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Effect of Blood Donor Characteristics on Transfusion Outcomes: A Systematic Review and Meta-Analysis

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ABSTRACT

Optimal selection of blood donors is critical for ensuring the safety of blood products. The current selection process is concerned principally with the safety of the blood donor at the time of donation and of the recipient at the time of transfusion. Recent evidence suggests that the characteristics of the donor may affect short- and long-term transfusion outcomes for the transfused recipient. We conducted a systematic review with the primary objective of assessing the association between blood donor characteristics and red blood cell (RBC) transfusion outcomes. We searched MEDLINE, EMBASE, and Cochrane Central databases and performed manual searches of top transfusion journals for all available prospective and retrospective studies. We described study characteristics, methodological quality, and risk of bias and provided study-level effect estimates and, when appropriate, pooled estimates with 95% confidence intervals using the Mantel-Haenszel or inverse variance approach. The overall quality of the evidence was graded using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. From 6121 citations identified by our literature search, 59 studies met our eligibility criteria (50 observational, 9 interventional). We identified the evaluation of association of 17 donor characteristics on RBC transfusion outcome. The risk of bias and confounding of the included studies was high. The quality of evidence was graded as very low to low for all 17 donor characteristics. Potential associations were observed for donor sex with reduced survival at 90 days and 6 months in male recipients that receive donated blood from females (hazard ratio 2.60 [1.09, 6.20] and hazard ratio 2.40 [1.10, 5.24], respectively; n = 1), Human Leukocyte Antigen - antigen D Related (HLA-DR) selected transfusions (odds ratio [OR] 0.39 [0.15, 0.99] for the risk of transplant alloimmunization, n = 9), presence of antileukocyte antibodies (OR 5.84 [1.66, 20.59] for risk of transfusion-related acute lung injury, n = 4), and donor RBC antigens selection (OR 0.20 [0.08, 0.52] for risk of alloimmunization, n = 4). Based on poor quality evidence, positive antileukocyte antibodies, female donor to male recipients, HLA-DR selected RBC transfusion, or donor RBC antigen selection may affect RBC transfusion outcome. Our findings that donor characteristics may be associated with transfusion outcomes warrant establishing vein-to-vein data infrastructure to allow for large robust evaluations. PROSPERO registration number: CRD42013006726.

Contents

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Transfusion of red blood cells (RBCs) is one of the most commonly used medical interventions in hospital, accounting for more than 108 million yearly units worldwide [1]. The supply of RBCs in North America relies on voluntary whole blood donation. The quality of RBC products can be greatly affected by characteristics of these donors (health status, phenotypes), and an important aim of current measures in reducing risks for recipients is to better select blood donors. Many infectious pathogens can be transmitted by blood transfusion and can lead to recipient contamination potentially affecting their long-term outcome. Such is the case of human immunodeficiency virus (HIV) and other viruses. These risks can be reduced by a variety of measures, including donor questionnaires that assess infectious risk, infectious disease blood screening, and other quality measures already implemented by blood supply agencies [2,3]. For example, better screening of donors and microbiological testing of the blood products have led to the reduction of transfusion-related infections [4]. Other characteristics have been suggested to affect outcome of transfusion recipients, notably in plasma transfusion. For example, female sex, a history of pregnancy, and the presence of antileukocytes antibodies in blood products have been associated with the risk of transfusion-related acute lung injury (TRALI) which is the current leading cause of mortality after transfusion [5]. These findings have led to potentially successful interventions (transfusion of predominantly male plasma), with a subsequent decrease in the occurrence of TRALI in Canada [5,6].

Although one could easily draw comparisons between RBC transfusions ("transplanting" blood from a donor to a suitable recipient) and solid organ or bone marrow transplantation, there is a paucity of data regarding the impact of donor characteristics on transfusion outcome. In contrast, the medical literature is extensive regarding the impact of donor characteristics on outcome of solid organ and bone marrow transplanted patients [7–11]. Donor characteristics (age, sex, blood groups, comorbities, etc) are used routinely to determine if a specific organ may be suitable for transplantation, to select the best recipient for a particular organ, and to optimize follow-up of transplanted patients when some characteristics from the donor are not optimal. Given the variability in the donor population, such characteristics may also affect RBC transfusion outcome. Identification of donor characteristics associated with transfusion recipient outcomes may lead to optimal selection of blood donors and donor-recipient matching. For example, findings suggesting that donations from donors with specific characteristics negatively affect transfusion outcomes may lead to revised donation practices with the exclusion of such donors from the donor pool.

We hypothesize that donor characteristics, other than the screening measures undertaken aiming mostly to reduce the risk of transfusion transmissible infection, may be associated with RBC transfusion outcome. To inform transfusion policy and decision making and research, and in light of the absence of published reviews addressing the clinical impact of donor characteristics on RBC transfusion recipient outcomes, we conducted a comprehensive systematic review of the evidence.

Research Objectives

The primary objective of our systematic review is to evaluate the association of blood donor characteristics (eg, age, sex, RBC antigen) and the risk of short-term and long-term clinical outcomes of RBC transfusion recipients. Our secondary objectives are (1) to assess the methodological quality and the risk of bias of eligible studies and (2) to identify knowledge gaps and potential future research directions in the selection of blood donors based on their characteristics.

Material and Methods

We conducted a systematic review of studies evaluating the association between whole blood donor characteristics and RBC

transfusion outcome. The protocol of this systematic review has been published previously and registered in PROSPERO (www.crd.york.ac.uk/prospero) CRD42013006726 [12].

