Estimating the effect of donor sex on red blood cell transfused patient mortality: A retrospective cohort study using a targeted learning and emulated trials-based approach

*Peter Bruun-Rasmussen,[a,b] Per Kragh Andersen,[c] Karina Banasik,[b] Søren Brunak,[b] and Pär Ingemar Johansson[a]**

[a]Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, DK-2200 Copenhagen, Denmark
[b]Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark
[c]Department of Public Health, Section of Biostatistics, University of Copenhagen, DK-1014 Copenhagen, Denmark

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Summary

Background Observational studies determining the effect of red blood cell (RBC) donor sex on recipient mortality have been inconsistent. Emulating hypothetical randomized target trials using large real-world data and targeted learning may clarify potential adverse effects.

Methods In this retrospective cohort study, a RBC transfusion database from the Capital Region of Denmark comprising more than 900,000 transfusion events defined the observational data. Eligible patients were minimum 18 years, had received a leukocyte-reduced RBC transfusion, and had no history of RBC transfusions within the past year at baseline. The doubly robust targeted maximum likelihood estimation method coupled with ensembled machine learning was used to emulate sex-stratified target trials determining the comparative effectiveness of exclusively transfusing RBC units from either male or female donors. The outcome was all-cause mortality within 28 days of the baseline-transfusion. Estimates were adjusted for the total number of transfusions received on each day *k*, hospital of transfusion, calendar period, patient age and sex, ABO/RhD blood group of the patient, Charlson comorbidity score, the total number of transfusions received prior to day *k*, and the number of RBC units received on each day *k* from donors younger than 40 years of age.

Findings Among 98,167 adult patients who were transfused between Jan. 1, 2008, and Apr. 10, 2018, a total of 90,917 patients (54.6% female) were eligible. For male patients, the 28-day survival was 2.06 percentage points (pp) (95 % confidence interval [CI]: 1.81-2.32, $P<0.0001$) higher under treatment with RBC units exclusively from male donors compared with exclusively from female donors. In female patients, exclusively transfusing RBC units from either male or female donors increased the 28-day survival with 0.64pp (0.52-0.76, $P<0.0001$), and 0.62pp (0.49-0.75, $P<0.0001$) compared with the current practice, respectively. No evidence of a sex-specific donor effect was found for female patients (0.02pp [-0.18-0.22]). The sensitivity analyses showed that a large unknown causal bias would have to be present to affect the conclusions.

Interpretation The results suggest that a sex-matched transfusion policy may benefit patients. However, a causal interpretation of the findings relies on the assumption of no unmeasured confounding, treatment consistency, positivity, and minimal model misspecifications.

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Keywords: Red blood cell transfusion; Donor sex; Causal inference; Target trial emulation; Targeted maximum likelihood estimation; Machine learning

*Corresponding author at: Center for Endotheliomics CAG, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
E-mail address: per.johansson@regionh.dk (P.I. Johansson).

Introduction

Red blood cell (RBC) transfusion is often a life-saving medical treatment, and no substitutes are currently

Research in context

Evidence before this study

A PubMed search with the terms "donor sex red blood cell transfusion" with no language restrictions was conducted on January 14, 2022. The most recent systematic review and meta-analysis, including five cohort studies with a total of 86,737 patients, found an association between sex-mismatched RBC transfusions and increased recipient mortality. However, the certainty of the evidence was regarded as very low, and the sex-stratified analyses results were inconsistent. Further, an observational study of 30,503 patients found an association between treatment with RBC units from female donors and increased mortality in patients of both sexes. However, when the study was replicated by Edgren et al. in three large cohorts (the Kaiser Permanente Northern California [KPNC], Recipient Epidemiology and Donor Evaluation Study-III [REDS-III], and the Scandinavian Donations and Transfusions [SCANDAT] database) no evidence of an association was found when using a non-linear term to adjust for the total number of transfusions received. A RCT enrolling 8850 patients and comparing male-only to female-only donor transfusions is currently being conducted. The RCT is powered to detect a risk difference down to 2 percentage points; however, smaller effect estimates are clinically relevant given the large number of patients transfused yearly. Further, larger RCTs are required to detect risk differences in subgroups of male and female patients.

