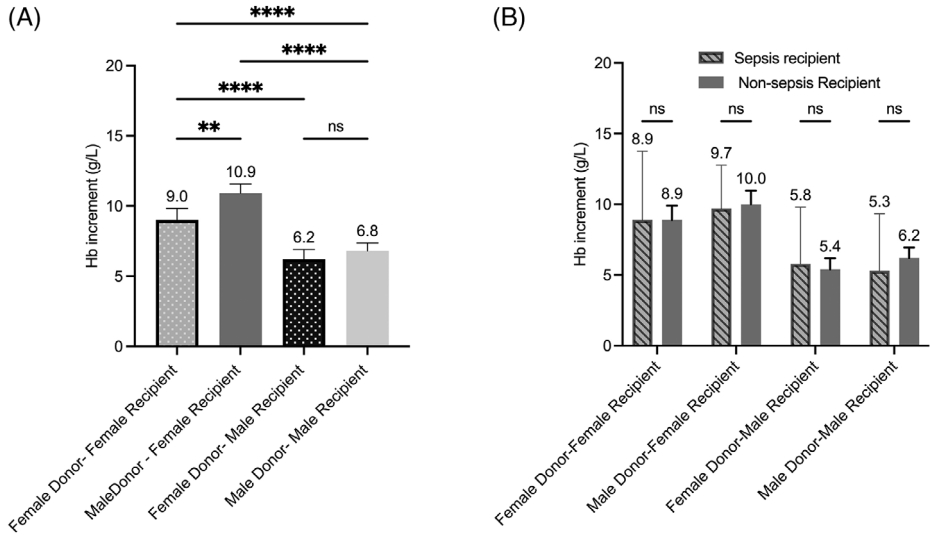

FIGURE 3 The impact of single-sex transfusion on Hb increment in different groups. (A) The effect of single-donor sex transfusion on Hb increment among the four groups (female–male, male–female recipient, female–male recipient, male–male recipient); mean with 95% CI (error bar), the mean value presented, one-way ANOVA performed. (B) Hb increment in hospital-onset sepsis and non-sepsis patients stratified by donor and recipient sex; mean 95% CI (error bar), mean value presented, one-way ANOVA performed. $^{**}p < 0.01$; $^{****}p < 0.0001$; ns, not significant.

3.5 | The linear regression model estimating Hb increment in critically ill patients receiving red blood cell transfusions

Multivariate analysis revealed donor pre-donation Hb, duration from pre-transfusion Hb testing to transfusion (the duration between the measurement of pre-transfusion Hb levels and the execution of the actual RBC transfusion procedure), other transfusion before RBC transfusion, recipient sex, age, and pre-transfusion Hb were significant predictors of Hb increment in the recipient (Table 5). Each 10 g/L increase in blood donor pre-donation Hb resulted in a 0.3 g/L Hb increment in the recipient post-transfusion. Each 10 g/L increase of pre-transfusion Hb in the recipient resulted in an Hb decrease of 4.4 g/L in the recipient post-transfusion. Compared to female blood, male blood would result in 1.4 g/L higher Hb increment in the female recipient. When considering both male and female recipients, donor pre-donation Hb was a significant contributor to Hb increment.

3.6 | Hb increment in the hospital-onset-sepsis and non-sepsis critically ill patients

To further explore the relationship between Hb increment and HO-sepsis in critically ill patients post-transfusion, the Hb increment in both HO-sepsis and non-sepsis group was analyzed, with further stratification by donor sex and recipient sex (Table S6). Out of an initial 3,487 patients who received a single unit of RBC (Figure 1), 1,097 patients with community onset sepsis were excluded, leaving a cohort of 2,390 patients for analysis. There was no statistical difference in Hb increment between HO-sepsis and non-sepsis critically ill patients (Table S6). Hb increment in male recipient was lower than female recipients regardless of HO-sepsis status and donor sex ($p = 0.51$; Figure 3B).