Search Strategy

We developed a comprehensive, systematic search strategy with an information specialist trained in the conduct of systematic reviews. We searched MEDLINE, EMBASE, and Cochrane Central databases (that include the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Cochrane Methodology Register, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database) from inception to December 31, 2013, irrespective of language. We used MeSH (or EMTREE equivalent) terms in addition with free-text terms representing the included population, exposure to blood products and donor characteristics and outcomes, to be sensitive and inclusive (Appendix 7). At the stage of the literature search, we applied no restriction on the type of blood product to ensure the most sensitive search strategy. Reference lists of published narrative reviews, systematic reviews, and eligible studies were searched for additional references up to January 2015. We performed manual screening of published articles since the year 2000 of 5 journals in the field of transfusion medicine, according to the 2012 Thomson Reuters' impact factor and from expert opinion of the most clinically relevant journals in the field (*Blood*, *Transfusion Medicine Reviews*, *British Journal of Hematology*, *Vox Sanguinis*, and *Transfusion*).

Study Screening and Inclusion

We obtained title and abstracts of citations identified by our search strategy. When an abstract was not available, full text was obtained unless the title was clearly irrelevant. All abstracts and titles were screened by 2 independent reviewers using prespecified inclusion and exclusion criteria. Full-text copies of relevant reports were then obtained for independent analysis by 2 reviewers for final inclusion decision. Eligible studies were then abstracted by 2 independent reviewers using a piloted, standardized electronic form. Disagreements were resolved by consensus and by consultation with a third independent reviewer when needed.

Inclusion Criteria for Review

Study Type

We included observational studies and interventional studies.

Population

The population of interest was patients (in-hospital or outpatient) with any medical condition requiring at least 1 RBC unit. We included neonatal, pediatric, and adult patient populations.

Intervention (Exposure)

For this review, we were interested in the impact of whole blood donor characteristics in relation to transfusion of RBC products. We included all studies evaluating at least 1 donor characteristic and its clinical effect on recipients. When a study included recipients of blood products other than RBCs, the study was eligible only if we could extract data regarding the RBC transfusions either from the manuscript or after contacting the corresponding author. When the intervention was labeled as "whole blood transfusion" specifically, the study was excluded because these products contain a significant proportion of plasma. Studies reporting "blood products" without any further description regarding the type of blood products transfused were also excluded after contacting the corresponding author of the study.

Outcomes, Setting, and Timeframe

Our primary outcome was mortality. However, we did not restrict outcomes in the search strategy or for inclusion. We included any clinical or surrogate outcomes related to donor characteristics.

Exclusion Criteria

We excluded studies in which the study population included nontransfused patients and from which it was impossible to obtain results for transfused patients. To be eligible, a study also had to report a measure of association between a donor characteristic and a transfusion outcome. We excluded studies reporting expected associations between donor and recipients (eg, using mathematical modeling). Case series were excluded unless an interrupted time-series design was used. We excluded case reports (≤2 cases) and duplicates or "subcohorts" of already published studies.

Analysis Plan

Study Synthesis

For each eligible study, we described the study origin (country, date) and design characteristics (retrospective, prospective, interventional, etc). We provided a description of the population studied including the total number of patients, clinical characteristics, the number of transfused patients, the blood products transfused with the proportion for each type of blood product, the characteristics of included patients (age, sex, and reasons for transfusion), and inclusion and exclusion criteria.

Methodological Quality Assessment

The methodological quality of the included studies in this systematic review was evaluated by 2 independent reviewers using the Downs and Black tool for assessing risk of bias (Appendix 3) [13]. Specific coding instructions were provided to the reviewers and were piloted before implementation.

Primary Analysis

For each of the donor characteristics, we abstracted the number of exposed and nonexposed patients with the studied outcome. We also abstracted unadjusted and adjusted odds ratios (ORs), relative risks, risk ratios (RRs), or hazard ratios (HRs). When appropriate, we provided pooled effect estimates as pooled log-odds ratios or risk ratios with 95% confidence intervals (CI) using a random effects modeling approach. For dichotomous variables, we used the Mantel-Haenszel approach and computed odds ratios and 95% CIs when the number of exposed and nonexposed patients was available. For continuous outcomes or when the number of exposed and nonexposed patients was not provided, we computed mean differences and 95% CIs using the DerSimonian and Laird method. Statistical heterogeneity was reported using the I^2 test with 95% CIs. To investigate publication bias, the funnel plot techniques was used. All analyses were performed using RevMan version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Planned Subgroup or Sensitivity Analysis

To explore clinical and statistical heterogeneity, we planned to report if possible pooled log-odds ratio for the following subgroups: (1) adults ≥18 years vs mixed children/adults, only children vs only adults, and we considered subgroups among children (<1 month and neonates vs other children <18 years); (2) hospitalized patients vs outpatient transfused patients; (3) patients transfused in an intensive care unit vs hospitalized but not in an intensive care unit; (4) significant changes in donor inclusion criteria or manufacture strategy; (5) surgical vs medical populations (≥75% of included patients); (6) patients with acute vs chronic anemia; and (7) continent where the studies were conducted.

Quality of Evidence

Two reviewers evaluated the quality of the evidence according to 5 domains: study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias using the GRADE methodology [14]. We reported the quality as very low, low, moderate, or high.

Results

Result of the Search

Our search strategy identified 6121 citations of which 6044 citations were obtained from our electronic search and 77 citations were found by hand search (Fig 1). Following the screening of titles and abstracts to exclude nonrelevant and duplicate studies by 2 reviewers independently, 105 reports remained for full-text screening and abstraction. A further 46 reports were excluded because the main focus was either whole blood or unspecified blood components (Appendix 2 for description of excluded reports), and thus, 59 studies remained for the review (Appendix 1).

Study Characteristics

Overall, 9 studies (n = 5143 patients) were interventional (5 randomized) and 50 were observational (n > 417278, not reported in all studies). Of the observational studies, 39 were retrospective and 11 prospective. Observational designs included time-series (n = 18), cohort studies (n = 19), look-back (n = 3), trace-back (n = 5), and case-control (n = 5). All but 6 studies (1 Uganda, 1 Jamaica, 1 Columbia, 1 Kuwait, and 2 Japan) were conducted in North America (n = 26) or Europe (n = 27). Publication years ranged from 1976 to 2013, with 35 (59.3%) published since 2000. We included 2 studies where the exact proportion of RBC transfusions was not reported but the authors reported an adjusted analysis by blood component [15,16]. One study reported RBC-related TRALI events without denominator data [17]. For 24 studies, we were able to extract data for patients that received RBCs only (ie, no other blood products). Five studies reported RBC donor-recipient antigen matching strategies, 4 donor sex, 12 selective HLA-DR matching in transplant populations, and 2 donor age.