Added value of this study

Using a causal inference methodology where hypothetical randomized trials are emulated, the power of large observational data can be leveraged to detect small but clinically relevant effect estimates. Further, by using real-world data, the effects of potential blood banking policy changes can be estimated. Target maximum likelihood estimation (TMLE) coupled with data-adaptive machine learning can be used to estimate average treatment effects between exclusively transfusing RBC units from male or female donors. TMLE is a doubly robust method that further minimises model misspecification bias.

Implications of all the available evidence

The findings from previous observational studies have been conflicting. Using a causal inference methodology, we found that transfusing RBC units from female donors is harmful to male patients. Further, female patients benefit from receiving RBC units exclusively from either male or female donors. Our findings suggest beneficial effects of a sex-matched transfusion policy.

available in routine clinical practice. More than 110 million RBC units are transfused annually worldwide. In addition to hemolytic reactions and viral or bacterial transmissions, consistent observations have indicated that RBC transfusions induce adverse effects in recipients.[1] However, the underlying mechanism remains poorly understood.[2] Several observational studies have examined the effects of donor sex on recipient survival.[3–6] Conflicting evidence has been reported, and differences in the applied statistical methods have been shown to affect the estimates.[6] A randomized controlled trial (RCT) where 8850 adult patients are assigned male-only or female-only donor transfusions is currently being conducted to clarify these discrepancies.[7] The RCT is powered to detect a risk difference down to two percentage points; however, given the large number of RBC transfusions performed annually, even smaller effects would impose a substantial clinical impact thus requiring larger RCTs to be conducted.[8] Moreover, a potential effect is likely to depend on the patient's sex thus increasing the power demands of RCTs further. As an alternative, we introduce a causal inference approach where the power of large real-world data can be leveraged to emulate randomized trials determining the safety of RBC transfusion interventions.[9–11] Further, the use of real-world data enables effect estimation of potential blood banking policy changes.

We hypothesize that the donors' sex may affect the survival of RBC transfused patients. Using large Danish observational data, we explicitly emulated several sex-stratified target trials determining the causal effect of donor sex on the risk of death after RBC transfusion in male and female patients, respectively. The doubly robust targeted maximum likelihood estimation (TMLE) method coupled with ensembled machine learning was used to adjust for confounding and estimate average treatment effects (ATEs) of actionable interventions.[12–15]

Methods

In this retrospective cohort study, we used real-world data from the Danish Capital Region Blood Bank Transfusion Database to emulate several hypothetical randomized trials (target trials).[9] For each of the following emulated target trials, we used TMLE to estimate the ATEs had the entire study population received the treatment from baseline up to 28 days after the start of follow-up:

1. Transfuse the patients with RBC units exclusively from female donors.
2. Transfuse the patients with RBC units exclusively from male donors.

The patients and donors were characterized as males or females based on the Danish civil registration system,[16] and all trials were conducted separately for male and female patients. Under the dynamic treatment

strategies, the patients received the same number of RBC transfusions that they had actually received.[17]

This study is register-based and informed consent for such studies is waived by the Danish Data Protection Agency. Data access was approved by the Danish Patient Safety Authority (3–3013–1731), the Danish Data Protection Agency (DT SUND 2016–50 and 2017–57) and the Danish Health Data Authority (FSEID 00003092 and FSEID 00003724). The manuscript adheres to the STROBE reporting guidelines.

Study population

The transfusion database contained information on donor and recipient age, sex, and ABO/RhD blood group, as well as the date, time, and location of transfusion and donation. The recipients' disease history and death registrations were obtained from the Danish National Patient Registry (DNPR),[18] and the Danish Registry of Causes of Death (DRCD),[19] respectively.

Target trial protocols

In the following, we specify the main components of the protocols for the target trials comparing the effectiveness of each intervention[9]:

Eligibility criteria: We included patients of 18 years or older receiving an in-hospital RBC transfusion in the Capital Region of Denmark between January 1, 2009, and April 10, 2018, with no history of RBC transfusions within the past year at baseline. The first transfusion episode meeting the eligibility criteria was defined as the baseline-transfusion (day k = 0), and all transfusion episodes up to 28 days from the baseline-transfusion represented a transfusion history (day k = {0..28}). Patients were only allowed to participate once; thus, only the first baseline-transfusion meeting the eligibility criteria was included. To ensure that no transfusions had been given in the past year prior to baseline, only transfusion episodes given one year after the start of the transfusion database could be considered baseline-transfusions. Inclusion ended one month before the end of the transfusion database to allow for complete follow-up. Only leukoreduced RBC transfusions were included in the study (implemented on January 1, 2009).

