COMMENTARY

blood advances

TO THE EDITOR:

Is donor-recipient sex associated with transfusion-related outcomes in critically ill patients?

Henry Wood[1,2] and Suzy Morton[3,4]

[1]Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, United Kingdom; [2]School of Cancer & Pharmaceutical Sciences, King's College London, London, United Kingdom; [3]NHS Blood and Transplant, Medical Department, Birmingham, United Kingdom; and [4]Centre for Clinical Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

Alshalani et al[1] state in their recent article that the transfusion of red blood cells (RBCs) from female donors to male recipients vs female recipients increases the risk of intensive care unit (ICU) mortality, and that receiving RBCs from female donors is associated with a trend toward acute respiratory distress syndrome. The comparison between male and female recipients of female donor RBCs and its presentation in the visual abstract is misleading. Scrutiny of the evidence presented in this article raises a number of other issues of concern, both in terms of the analysis and biological plausibility.

The evidence cited by Alshalani et al includes studies on much larger populations (up to 30 503 transfusion recipients)[2-4] that indicated an 8% to 23% increase in the risk of mortality following sex-mismatched RBC transfusion. Another study of 31 118 transfusion recipients[5] identified a 13% increase in the risk of mortality in men who received RBCs from ever-pregnant female donors when compared with transfusions from male donors. However, the largest studies, comprising 93 726 and 968 264 transfusion recipients,[6,7] showed no association between survival and donor sex. Of note, Edgren et al[7] identified the potential for apparent associations to arise when the model is not adjusted for number of transfusions. The absence of association between mortality and donor/recipient sex was confirmed in an analysis of 3 large cohorts in Scandinavia and the United States totaling 1 047 382 patients.[8] Results presented by Alshalani et al are taken from a retrospective cohort of only 403 transfusion recipients, representing a very small proportion of patients already reported in the literature.

The effect of patient sex on survival is not accounted for. The authors acknowledge previous evidence that male patients require higher intensity treatment and have higher ICU mortality,[9-11] yet do not include this factor in their analyses. The separation of the curves in the Kaplan-Meier plot of patients categorized according to donor and recipient sex indicates that the men in the cohort tend toward higher mortality. Higher proportions of cardiovascular insufficiency (also a risk factor for transfusion associated circulatory overload) and mechanical ventilation in these men on admission to ICU may contribute to the trend but were not included as confounders in the analysis because the differences between groups were not shown to be significant.

It is clearly more pertinent to assess the role of donor sex within recipient sex groups, namely comparisons of survival between men transfused with RBCs from female vs male donors and between women transfused with RBCs from female vs male donors. The female-to-female group were chosen as the reference group because they had the best outcomes, but the selection should have been defined prospectively in the methods. Choosing the reference group after the analysis is not methodologically sound and it is not surprising that an association has been found in 1 of the 6 possible pairs. In the context of these limitations, the quoted odds ratio of 2.43 for increased ICU mortality in male vs female recipients of female donor RBCs is misleading. The selection of the two arms that were found to be significant by direct comparison for the visual abstract does not adequately represent the full scope of the data. Inclusion of a complete scale on the y-axis would also be more appropriate.

Submitted 27 June 2022; accepted 26 August 2022; prepublished online on *Blood Advances* First Edition 14 September 2022. https://doi.org/10.1182/bloodadvances.2022008432.

The suggestion that transfusion of one to two units of leukoreduced red cells in additive solution has a significant impact on mortality and that this is mediated by transfusion-related acute lung injury (TRALI) is difficult to countenance from the perspective of biological plausibility.[12,13] Although the small volume of plasma in a RBC unit has been shown to cause TRALI,[14,15] are the authors suggesting that at an estimated rate of 1 in 100 000 transfusions,[16] TRALI is responsible for the apparent excess mortality they report?

Furthermore, RBC transfusions before ICU admission (which are unlikely to have been consistent with the donor/recipient sex categories used in the analysis) and differences in platelet and plasma transfusion between groups would also be anticipated to have more significant roles in such transfusion-related complications.