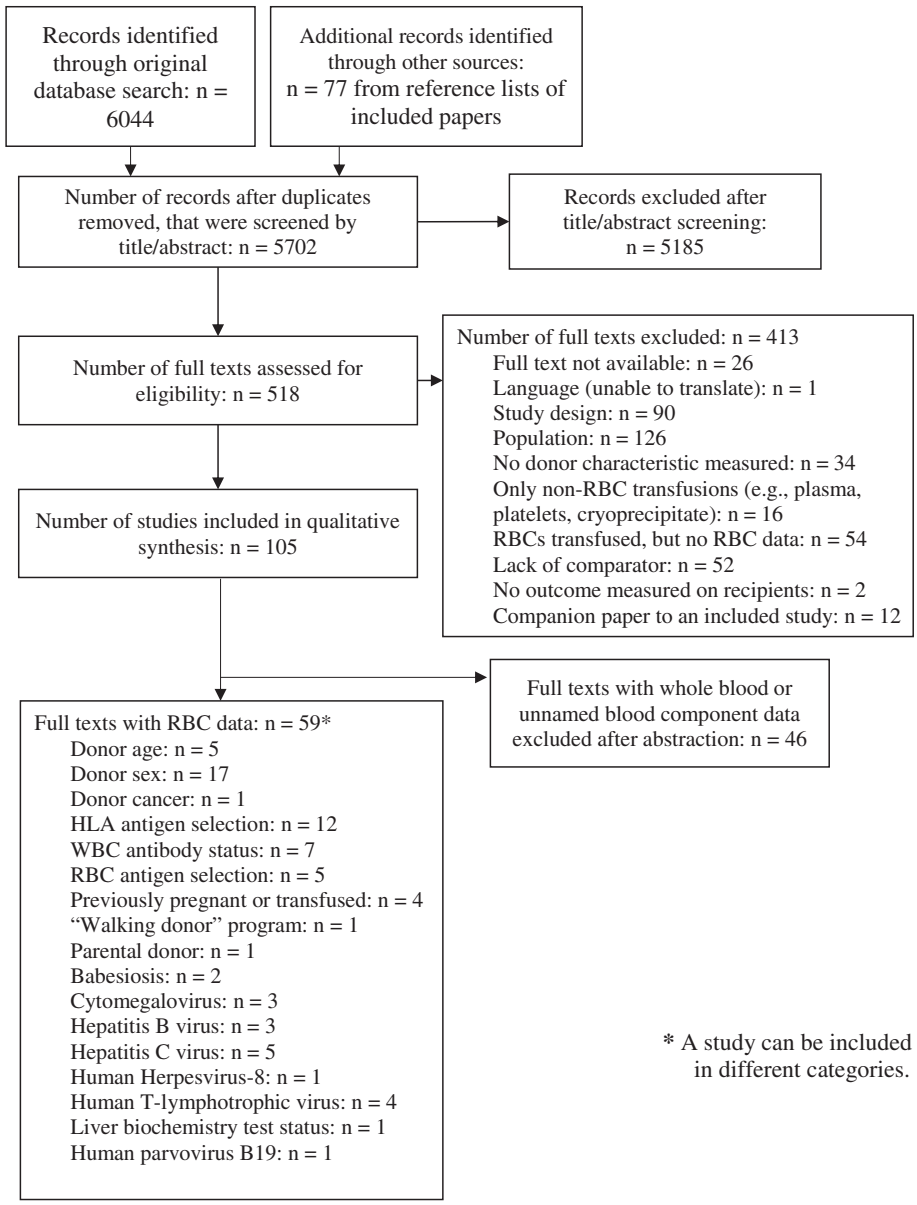

Fig 1. PRISMA flowchart.

Donor Characteristics

We identified 17 different donor characteristics studied (Fig 1). Detailed results of our analyses are presented in Tables 1-5 and in Appendix 6. We summarized the results by patients either receiving RBC products only and those receiving RBC and other blood products.

Donor Age

We identified 5 studies that provided clinical outcome estimates for donor age (Table 1 and Appendix 6). The outcomes of interests were mortality (n = 1), TRALI (n = 3), change in human T-lymphotropic virus (HTLV) infection status (n = 1), and HIV infection (n = 1). All were retrospective and included a total of 586 recipients.

RBC Transfusions Only. Two studies [18,19] presented data for patients receiving RBC transfusions only. One study reported the incidence of acute lung injury [18], whereas the other study reported the rate of immune-mediated vs non–immune-related TRALI [19]. Both studies reported no significant association between donor age and the risk of TRALI (age difference, −0.18 [−6.67, 6.31] for maximum donor age) or immune-related TRALI (age difference, 7.0 [−13.64, 27.64] for maximum donor age).

RBC Transfusions and Other Blood Components. In 3 studies reporting donor age as a potential risk factor for adverse RBC transfusion outcome, recipients were also transfused other blood products in addition to RBCs (Table 1) [15,20,21]. From data provided by the author of 1 study [15], maximum donor age was on average 6.24 years lower in patients who survived hospitalization (age difference, −6.24 [−12.43, −0.05]). Despite design limitations (retrospective case-control study) and the fact that all patients also received plasma transfusion, this study was of good reporting quality with low risk of bias. Two additional studies tested the association between donor age and HIV [20] or HTLV [21] transmission. No numerical values were provided by either study, but the association was reported as not significant. Those studies had poor reporting quality and were at high risk of bias and confounding (Appendix 5).