Assignment procedure: Treatment randomization was emulated using TMLE by adjusting for the confounding identified using a causal directed acyclic graph (DAG) (Figure 1, Supplementary).[11,20]

Follow-up period: The study started at randomization and ended at the occurrence of the outcome, or 28 days after baseline, whichever occurred first.

Outcome: 28-day all-cause mortality.

Causal contrast of interest: We focused on the observational analog to the per-protocol effect, that is, the effect that would have been observed if all recipients were treated according to the prescribed intervention.

Statistical analysis plan

We used the doubly robust approach, TMLE, to estimate the risk of death 28 days after the baseline-transfusion under each intervention (Supplementary Methods).[12,15] The transfusion history of each patient was split into consecutive person-day periods, one per day k, from baseline until the end of follow-up. On each day k, the treatment status of the patients was defined as the number of RBCs received from male donors divided by the total number of RBC units received on day k (Supplementary Methods). On days where no transfusions were received the treatment status was set to 0.5. Thus, the ratio between transfused RBCs units from male and female donors was not affected by days where no transfusions were received.

The Danish blood banks follow a first-in-first-out (FIFO) policy where the oldest blood type matching RBC units is selected. Therefore, by nature, the treatment with RBC units from male or female donors is randomized because the donor's sex is not considered when distributing RBC units from the blood banks. Thus, confounding by indication is non-existent. However, because of demographic differences, the stock levels of male and female donated RBCs may vary by hospital while the patients' disease severity also varies by hospital (Supplementary, Table 1). Therefore, we considered the hospital of transfusion a confounder. Further, given that the distribution of male and female donors is not exactly fifty-fifty (Table 1), patients receiving many transfusions may receive more RBCs from the most frequent donor sex (males) while a higher number of transfusions is also associated with increased mortality. Patients receiving many transfusions are also more likely to have received a mix of RBC units from both males and females. Therefore, the number of transfusions received on each day k should also be adjusted for. We presented our assumptions in a DAG to identify all variables to adjust for to eliminate confounding (Figure 1, Supplementary). Using the DAG we estimated that the minimal sufficient adjustment set[21] of covariates needed to block confounding consisted of the total number of transfusions received on day k, the hospital of transfusion, and the calendar period (Figure 1, Supplementary). However, due to potential random variability, we adjusted for additional covariates that were not deemed essential for obtaining unbiased estimates. Nonetheless, confounding from random variability was assumed to be minimal given the large number of patients included.

The baseline covariates included: patient age and sex, the ABO/RhD blood group of the patient (each blood group as a separate categorical), and the year and month at the baseline transfusion (using a cosine and sine