4 | DISCUSSION

Our findings indicated that donor sex was not associated with HO-sepsis (Tables 3 and 4). Infection or nosocomial infection is usually the cause of HO-sepsis [23]. Our finding suggests that, in comparison to the influence of donor sex, recipient characteristics, particularly the number of RBC units transfused, recipient age, and most responsible diagnosis, are closely correlated with the development of HO-sepsis (Table 4). In our study, critically ill patients showed an increased vulnerability to HO-sepsis with each added unit of RBC transfusion, highlighting the association of their compromised immune functions, including a potentially diminished capacity to recycle old RBCs [24]. Notably, the efficiency of the phagocytic system, responsible for this recycling, reportedly declines with age [25], which could further elevate the risk for older recipients. The role of trauma as a significant predictor to HO-sepsis further compounds this risk. While our data do not robustly link recipient sex to sepsis onset (Table 4), an intriguing trend emerged: female recipients had higher ORs for developing HO-sepsis than males in bivariate analysis (Figure 1). Further investigations are warranted to consider these relationships to examine the impact of the number of RBC units transfused on the development of HO-sepsis in critically ill patients.

Our findings indicated that donor sex significantly influenced Hb increase in female critically ill RBC recipients but not in the male cohort. This finding differs from earlier research where donor sex was believed to impact all hospitalized patients, irrespective of recipient sex [26]. Upon stratification by recipient sex, it was evident that donor sex did not significantly influence the Hb increment in male recipients. However, for female recipients, donor sex remained a significant determinant of Hb increment (Table 5). Pre-donation Hb levels emerged as a significant determinant of Hb increment for all recipients in our study (Table 5). This emphasizes the relevance of the transfused Hb

TABLE 5 Linear regression analysis for Hb increment among critically ill patients.

	Model with interaction				Model with main effect			
	p-Value	Mean difference	95% CI		*p*-value	Mean difference	95% CI	
Recipient age (one year older)	<0.0001	0.05	0.03	0.07	<.0001	0.05	0.031	0.075
ABO group	0.37				0.36			
A vs. O	0.11	−0.54	−1.21	0.12	0.10	−0.55	−1.22	0.12
AB vs. O	0.86	0.13	−1.38	1.64	0.88	0.11	−1.40	1.63
B vs. O	0.98	0.01	−0.99	1.02	0.95	0.03	−0.97	1.04
Most responsible diagnosis	0.02				0.02			
Circulatory diseases vs. other	0.63	0.25	−0.78	1.29	0.61	0.27	−0.76	1.30
Digestive diseases vs. other	0.19	0.93	−0.46	2.34	0.18	0.95	−0.45	2.35
Infectious diseases vs. other	0.25	−0.84	−2.29	0.60	0.24	−0.87	−2.31	0.57
Musculoskeletal disorders vs. other	0.60	0.56	−1.57	2.70	0.61	0.56	−1.57	2.70
Neoplasms vs. other	0.01	1.94	0.46	3.44	0.01	1.91	0.42	3.40
Respiratory diseases vs. other	0.13	1.08	−0.31	2.49	0.11	1.15	−0.25	2.55
Donor age (one year older)	0.49	−0.01	−0.03	0.01	0.51	−0.01	−0.03	0.01
Donor pre-donation Hb (per 10 g/L increase)	0.03	0.31	0.03	0.59	0.03	0.31	0.03	0.59
Recipient pre-transfusion Hb (per 10 g/L increase)	<0.0001	−4.42	−4.69	−4.17	<.0001	−4.43	−4.69	−4.17
Duration from pre-transfusion Hb to transfusion (one more hour)	0.0028	0.13	0.047	0.22	0.0023	0.14	0.05	0.23
Duration from transfusion to post Hb (one more hour)	0.51	−0.02	−0.08	0.04	0.49	−0.021	−0.08	0.04
Other transfusion before RBC transfusion								
Platelets (yes vs. no)	<0.0001	−2.69	−3.63	−1.75	<.0001	−2.68	−3.62	−1.74
Plasma (yes vs. no)	0.0004	−1.82	−2.83	−0.81	0.0004	−1.82	−2.83	−0.81
Cryo (yes vs. no)	0.20	−1.68	−4.24	0.89	0.21	−1.66	−4.23	0.91
Recipient sex and donor sex	<0.0001							
Female: female blood vs. male blood	0.007	−1.39	−2.40	−0.38				
Male: female blood vs. male blood	0.75	−0.15	−1.07	0.77				
Female recipient vs. male recipient					<.0001	2.35	1.71	2.99
Female donor vs. male donor					0.06	−0.70	−1.43	0.04

Notes: Duration from pre-transfusion Hb to transfusion: the time interval between the measurement of pre-transfusion hemoglobin levels and the execution of the actual RBC transfusion procedure. Duration from transfusion to post Hb: the time interval between the execution of the actual RBC transfusion procedure and the measurement of post-transfusion hemoglobin levels.
Abbreviations: CI, Confidence interval; RBC, red blood cell.