Donor Sex

Seventeen studies (1 prospective, 16 retrospective) were eligible for review for the donor sex characteristic (Table 2). Six studies were time series studying "before and after" an organizational policy change for blood donation [17,22–27]. Nine studies were case-control (n = 3) [15,28,29], cohorts (n = 4) [21,30–32], or trace-back studies (n = 2) [19,33]. One study reported both a case-control study and a before-and-after study [5]. Four studies reported data for RBC transfusions separately [19,30,32,34]. Two types of donor sex comparisons were available from the included studies: donor sex alone and donor-recipient sex mismatch. The reported outcomes were mortality (n = 2), TRALI (n = 13), change in HTLV infection status (n = 1), mosaicism (n = 1), and the risk of necrotizing enterocolitis (n = 1).

RBC Transfusions Only. Three studies [19,30,32] reported a measure of association between donor sex and transfusion outcome and 1 study for donor-recipient sex mismatch [34]. In a retrospective cohort of 122 patients, Paul and colleagues [32] found that in neonates developing necrotizing enterocolitis within 48 hours after transfusion, 84% of RBC units transfused were from male donors compared with 62% in neonates that developed necrotizing enterocolitis greater than 48 hours after transfusion ($P = .03$). A study including 10 patients by Porretti et al [19] did not find an association between donor sex and immune-mediated TRALI. Finally, a study of 10 neonates [30] receiving RBC transfusions found no evidence of karyotype mosaicism according to donor sex. The risk of bias was high for all studies.

For donor sex mismatch, Middelburg et al [34] found an improved survival at 90 days and 6 months among male recipients younger than 55 years who received only red cell transfusion from male donors (HR 2.60 [1.09, 6.20] and HR 2.40 [1.10, 5.24], respectively). Statistical significance was no longer observed at 5 years (HR 1.40 [0.94, 2.08]). There was no such association in female recipients. Reporting quality was good and the risk of bias low.

RBC Transfusions and Other Blood Components. For donor sex, 7 studies reported the rate of RBC-related TRALI before and after policy changes that included implementation of predominantly male plasma donors and, in some reports, the exclusion of previously alloexposed donors [5,17,23–27]. In those studies, the interventions were aiming to reduce exposure of female blood in plasma products, but we extracted RBC-related TRALI. A meta-analysis of those 7 included reports showed a reduced risk of TRALI in favor of the policy change of reduced exposure to female blood donations (RR 0.50 [0.35, 0.72], I^2 0%). Patients included in those studies also received other blood products in a proportion ranging between 14.6% and 100% for plasma. Given the design (before-and-after studies) of those reports [5,17,23–27], the risk of bias and confounding was high for all included studies. We pooled 4 studies (3 case-control and 1 trace-back study) directly measuring the risk of TRALI in RBC recipients and found no such association (OR 1.03 [0.64, 1.68], I^2 0%) [5,15,19,28]. One before-and-after study reported cases of RBC-associated TRALI and the total number of units transfused during the study period and found no evidence of association [22]. One recipient trace-back study reported a significantly increased risk of TRALI-related death for recipients of blood from antibody-positive female donors compared with male donors or antibody-negative donors (RR 9.00 [1.92, 42.24]) [33]. This study was of low reporting quality, included 18 recipients, and was at risk of confounding, and 59% of the blood products transfused were plasma. One study looking at the risk of HTLV transmission found no association with donor sex [21].

One report estimated the risk of mortality and of acute lung injury for donor sex mismatch [15]. In this study, for the subgroup of patients that received RBCs, there was no association between donor sex and the risk mortality or acute lung injury (OR 1.04 [0.50,

Table 1
Estimates of association between donor age and RBC transfusion outcomes

Outcome or subgroup	Studies	Effect estimate (with 95% CI)	Interpretation
Donor age			
Hospital mortality			
Mean donor age	1	MD −4.62 [−9.92, 0.64]	Null, favors older donors
Maximum donor age	1	MD −6.24 [−12.43, −0.05]	Favors older donor
ALI ≤6 h after transfusion			
Mean donor age	2	MD 3.40 [−4.97, 11.78]	Null
Maximum donor age	2	MD 0.47 [−5.73, 6.66]	Null, favors younger donors
ALI ≤ 72 h after transfusion	1	OR 1.14 [0.52, 2.49]	Null, favors no donor >63
ALI 72 h to 28 d after transfusion	1	OR 0.86 [0.38, 1.96]	Null, favors at least 1 donor >63
ALI ≤28 d after transfusion	1	OR 0.98 [0.51, 1.88]	Null
HTLV transmission	1	Multivariate model including donor age as a risk factor for HTLV-I conversion. 54 patients analyzed. Numerical value not provided. Reported as not significant.	Null
HIV transmission	1	Maximum likelihood estimation of HIV transmission adjusted for covariates. Reported as: "The HIV-1 transmission rate did not vary by the donor's age…"	Null