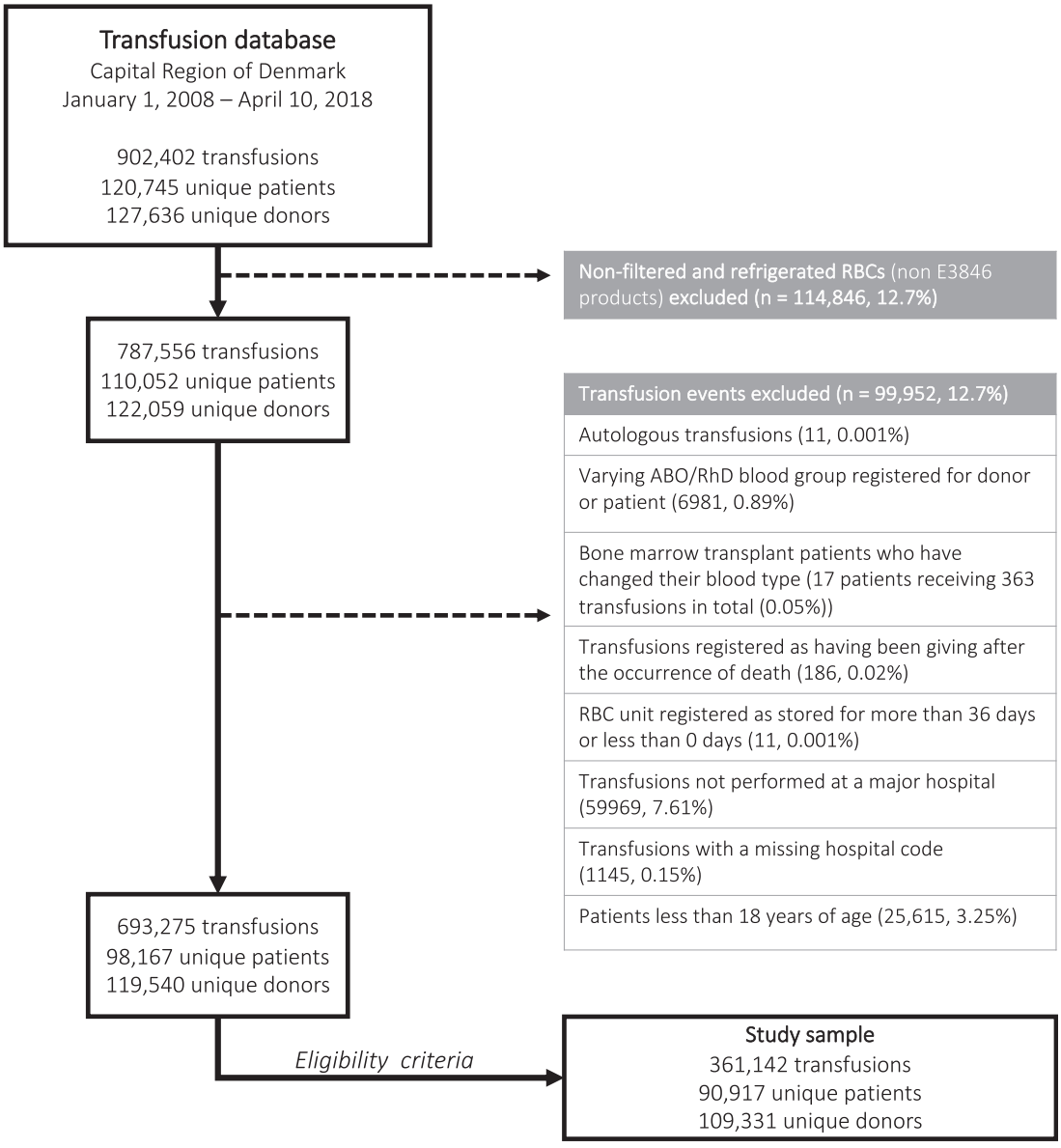

Figure 1. Flowchart of eligible patients and transfusion records for each study design, the Capital Region Blood Bank Transfusion Database, 2008–2018.

transformation for the month). The time-varying covariates included: Charlson comorbidity score[22] at the time of transfusion, hospital of transfusion, the number of transfusions received on day k, and the total number of transfusions received prior to day k. In addition, to adjust for random variability of donor age, the number of RBC units received on each day k from donors younger than 40 years of age was included as a covariate.

To minimize modelling assumptions and model misspecifications, we coupled TMLE with an ensemble of machine learning algorithms (super learning) (Supplementary Methods).[14] The super learner included logistic regression, logistic regression with L1-regularization (LASSO), multivariate adaptive regression splines (MARS),[23] and four different configurations of extreme gradient boosting (XGBoost).[24] The individual learners and the super learner were fitted using 5-fold cross-validation. The entire treatment and covariates histories were used for prediction. A thorough explanation of TMLE is given elsewhere.[12,15]

The analyses were conducted separately for each target trial. Statistical analyses were performed in R (version 4.1.0). We used the R library "lmtp" to utilize TMLE.[15] P-values were two-sided and values < 0.05 were deemed statistically significant. The data processing pipeline was made in Python (anaconda3/5.3.0)