In summary, there is already a body of retrospective evidence showing no clear impact of donor sex on patient outcomes, and further analyses on small patient numbers adds little to the literature. We acknowledge that the authors stated in their abstract, "this was an exploratory study with potential uncontrolled confounders that limits broad generalization of the findings. Results warrant further studies investigating biological mechanisms underlying the association between donor sex with adverse outcomes as well as studies on the benefit of matching of blood between donor and recipient." However, it is important to emphasize that the conclusions of the article by Alshalani et al are not well supported by the evidence presented and should not be used to guide patient care.

Contribution: H.W. and S.M. reviewed the evidence and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: H.W., 0000-0002-3503-5399; S.M., 0000-0003-2263-3223.

Correspondence: Henry Wood, Departmental of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, SE5 9RS, United Kingdom; email: henrywood@nhs.net.

References

1. Alshalani A, Uhel F, Cremer OL, et al. Donor-recipient sex is associated with transfusion-related outcomes in critically ill patients. *Blood Adv*. 2022;6(11):3260-3267.
2. Chassé M, Tinmouth A, English SW, et al. Association of blood donor age and sex with recipient survival after red blood cell transfusion. *JAMA Intern Med*. 2016;176(9):1307.
3. Bjursten H, Dardashti A, Björk J, Wierup P, Algotsson L, Ederoth P. Transfusion of sex-mismatched and non–leukocyte-depleted red blood cells in cardiac surgery increases mortality. *J Thorac Cardiovasc Surg*. 2016;152(1):223-232.e1.
4. Heddle NM, Cook RJ, Liu Y, et al. The association between blood donor sex and age and transfusion recipient mortality: an exploratory analysis. *Transfusion*. 2019;59(2):482-491.
5. Caram-Deelder C, Kreuger AL, Evers D, et al. Association of blood transfusion from female donors with and without a history of pregnancy with mortality among male and female transfusion recipients. *JAMA*. 2017;318(15):1471.
6. Roubinian NH, Westlake M, St. Lezin EM, et al. Association of donor age, body mass index, hemoglobin, and smoking status with in–hospital mortality and length of stay among red blood cell–transfused recipients. *Transfusion*. 2019;59(11):3362-3370.
7. Edgren G, Ullum H, Rostgaard K, et al. Association of donor age and sex with survival of patients receiving transfusions. *JAMA Intern Med*. 2017;177(6):854.
8. Edgren G, Murphy EL, Brambilla DJ, et al. Association of blood donor sex and prior pregnancy with mortality among red blood cell transfusion recipients. *JAMA*. 2019;321(22):2183.
9. Xu J, Tong L, Yao J, et al. Association of sex with clinical outcome in critically Ill sepsis patients: a retrospective analysis of the large clinical database MIMIC-III. *Shock*. 2019;52(2):146-151.
10. Li G, Cook DJ, Thabane L, et al. Risk factors for mortality in patients admitted to intensive care units with pneumonia. *Respir Res*. 2016;17(1):80.
11. Samuelsson C, Sjöberg F, Karlström G, Nolin T, Walther SM. Gender differences in outcome and use of resources do exist in Swedish intensive care, but to no advantage for women of premenopausal age. *Crit Care*. 2015;19(1):129.
12. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 2019;133(17):1840-1853.
13. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood*. 2012;119(7):1757-1767.
14. Vlaar APJ, Hofstra JJ, Determann RM, et al. The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study. *Blood*. 2011;117(16):4218-4225.
15. Win N, Chapman CE, Bowles KM, et al. How much residual plasma may cause TRALI? *Transfus Med*. 2008;18(5):276-280.
16. Meyer DE, Reynolds JW, Hobbs R, et al. The incidence of transfusion-related acute lung injury at a large, Urban Tertiary Medical Center. *Anesth Analg*. 2018;127(2):444-449.