Table 2
Estimates of association between donor sex and RBC transfusion outcomes

Outcome or subgroup	Studies	Effect estimate (with 95% CI)	Interpretation
Donor sex			
RBC-associated TRALI risk after policy change	7	RR 0.50 [0.35, 0.72], I^2 0%	Favors after policy change
RBC-associated TRALI from male vs mixed donors	4	OR 1.03 [0.64, 1.68], I^2 0%	Null
Nonfatal TRALI risk/unit distributed	1	OR 0.87 [0.40, 1.88]	Null, favors male donors only
Fatal TRALI risk/unit distributed	1	OR 0.37 [0.07, 1.93]	Null, favors male donors only
TRALI-related death vs non–TRALI-related death	1	RR 9.00 [1.92, 42.24]	Favors male donors and antibody-negative female donors
Transfusion reactions	1	OR 1.06 [0.94, 1.19]	Null
TRALI/no. of units			
Male donors	1	OR 0.96 [0.73, 1.26]	Null
Female donors	1	OR 1.03 [0.75, 1.41]	Null
Antibody-mediated TRALI vs non–antibody-mediated	1	OR 4.20 [0.12, 151.96]	Null, favors male donors
Genetic mosaicism	1	Male vs usual donor populations. Statistical method unclear. Authors report: "Given the male to female donor ratio in our blood bank of approximately 1:1, the probability of any patient being transfused with blood from a donor of opposite sex is 50%. The observation of no instances of even mosaic discordant karyotypic sex in any of our 10 patients is highly significant, with a likelihood of 0.001."	Null
Necrotizing enterocolitis	1	84% of RBC units were from males in the NEC within 48 h of transfusion group, 62% of RBC units were from males in the NEC >48 h group. Authors report a *P* value of .03.	Favors female donors
HTLV infection	1	Multivariate model including donor sex as a risk factor for HTLV-I conversion. 54 patients analyzed. Numerical value not provided. Reported as not significant.	Null
Donor sex mismatch			
Hospital mortality			
Female recipients	1	OR 1.05 [0.22, 5.13]	Null
Male recipients	1	OR 0.70 [0.18, 2.75]	Null, favors sex mismatch
All recipients	1	OR 1.05 [0.40, 2.73]	Null
Survival 1 mo posttransfusion			
Female recipients	1	HR 1.10 [0.43, 2.84]	Null, favors no sex mismatch
Male recipients	1	HR 2.20 [0.86, 5.64]	Null, favors no sex mismatch
All recipients	1	HR 1.40 [0.73, 2.68]	Null, favors no sex mismatch
Survival 90 d posttransfusion	1		
Female recipients	1	HR 1.50 [0.59, 3.79]	Null, favors no sex mismatch
Male recipients	1	HR 2.60 [1.09, 6.20]	Favors no sex mismatch
All recipients	1	HR 1.80 [1.00, 3.24]	Favors no sex mismatch
Survival 6 mo posttransfusion	1		
Female recipients	1	HR 1.20 [0.56, 2.59]	Null, favors no sex mismatch
Male recipients	1	HR 2.40 [1.10, 5.24]	Favors no sex mismatch
All recipients	1	HR 1.60 [0.96, 2.67]	Null, favors no sex mismatch
Survival 5 y posttransfusion	1		
Female recipients	1	HR1.20 [0.69, 2.09]	Null, favors no sex mismatch
Male recipients	1	HR 1.70 [0.92, 3.14]	Null, favors no sex mismatch
All recipients	1	HR 1.40 [0.94, 2.08]	Null, favors no sex mismatch
Acute lung injury	1		
Female recipients	1	OR 0.78 [0.20, 3.01]	Null, favors sex mismatch
Male recipients	1	OR 1.38 [0.35, 5.44]	Null, favors no sex mismatch
All recipients	1	OR 1.05 [0.40, 2.73]	Null

2.73] for mortality, 1.05 [0.40, 2.73] for acute lung injury). All patients also received plasma. Reporting quality was good and the risk of bias low.

White Blood Cell Antibodies

Seven studies assessed at least 1 donor antibody directed to any type of white blood cell (WBC) antibodies (Table 3). One study found no association between donor WBC antibodies and mortality [15]. Four observational studies suggested an increased risk of TRALI (OR 5.84 [1.66, 20.59], I^2 62%) [15,33,35,36]. The risk of bias and the statistical heterogeneity for the 4 studies were high. One study measured the risk of TRALI in relation to the anti-WBC antibodies titers and reported a significant association, favoring low-antibody titers (OR 3.20 [1.52, 6.74]) [5]. All studies included patients that received RBC and other blood products.

RBC Antigen Selection

Five studies (4 observational, 1 nonrandomized intervention study) reported the association of donor RBC antigen selection on transfusion outcome (Table 3) [37–41]. One study found no association between a donor-recipient cross-match (vs no crossmatch) and the risk of clinical hemolysis (OR 0.74 [0.03, 15.83]) [38]. Three studies reported the risk of alloimmunization after transfusion of mismatched vs matched blood [37,39,40]. Overall, transfusion of matched RBC products was associated with a reduction in the risk of alloimmunization (OR 0.20 [0.08, 0.52], I^2 58%). The heterogeneity and risk of bias were high for all studies.

HLA-DR Selection

We identified 12 studies (2 RCTs, 3 nonrandomized intervention studies, 5 prospective cohorts, and 2 retrospective cohorts) reporting the association between HLA-DR selection and RBC transfusion outcome (Table 3). All recipients were transplant candidates (renal in 11 studies and cardiac in 1 study). All patients received only RBC transfusions. There was no evidence of association between HLA-DR selection and mortality (n = 1 study) [42], patient survival (n = 2 studies) [42,43], graft survival (n = 4 studies) [43–46], and microchimerism (n = 1

Table 3
Estimates of association between donor antibodies or antigen and RBC transfusion outcomes