	Male patients (N = 41,256)	Female patients (N = 49,661)
Patient age (years)		
Median [25th, 75th]	70.0 [61.0, 79.0]	73.0 [59.0, 83.0]
Patient Charlson score		
Median [25th, 75th]	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]
ABO blood group patient		
0	16,956 (41.1%)	20,531 (41.3%)
A	18,082 (43.8%)	21,510 (43.3%)
AB	1716 (4.2%)	2212 (4.5%)
B	4502 (10.9%)	5408 (10.9%)
RhD blood group patient		
Negative	6386 (15.5%)	7868 (15.8%)
Positive	34,870 (84.5%)	41,793 (84.2%)
Hospital		
Bispebjerg	4606 (11.2%)	6666 (13.4%)
Bornholm	1005 (2.4%)	1204 (2.4%)
Herlev	8803 (21.3%)	10868 (21.9%)
Hvidovre	6343 (15.4%)	10399 (20.9%)
Nordsjaelland	5893 (14.3%)	7776 (15.7%)
Rigshospitalet	14,606 (35.4%)	12,748 (25.7%)
Medical specialty		
Hematology	2036 (4.9%)	1737 (3.5%)
Oncology	3184 (7.7%)	3959 (8.0%)
Gynecology & obstetrics	0 (0%)	4885 (9.8%)
Thoracic surgery	3162 (7.7%)	1944 (3.9%)
Abdominal surgery	6397 (15.5%)	6692 (13.5%)
Other surgery	6162 (14.9%)	4038 (8.1%)
Intensive care	1532 (3.7%)	1244 (2.5%)
Trauma	925 (2.2%)	383 (0.8%)
Orthopaedics	5240 (12.9%)	11,549 (23.3%)
Cardiology	2804 (6.8%)	2430 (4.9%)
Internal medicine[a]	6644 (16.1%)	7541 (15.2%)
Infectious diseases	452 (1.1%)	448 (0.9%)
Other	2618 (6.3%)	2811 (5.7%)
Follow-up time		
Mean (SD)	26.3 (7.18)	27.0 (6.26)
Death during follow-up		
Yes	6155 (14.9%)	5581 (11.2%)
No	35,101 (85.1%)	44,080 (88.8%)
Total number of RBCs received		
Mean (SD)	4.71 (6.82)	3.36 (4.19)
Median [25th, 75th]	3.00 [2.00, 5.0]	2.00 [2.00, 4.0]
Percentage of RBCs from male donors		
Mean (SD)	51.3 (32.3)	52.3 (34.5)
Median [25th, 75th]	50.0 [33.3, 75.0]	50.0 [33.3, 80.0]

***Table 1*: Study sample characteristics stratified on patient sex.**
[a] Internal medicine including neurology.

using snakemake. DAGitty was used to construct the DAGs and identify the minimal sufficient adjustment sets.[25] The analysis code is available from https://github.com/peterbruun/tmle_donor_sex_study.

For sensitivity analyses, we assessed the potential change of estimates that would be seen if our analyses were affected by an unknown causal bias up to three times larger than that adjusted for by the measured confounders (S1-2, Supplementary).[26]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. P.B-R and P.I.J. had access to the dataset and had the final responsibility for the decision to submit the manuscript for publication.

Results

Of 98,167 patients recorded in the transfusion database, 90,917 patients (54.6% female) met the eligibility criteria (Figure 1, and Table 1). On average, male donors donated 52.3% and 51.3% of the RBCs transfused to female and male patients, respectively (Table 1). During the current practice, 85.1% of male and 88.8% of female patients survived the 28 days of follow-up.

Intervention effects

In male patients, transfusing RBC units exclusively from male donors compared with exclusively from female donors was found to increase the 28-day survival by 2.06 percentage points (pp) (95% confidence interval [CI]: 1.81-2.32, $P<0.0001$), while no evidence of an effect was found for female patients (0.02pp [-0.18-0.22, P=0.84]) (Table 2, Figure 2, and Supplementary Figure 2). Transfusing RBC units exclusively from male donors compared with the current transfusion practice was found to increase the 28-day survival by 1.83pp (1.67-2.00, $P<0.0001$) in male patients. In female patients, the estimated ATEs between the current practice and exclusively transfusing RBC units from either female or male donors were similar, with an increased 28-day survival of 0.62pp (0.49-0.75, $P<0.0001$), and 0.64pp (0.52-0.76, $P<0.0001$), respectively.

The sensitivity analyses showed that, in the studies of male patients, a causal bias smaller than that adjusted for by the measured confounders would induce a non-statistically significant ATE of the contrast between the treatment with RBC units exclusively from female donors and the current practice (S1, Supplementary). However, for all other analyses, a large unknown causal bias needed to be present to affect the conclusions (S1-2, Supplementary). The super learner assigned the largest weights to LASSO and XGBoost for the outcome model (g-computation), and MARS and XGBoost for the assignment model (inverse probability weighting) (Supplementary Table 2).