volume, and by extension, the total RBC units. This perspective aligns with prior findings highlighting the critical role of the number of RBC units transfused in the onset of sepsis in hospital (Table 4). Additionally, the disparity between male and female recipients may be due to body mass differences, which has been identified as a contributing factor. Males represent 60% of the patient population with higher body mass ranges (80–140 kg), and an increase in body mass has been associated with a decreased hemoglobin response to RBC transfusions [27]. Specifically, for every 20 kg increase in patient weight, there is an estimated 6.5% reduction in hemoglobin increment per RBC unit transfused, as determined by multivariate linear regression analysis [27]. This factor should be taken into consideration in future transfusion studies.

Our study showed that male recipients, regardless of whether the blood was sourced from male (6.8 g/L) or female donors (6.2 g/L) (Figure 3A), experienced a poorer average Hb increment which was below the 10.4 g/L documented by Roubinian et al. [26]. Among those who received a single RBC unit, the Hb increment in septic male recipients mirrored those without sepsis, irrespective of donor sex (Figure 3B). But there was no difference observed in non-septic males receiving blood from male (5.4 g/L) or female donors (6.2 g/L, Figure 3B). This suggests that HO-sepsis is not associated with Hb increment in critically ill patients receiving a single RBC, which is different from finding that a poor Hb increment is associated with infection.

This study has several strengths. First, it delves into the connection between the transfusion of RBCs and sepsis by focusing on HO-sepsis

rather than community-onset sepsis. The approach used in this study provided a clearer perspective on HO-sepsis in relation to transfusion by leveraging microbiology test timings. As both suspected and confirmed infections can serve as potent markers for sepsis diagnosis [23], this approach broadens the scope of the population under analysis. Second, RBC units were randomly allocated among recipients regardless of donor characteristics, such as blood donor sex and age, as is current transfusion practice, rendering it a double-blinded study. Therefore, the chance of having systematic confounders among the study groups is minimal.

As an observational study relying on an administrative database, it carries certain constraints. First, the identification of sepsis cases through ICD-10-CA codes depends on the precision of documentation and coding. A good mitigation was that the codes selected for sepsis identification in this research have been referenced in prior studies that utilized administrative data [19–21]. A validation study found that these codes offer a reasonably reliable measure when used to define sepsis from administrative databases [28]. Second, the significant difference in the recipient population, particularly a notably higher percentage of male recipients with circulatory diagnoses that received platelet and plasma transfusions compared to female recipients could be potential confounder. These variables could be included in a subgroup analysis in future studies. Third, while utilizing the timing of the microbiology test helps to ascertain that sepsis occurred in the hospital, it does not conclusively ensure that the RBC transfusion was administered before sepsis onset. Fourth, given the small-sample size of sepsis patients examined in this study, that may limit the generalizability of the findings. Given more comprehensive access to larger clinical data, we could more precisely delineate the relationship between the association of blood donor sex and the onset of sepsis in critically ill patients.

5 | CONCLUSION

In summary, blood donor sex was not associated with HO-sepsis in critically ill patients receiving RBC transfusion. Male donor to female recipient transfusions were found to be associated with a higher Hb increment in critically ill patients. In addition, the pre-donation Hb level, rather than the donor sex, significantly affected Hb increment in critically ill patients. This factor should be considered when determining the number of RBC units to be transfused to critically ill patients, given its substantial influence on HO-sepsis risk. These insights emphasize the importance of considering both donor and recipient factors in making decisions about RBC transfusion for critical care patients to enhance the quality of care.

AUTHOR CONTRIBUTIONS

Wenhui Li, Nancy M. Heddle, and Jason P. Acker designed the study. Yang Liu and Wenhui Li performed the data analysis and all authors were involved in the data interpretation. Wenhui Li prepared the manuscript. Kayla J. Lucier coordinated the study, and all authors reviewed the manuscript prior to submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are provided within the manuscript or supporting information files. Data will be made available upon request to the authors.

ETHICS STATEMENT

The Hamilton Integrated Research Ethics Board (HIREB-#14539-C), Canadian Blood Services Research Ethics Board (CBSREB # 2022.015), and University of Alberta Institutional Review Board (Pro00119217) approved a waiver of consent for this study.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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