Outcome or subgroup	Studies	Effect estimate (with 95% CI)	Interpretation
WBC antibody			
Mortality	1	OR 0.45 [0.14, 1.48]	Null, favors presence of antibody
TRALI	4	OR 5.84 [1.66, 20.59], I^2 62%	Favors absence of antibody
TRALI—after implementation of a no WBC antibody policy	1	RR 0.64 [0.07, 5.85]	Null, favors after policy change
Fatal vs nonfatal TRALI	1	OR 0.71 [0.11, 4.65]	Null, favors presence of antibody
Increase of TRALI risk by antigen titer increase	1	OR 3.20 [1.52, 6.74]	Favors low antibody titer
RBC antigen selection			
Hemolysis	1	OR 0.74 [0.03, 15.83]	Null, favors positive cross-match
Alloimmunization	4	OR 0.20 [0.08, 0.52], I^2 58%	Favors matched blood
HLA-DR antigen selection			
Mortality	1	OR 0.45 [0.16, 1.29]	Null, favors HLA-DR matched
1-y graft survival	3	OR 1.27 [0.37, 4.36], I^2 49%	Null, favors HLA-DR mismatched
5-y graft survival	2	OR 1.10 [0.56, 2.18], I^2 0%	Null, favors HLA-DR mismatched
1-y patient survival posttransplant	2	OR 0.45 [0.10, 2.02], I^2 0%	Null, favors HLA-DR matched
5-y patient survival posttransplant	2	OR 1.02 [0.11, 9.79], I^2 68%	Null
Acute renal rejection < 6 mo posttransplant	2	OR 0.36 [0.14, 0.91], I^2 0%	Favors HLA-DR matched
Acute renal rejection at any time after transplant	1	OR 0.47 [0.16, 1.35]	Favors HLA-DR matched
>1 acute renal rejection episode over follow-up	2	OR 0.50 [0.29, 0.88], I^2 0%	Favors HLA-DR matched
Alloimmunization	9	OR 0.39 [0.15, 0.99], I^2 66%	Favors HLA-DR matched
Microchimaerism			
1-4 d posttransfusion	1	Not estimable	Not estimable
5-7 d posttransfusion	1	OR 17.89 [0.76, 420,49]	Null, favors HLA-DR mismatched
2-4 wk posttransfusion	1	OR 11.67 [0.92, 147.56]	Null, favors HLA-DR mismatched
5-8 wk posttransfusion	1	OR 1.33 [0.10, 17.10]	Null

study) [47]. Pretransplantation HLA-DR matched transfusion reduced the rate of renal rejection <6 months after transplantation in 2 studies (OR 0.50 [0.29, 0.88], I^2 0%) [43,48] and at any time after transplantation in 1 study (OR 0.47 [0.16, 1.35]) [43], and the number of rejection episodes posttransplant in 2 studies (OR 0.50 [0.29, 0.88], I^2 0%) [42,45]. In 9 studies (1 RCT, 3 nonrandomized intervention trials, and 5 observation studies), the rate of alloimmunization posttransplantation was reported. The overall risk of alloimmunization was reduced by the transfusion of HLA-DR matched RBC products (OR 0.39 [0.15, 0.99], I^2 66%) [44–46,48–53]. All studies were of different designs and at high risk of bias and confounding, and the statistical heterogeneity was high.

Other Noninfectious Donor Characteristics

An additional 4 noninfectious donor characteristics were identified (Table 4).

RBC Only. One study published in 1976 with 123 patients assessed cytomegalovirus (CMV) and hepatitis B virus (HBV) infection risks in pediatric recipients of RBCs from "walking donors" vs "usual" donor and found no association (OR 1.67 [0.18, 15.02] for CMV, not estimable for HBV) [54]. One RCT in 40 neonates found no association between maternal donors, paternal donors, or unrelated donors and the risk of transfusion reaction, change in hematocrit, and abnormal posttransfusion creatinine and bilirubin level [55]. Both studies were at high risk of bias.

Table 4
Estimates of association between other noninfectious donor characteristics and RBC transfusion outcomes

Outcome or subgroup	Studies	Effect estimate (with 95% CI)	Interpretation
Donor cancer			
Recipient cancer	1	RR 1.00 [0.94, 1.06]	Null
Previous alloexposure			
Mortality	1	OR 1.48 [0.48, 4.51]	Null, favors alloexposure
TRALI	2	OR 0.86 [0.59, 1.27], I^2 0%	Null, favors no alloexposure
TRALI risk after policy change	2	OR 0.78 [0.45, 1.35], I^2 0%	Null, favors after policy change
Walking donors vs random donors			
CMV infection	1	OR 1.67 [0.18, 15.02]	Null, favors no walking donor
HBV infection	1	Not estimable	Not estimable
Parental donors vs unrelated donors			
Transfusion reaction			
Maternal	1	Not estimable	Not estimable
Paternal	1	OR 3.62 [0.14, 95.78]	Null, favors random donor
Parental	1	OR 2.33 [0.09, 60.85]	Null, favors random donor
Change in hematocrit			
Maternal	1	MD 0.0 [−3.45, 3.45]	Null
Paternal	1	MD −0.20 [−3.36, 2.96]	Null
Abnormal creatinine			
Maternal	1	OR 0.65 [0.02, 17.65]	Null, favors parental donor
Paternal	1	OR 1.14 [0.07, 20.02]	Null, favors random donor
Parental	1	OR 0.73 [0.04, 12.52]	Null, favors random donor
Abnormal bilirubin	1	Not estimable	Not estimable
Maternal donors vs paternal donors			
Transfusion reaction	1	OR 0.57 (0.02, 15.58]	Null, favors maternal donor
Change in hematocrit	1	MD 0.20 [−3.37, 3.77]	Null
Abnormal creatinine	1	OR 0.57 [0.02, 15.58]	Null, favors maternal donor
Abnormal bilirubin	1	Not estimable	Not estimable

Table 5
Estimates of association between infectious donor characteristics and RBC transfusion outcomes

Outcome or subgroup	Studies	Effect estimate (with 95% CI)	Interpretation
Babesiosis screening			
Babesiosis infection	2	RR 0.16 [0.02, 1.31], I^2 0%	Null, favors after screening
CMV-positive donors			
Seroconversion to CMV			
Screened vs not screened	2	OR 1.13 [0.86, 1.48], I^2 85%	Null, favors screened
High titer vs low titer	1	OR 7.04 [1.44, 34.49]	Favors low titer
HBV-positive donors			
Anti-HBc seroconversion	1	OR 0.33 [0.09, 1.27]	Null, favors anti-HBs positive
Any hepatitis	1	OR 0.61 [0.32, 1.17]	Null, favors screening
Non-A non-B hepatitis	1	OR 0.17 [0.01, 3.21]	Null, favors anti-HBc positive
HCV-positive donors			
HCV infection (before and after policy change)	3	OR 0.12 [0.02, 0.84], I^2 91%	Favors after policy change
HCV infection (positive vs negative blood)	2	OR 0.65 [0.44, 0.95], I^2 0%	Favors negative donor
HHV8 positive donors			
HHV8 seroconversion	1	OR 0.52 [0.27, 0.98]	Favors HHB8-negative donor
HTLV-positive donors			
HTLV seroconversion	4	OR 54.87 [11.49, 262.01], I^2 75%	Favors HTLV-negative donor
Parvovirus B19–positive donors			
Seroconversion			
DNA positive	1	OR 0.03 [0.00, 0.58]	Favors low donor viral load
IgM positive	1	OR 0.53 [0.04, 6.51]	Null, favors low donor viral load
IgG positive	1	OR 0.04 [0.00, 0.34]	Favors low donor viral load
Donor abnormal liver function test			
Posttransfusion hepatitis	1	OR 1.63 [0.85, 3.12]	Null, favors normal donor liver function test result
Post/transfusion HCV infection	1	OR 3.39 [0.93, 12.35]	Null, favors normal donor liver function test result