Discussion

The results obtained from emulating trials using targeted learning suggest that treating male patients with RBC units exclusively from male donors increases the 28-day survival compared with the current practice. Further, transfusing female patients with RBC units exclusively from donors of either sex increases patient survival compared with the current practice where patients can receive a mix of female and male donated RBC units. If a sex-matched transfusion policy was implemented across all blood banks in Denmark, where ≈40.000 patients are transfused annually, our estimates suggest that, annually, 732 (95% CI: 668-800) males and 248 (196-300) females could be saved within 28-days of the first transfusion. In the United States (US), the estimates would translate to 45,750 (41,750-50,000) male, and 15,500 (12,250-18,750) female patients (assuming clinical practices similar to the Danish standards and no effect-measure modification).[8] These estimates resemble the 60,661 traumatic brain injury related deaths that occur annually in the US, which is the leading cause of death from injury (in 2019).[27]

There is no established mechanism to explain how donor sex-related factors result in adverse outcomes related to RBC transfusion. However, RBC products contain 10 to 20 mL residual plasma, which is sufficient to cause transfusion-related acute lung injury (TRALI) in line with the finding that plasma from female donors is a robust risk factor for TRALI development.[28] Whether also other mechanisms are responsible for our findings remains to be investigated.

A previous observational study found an association between treatment with RBC units from female donors and increased mortality in patients of both sexes.[5] However, much larger replication studies found no association when using a non-linear term (restricted cubic splines) to adjust for the total number of transfusions received.[6] A meta-analysis of five cohort studies found an association between sex-mismatched RBC

		Female patients		Male patients	
Treatment contrast	**Day**	**ATE (95% CI)**	***P*-value**	**ATE (95% CI)**	***P*-value**
Male donors vs. natural course	28	**0.64 (0.52, 0.76)**	<0.0001	**1.83 (1.67, 2.00)**	<0.0001
Female donors vs. natural course	28	**0.62 (0.49, 0.75)**	<0.0001	**−0.23 (−0.40, −0.05)**	0.011
Male donors vs. female donors	28	0.02 (−0.18, 0.22)	0.84	**2.06 (1.81, 2.32)**	<0.0001

***Table 2*: The estimated sex-stratified average treatment effects in percentage points between treatment with RBC units from exclusively female donors vs. natural course, male donors vs. natural course, and male vs. female donors on day 28 after the baseline-transfusion. A positive ATE implies a higher survival for the treatment on the left-hand side of "vs." compared with the right-hand side.**

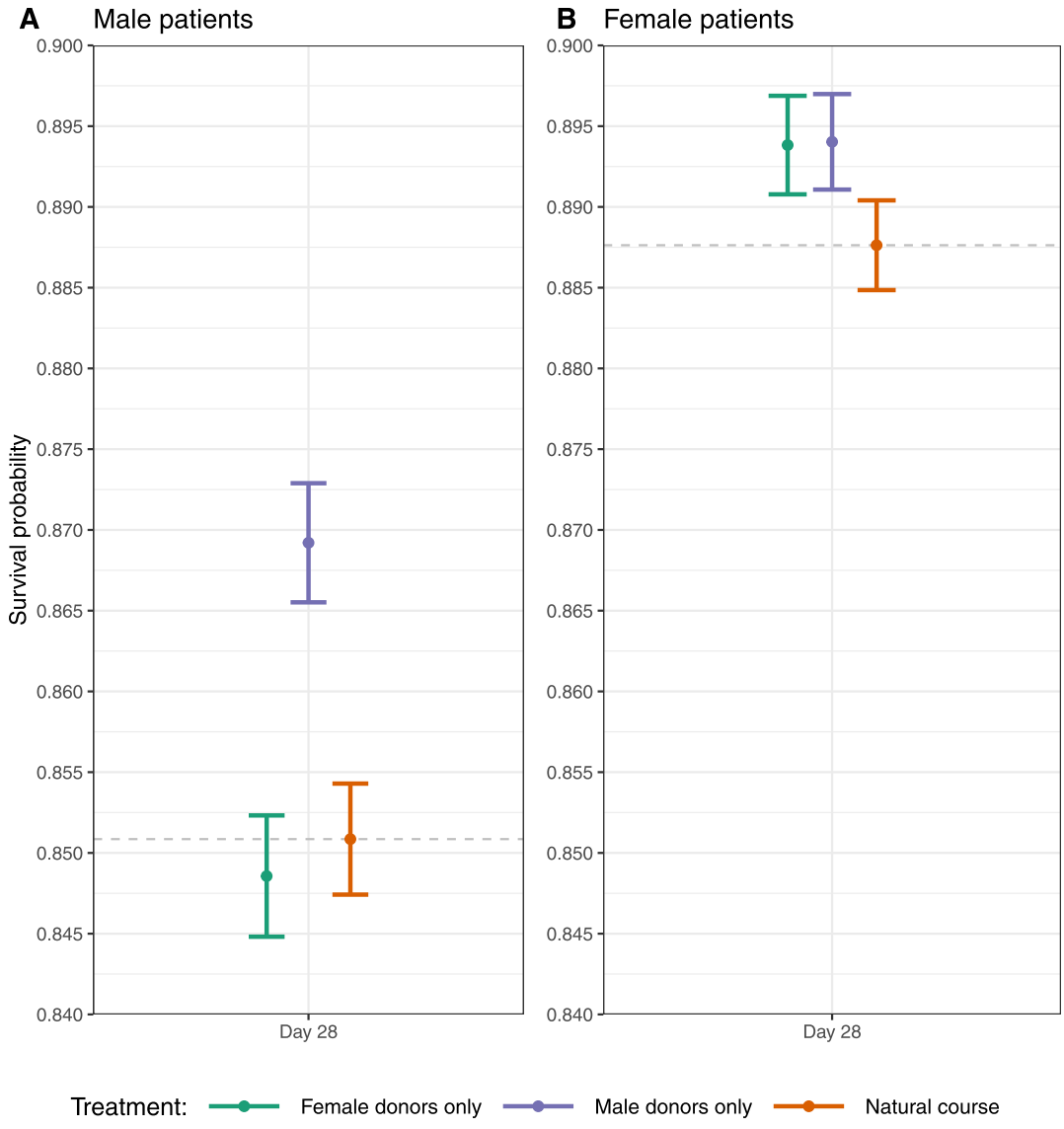

Figure 2. The estimated survival probability for (A) male and (B) female patients under treatment with RBC units from exclusively male donors, female donors, and by the current practice ("Natural course") on day 28 after the baseline-transfusion with 95% confidence intervals. The grey horizontal line indicates the survival probability for the current practice.

transfusions and increased recipient mortality; however, the certainty of the evidence was regarded as very low and the sex-stratified analyses results were not consistent.[3]

To address the limitations of previous studies, we used a causal inference methodology to emulate target trials based on explicitly outlined protocols and a DAG of the study assumptions. Further, we used the doubly robust TMLE approach coupled with data-adaptive super learning to minimize model misspecification bias and residual confounding, which may explain the differences in the published results. The double robustness shields TMLE against substantial model misspecifications, possibly even if a confounder is omitted.[13] Moreover, in longitudinal studies with time-varying treatment and confounding, TMLE enables unbiased estimates, contrary to traditional statistical methods.[11,29] Further, the probability that the target estimand (e.g. the ATE) is contained within the CIs obtained from misspecified parametric models converges to zero for larger sample sizes.[30] This bias can be alleviated using data-adaptive machine learning.[30] Specifically, the non-linear models (XGBoost and MARS) were assigned large weights by the super learner, thus suggesting that only

using linear models in this setting will impose model misspecification bias (Supplementary Table 2). Moreover, we identified (using a DAG) that to avoid confounded estimates, it was necessary to adjust for the number of transfusions received on each day *k*, which was not adjusted for in previous studies (Supplementary Figure 1).

Currently, a RCT comparing transfusion strategies with RBC units exclusively from male vs. female donors is being conducted.[7] Similar to our study, the RCT has applied broad eligibility criteria to enhance generalizability. However, the uncontrollable stock levels of RBC units in the blood banks have imposed a non-compliance to the protocol of 11%. Further, the findings from the RCT can not be generalized to patients with massive bleedings as they were excluded. The RCT will enroll 8850 patients and will be powered to detect a mortality difference of 2 percentage points. Even though the RCT is large and well-designed, it is unfortunately not sufficiently powered to detect the effect size estimates found in this study if the effect depends on the sex of the patient. Further, as illustrated earlier, small effect sizes have a significant clinical impact requiring much larger RCTs to be conducted. To determine the impact of a potential transfusion policy change, we also compared the interventions to the risk under the current transfusion practice (the natural course). The RCT will unfortunately not be able to provide such an estimate.