RBC and Other Blood Components. Four studies reported previous alloexposures (transfusion or pregnancy) as the exposure of interest, with no regard to the antibody status, and found no association with mortality or TRALI [5,15,56,57]. One large population study of good methodological quality and at low risk of bias found no association between donor cancer and the risk of cancer in transfusion recipients (RR 1.00 [0.94, 1.06]) [16]. The proportion of RBC transfusions was not reported, but the authors performed statistical adjustments by blood products showing no association with the type of product transfused.

Infectious Donor Characteristics

We identified 18 studies reporting infectious donor characteristics (Table 5). The studied pathogens were babesiosis (n = 2) [58,59], CMV (n = 3) [54,60,61], HBV (n = 3) [62–64], hepatitis C (n = 5) [64–68], human herpesvirus (HHV)8 (n = 1) [69], HTLV (n = 4) [21,70–72], and parvovirus B19 (n = 1) [73]. The included studies were in general at high risk of bias, used various designs, and had imprecise estimates. A total of 3 studies included patients that received RBC transfusions only (babesiosis n = 1, CMV n = 1, parvovirus B19 n = 1). Donor infectious testing was associated with a statistically significant reduced infection risk for HCV (OR 0.12 [0.02, 0.84], I^2 91% for policy change) [64,65,68], HHV8 (OR 0.52 [0.27, 0.98]) [69], HTLV (OR 0.02 [0.00, 0.09], I^2 75%) [21,70–72], and parvovirus B19 (OR 0.03 [0.00, 0.58] for DNA positive) [73] but nonsignificantly reduced risk for babesiosis (RR 0.16 [0.02, 1.31], I^2 0%) [58,59] and HBV (OR 0.61 [0.32, 1.17]) [64].

Subgroup or Sensitivity Analysis

Given the low number of eligible studies for each donor characteristics and outcome, no meaningful prespecified subgroup or sensitivity analysis stated in our protocol could be performed.

Risk of Bias

The overall risk of bias and study-specific risk of bias analyses are reported in Figure 2 and Appendix 5. Overall, the quality of reporting was variable. Eighty percent of studies clearly described objectives, exposures, outcomes, and study population, but less than 50% clearly described the distribution of confounders, measures of random variability, lost to follow-up, and measure of probability values. More than 50% of studies presented at least 1 serious risk of bias, especially concerning blinding of the subjects or outcome assessments, as well as the selection of the appropriate analysis for different lengths of follow-up. The risk of confounding was high in general, as more than 65% of studies did not appropriately consider confounding or losses of patients to follow-up. Five studies were randomized, but we were unable to determine if allocation concealment was appropriate. Given the low number of included studies for each donor characteristics and outcome, no funnel plots were produced to appropriately estimate the risk of publication bias.

Quality of Evidence

We applied the GRADE methodology to assess the quality of the evidence obtained from this review (Appendix 4). It was estimated to be very low for all outcomes except for donor cancer and risk of cancer in the recipient (low), the risk of alloimmunization after transfusion of HLA-DR selected RBCs in renal transplant recipients (low), and the change in hematocrit after transfusion of maternal vs paternal RBCs or random vs parental RBCs (low).

Discussion

In our systematic review, we identified 17 unique donor characteristics and their potential impact on RBC transfusion recipient outcomes from 59 studies. The quality of the evidence regarding the association between noninfectious donor characteristics and recipient outcomes was low to very low, suggesting that any estimate of effect is either uncertain or that additional research will likely have an important impact and affect our estimates [14]. Because the common design choice was observational (and retrospective), the risk of bias and confounding was high.

A very low number of studies reported donor age as a potential effect modifier of outcome in RBC transfusion recipients and was a stated outcome in only 1 small study [15]. No study reported any evidence of association between donor age and transfusion outcome. From personal communications with the authors of 1 study, we found that the maximum donor age was lower in patients who died in hospital vs patients who survived [15]. This analysis was performed on the subset of patients who received RBC transfusions, but all patients also received plasma. All studies were small and at high risk of confounding, and no conclusion can be drawn from the gathered evidence.

Fig 2. Risk of bias.

Whether the risk of TRALI is increased after RBC transfusion from female donors is unclear. From this review, we found very low quality evidence suggesting that a policy change limiting female plasma donors or plasma donors positive for antileukocytes antibodies reduces the risk of RBC-related TRALI. Such findings are surprising because female donors were not restricted in any included studies for RBC transfusions. Given the study design of those studies (before-and-after), the findings are potentially confounded by transfusion of other plasma-rich products to the recipients. This hypothesis is supported by a null association between female or mixed RBC donors and the risk of TRALI from an analysis including 4 observational studies (OR 1.03 [0.64, 1.68]), although most patients in those studies were also co-transfused with plasma-rich products. The association between female donors and TRALI has been associated with alloimmunization and the presence of WBC antibodies. When studying specifically the presence of WBC antibodies in the blood donor, our meta-analysis of 4 studies suggested that the presence of antibodies in the donor was associated with an increased risk of TRALI in RBC transfusion recipients (OR 5.84 [1.66, 20.59]). However, any result from such analyses should be hypothesis generating only, as the obtained estimate is likely unreliable because of poor study design and high risk of bias.