The validity of our estimates depends on severable untestable assumptions. First, we assume that all confounders that affect both treatment assignment and recipient mortality were identified. We believe that this assumption holds because the donors' sex is not in any way considered when selecting RBC units in the blood banks and thus the selection process is random by nature. However, e.g., the hospital of transfusion (stock levels, demographics) and the number of transfusions received on day *k* may still affect the probability of receiving more male or female donated blood products which we therefore adjusted for. Given that the donor's sex is not taken into account when selecting RBC units, we assume the positivity condition to hold, requiring the probability of receiving the treatment of each trial arm to be greater than zero conditional on the adjusted covariates. We assumed that the stable unit treatment values assumptions (SUTVA) hold, implying that the exposure of any patient did not affect the potential outcome of any other patient. Further, we restricted our analyses to leukoreduced, filtered, and refrigerated RBC units (product code: E3846), hereby ensuring treatment consistency. However, our analyses did not account for transfusions received with blood components other than RBC units. Further, measurement errors in the used registries could have affected the estimates.[18,19] The sensitivity analyses showed that large amounts of unknown causal bias would have to be present for the conclusive estimates to change substantially (S1-2, Supplementary).

Utilizing ensembled machine learning on large data imposes huge computational demands; therefore, we only included four different hyperparameter configurations of XGBoost. Better estimates may be obtained from extensive hyperparameter optimization, however, the potential gains are likely diminishing when considering that an ensemble of algorithms with different capacities was used.

Our results will have a causal interpretation if none of our study assumptions are strongly violated, that is, treatment consistency, positivity, SUTVA, and no unrecognized confounding, measurement errors, or model misspecifications.[11] Accordingly, our findings may generalize to the blood banking transfusion policy of adult patients given the broad inclusion criteria and the use of real-world data (high external validity), thus suggesting that on average patients would benefit from changing the current practice to a sex-matched transfusion policy. However, sex-matching RBC transfusions may not always be possible given the shortage of RBCs, and, importantly, our findings do not suggest that sex-matching is superior to not transfusing RBCs at all, as this question was not part of the investigation. Further, our effect estimates are averages across patients from different medical specialties and do not suggest that a sex-matched transfusion policy is beneficial in all situations. Thus, studies determining whether the observed treatment effects vary across clinical patient subgroups are warranted to optimize treatment effects.

In the absence of high-powered RCTs, explicitly emulating target trials using real-world data and targeted learning may provide better evidence on the effect of donor sex on patient mortality. In this study, exclusively transfusing RBC units from male donors to male recipients increased the 28-day survival compared with the current practice. In female patients, exclusively transfusing RBC units from either male or female donors increased the 28-day survival compared with the current practice. Further, transfusing RBC units from female donors was found to be harmful for male patients while no evidence of a sex-specific effect was found for female patients.

Contributors

P.B.-R.: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Validation, Writing – original draft, and Writing – review and editing. P.K.A.: Methodology, Writing – review and editing. K.B.: Supervision, Writing – review and editing. S.B.: Funding acquisition, Resources, Supervision, Writing – review and editing. P.I.J.: Conceptualization, Validation, Funding acquisition,

Investigation, Project administration, Resources, Supervision, and Writing — review and editing.

Data sharing statement

The study was conducted using anonymized personal sensitive patient data not publicly accessible. Data access may be granted by contacting the Danish Patient Safety Authority, the Danish Data Protection Agency, and the Danish Health Data Authority.

Declaration of interests

P.B.-R, P.K.A., and K.B, declares no potential conflicts of interest. P.I.J reports ownership of stocks in Trial-Lab AB, Endothel Pharma ApS, TissueLink ApS, and Moxie-Lab ApS. S.B. owns stocks in Intomics A/S, Hoba Therapeutics Aps, Novo Nordisk A/S, and Lundbeck A/S, ALK A/S. S.B. is compensated for managing board memberships in Proscion A/S and Intomics A/S. S.B. is member of the Scientific Advisory Board of Biocenter Finland, the Scientific Advisory Board, Health Data UK, the Scientific Advisory Board of the Finnish Center of Excellence in Complex Disease Genetics (CoECDG), the Academy of Finland, the Scientific Advisory Board of the ELIXIR node in Luxembourg, the Scientific Advisory Board of Lund University Diabetes Centre, Lund University, Sweden, the Scientific Advisory Board, SciLifeLab in Sweden, and is chair of the Advisory Board for the Deep Medicine programme Oxford Martin School, University of Oxford, UK.

P.I.J and S.B. declare that the financial interests listed have no impact on the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101628.

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