One study suggested that donor sex may be associated with survival when donor sex and recipient sex were mismatched. In this study by Middelburg and colleagues, the subgroup younger than 55 years that

received only female donor RBCs transfused in male recipients had a significantly decreased survival at 6 months (HR 2.40 [1.10, 5.24]). This association was also seen when not restricting to only RBC transfusions (HR 3.1 [1.5, 6.3]) [31]. If verified, the mechanism of such an association remains to be explained and will need further study. One could argue that this sex mismatch association may be due again to the presence of WBC antibodies. However, given the lack of association in female recipients who received blood from female donors and a trend for a decreased survival in females who receive blood from males, the presence of antibodies is unlikely to be the only explanation. One group proposed that microchimerism may be present in donor-recipient mismatch transfusion, but this was not observed in their study [47].

Other antibodies or antigens have been studied in RBC transfusions and assessed recipients' clinical outcomes. Compatibility of the pretransplantation histocompatibility complex (HLA-DR) has been studied in 8 studies in kidney transplantation and 1 in cardiac transplantation. We found no association with survival. However, transfusion of HLA-DR matched blood was reported to be associated with a reduced rate of graft rejection and alloimmunization. Such interventions are no longer used clinically to prevent graft rejection. It however supports that donor mismatch may affect recipient outcome by altering the recipient's immune response. In the general population, similar observations were obtained from 3 studies studying RBC antigen compatibility and the risk of clinical alloimmunization. Although routine testing for blood compatibility is performed before transfusion, for time and availability considerations, patients often receive unmatched blood for minor and sometimes major RBC antigens. This associated increased risk of alloimmunization is however of uncertain long-term clinical significance, and robust evaluations are still needed.

Three additional noninfectious characteristics were evaluated for their effect on RBC transfusion outcomes. One large binational study analyzed the association between diagnosis of cancer after blood donation and the risk of cancer in the transfusion recipient and showed no association. The estimate was not provided for RBC transfused patients only, but the authors reported a multivariable analysis by blood product that did not modify the risk estimate. This unique study provides weak evidence that precancerous patients may not increase the risk of cancer in the recipient. In pediatric populations, one study reported no difference in risk of transmission of CMV when using random donors or donors specifically asked to provide blood for pediatric care ("walking donors"). Another study comparing blood donated by the mother, the father, or random donors also showed no difference in clinical outcome. Given the observational methods used and the small sample size of those 2 last characteristics, whether such characteristics can affect transfusion outcome remains unclear.

Transfusion has long been a recognized risk of transmission for certain infections such as hepatitis and HIV. In our review, we identified studies that assessed the risk of transfusion-transmitted diseases. Our inclusion criteria required that we can measure a clinical outcome associated with RBC transfusions and that an effect estimate can be measured (rather than estimated); as such, several studies were excluded from this review (Appendix 2). It is therefore impossible to use the observed estimates to compare the risks of transmission of blood-transmissible pathogens with other blood products or with the overall risk of transmission when using whole blood. We however found 18 studies that reported a direct measure of association between donor infectious and transfusion outcome. As expected, despite the low number of studies meeting our inclusion criteria, we found a significant association between a positive infectious status for CMV (low viral titer), hepatitis C, HHV8, HTLV, and parvovirus B19. For hepatitis B and babesiosis, the included studies did not reach statistical significance, although the trend for infectious transmission was toward a protective effect of negative donors. No studies looking at HIV-positive donors and RBC transfusion met our inclusion criteria. It may seem at first surprising to find so few studies that assessed directly the risk of transmissible pathogens. Many studies published in the field tested for the infectious status of the donor, excluded such donors from the transfusion pool, and performed probabilistic estimations of the risk of having an infected unit in the released units for transfusion. Many more studies did not report the risk of transmission for RBC units, but only for the global transfused population, or for whole blood transfusion, rendering estimation of risk for RBC impossible.

We believe that our rigorous methodology allowed us to provide the most extensive systematic review of donor characteristics that may affect RBC transfusion outcome. We feel confident that our comprehensive search strategy, detailed risk of bias assessment, and review methodology allowed us to provide a comprehensive and complete review of the evidence regarding the associations of interest. The quality of the evidence gathered by this review is limited by the quality and design of the included studies. The pooled estimates provided are highly hypothesis generating in nature given the high statistical and clinical heterogeneity, the different study designs, and the high risk of bias and confounding of most included studies. Moreover, a significant number of studies were excluded because it was impossible to extract estimates for RBC transfusions. This affects mainly the effect estimates for infectious characteristics, as only 3 studies were excluded for the donor sex characteristic. In addition, we excluded only 5 studies that looked at noninfectious donor characteristics (prison donors [n = 1], drug users [n = 1], parental donors [n = 1], and paid donors [n = 2]), all observational in design. Those exclusions are very unlikely to influence the conclusions of our study for noninfectious donor characteristics.

Conclusions

In summary, based on very low to low-quality evidence, some donor characteristics may affect RBC transfusion outcome. Female donor sex, positive white blood cells antibodies, HLA-DR antigen selection, and donor RBC antigen selection may be associated with RBC transfusion outcomes. However, the designs and methodologies are at a high risk of bias and confounding, and the number of studies that support these findings is limited. The chosen clinical outcomes of interest are most commonly TRALI and change in infectious status, with survival outcomes rarely reported. Importantly, the evidence is insufficient to draw definitive conclusions for any donor characteristics. Given the potential outcome benefits or risks observed in some studies, further well-designed studies are needed to better evaluate if an improved selection of donors by their characteristics (age, sex, etc) improves RBC transfusion outcome. In the age of "big data," there are tremendous opportunities for establishing large vein-to-vein data infrastructure that allows for robust evaluations of the clinical impact of donor characteristics.

Competing Interests

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.tmrv.2016.01.002.

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