Shibata *et al. Critical Care (2024) 28:390*
https://doi.org/10.1186/s13054-024-05115-7

Critical Care

MATTERS ARISING

Open Access

Time-dependent intervention in the database study examining the efficacy of whole blood transfusion in traumatic patients

Taisuke Shibata[1], Saburo Minami[1] and Atsushi Shiraishi[1*]

Author's response

We read with great interest the database study by Aoki et al. [1], published in Critical Care. As highlighted in this article, whole blood (WB) transfusion for patients with trauma or severe hemorrhage has recently attracted worldwide attention for its promising potential in reducing mortality [2–4]. This study examines the association between the whole blood rate (WBR), defined as the number of WB units divided by the sum of WB units and packed red blood cells (PRBCs), and 24-h mortality in trauma patients requiring massive transfusion. The results suggest that a higher WBR is associated with improved survival and a lower risk of acute kidney injury (AKI) in patients who received whole blood transfusion within 4 h of hospital arrival. The study utilized generalized estimating equations to adjust for covariates, including clustering, and conducted sensitivity analyses that accounted for the heterogeneity of the lowest WBR group, further enhancing the robustness of the results. Therefore, this study has significant implications for current trauma resuscitation strategies. However, we believe there are some untreated biases, particularly time-dependent intervention bias, which warrant careful consideration.

Firstly, the intervention in this study design is time-dependent; that is, the risk of mortality could continuously influence the physician's decision to administer WB transfusion, and WB transfusion, in turn, could influence the risk of mortality. The risk of mortality and transfusion decisions interact dynamically over time during early trauma care. Component transfusion is routinely administered and readily available at many trauma centers, whereas WB transfusion often depends on the institution's system or regional blood bank, typically making it available later. In many cases, component transfusion is administered first, followed by WB transfusion. Under this assumption, WBR would be zero in the early phase when only component transfusion is being used, and would gradually increase once WB transfusion begins, ranging from zero to one. If, as the authors assume, the intervention, expressed as a continuous variable, affects outcomes, then the time-dependent WBR would impact outcomes differently over time. Thus, evaluating the relationship between a time-dependent intervention like WBR and outcomes at a specific point in time may not fully capture the true relationship.

Additionally, the relationship between WBR and outcomes may introduce immortal time bias. This bias occurs in epidemiological and clinical studies when there is a period during which participants cannot experience the outcome of interest, such as death [5]. Patients with severe trauma are at high risk of early death. Assuming that WBR increases over time, patients with a lower WBR may be those who died early due to severity, while patients with a higher WBR may have survived longer.

This comment refers to the article available online at https://doi.org/10.1186/s13054-024-05041-8.

*Correspondence:
Atsushi Shiraishi
shiraishi.atsushi@kameda.jp
[1] Department of Emergency and Trauma Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba 296-8602, Japan

Statistical models that account for time-dependent interventions and immortal time bias, such as Marginal Structural Models with Inverse Probability of Treatment Weighting (MSMs with IPTW), may be more appropriate [6, 7]. If the current data source does not sufficiently describe time-dependent interventions, prospective studies may be necessary to generate a more suitable dataset.

In conclusion, prospective studies or database studies that account for time-dependent interventions and biases such as immortal time bias are necessary. Future research incorporating these considerations will ensure results that are both statistically robust and clinically meaningful, ultimately contributing to improved trauma resuscitation strategies.

Abbreviations

WB	Whole blood
WBR	Whole blood rate
AKI	Acute kidney injury
TTE	Target trial emulation

Acknowledgements
Not capable.

Author contributions
All authors contributed to the manuscript conception and design. The first draft of the manuscript was written by Taisuke Shibata and all authors gave critical appraisal to the initial draft. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Further information on the original manuscript is available from the corresponding authors upon reasonable request. No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 September 2024 Accepted: 30 September 2024
Published online: 26 November 2024

References

1. Aoki M, Abe T, Komori A, Katsura M, Matsushima K. Association between whole blood ratio and risk of mortality in massively transfused trauma patients: retrospective cohort study. Crit Care. 2024;28(1):253.
2. Torres CM, Kent A, Scantling D, Joseph B, Haut ER, Sakran JV. Association of whole blood with survival among patients presenting with severe hemorrhage in US and Canadian adult civilian trauma centers. JAMA Surg. 2023;158(5):532–40.
3. Hazelton JP, Ssentongo AE, Oh JS, Ssentongo P, Seamon MJ, Byrne JP, et al. Use of cold-stored whole blood is associated with improved mortality in hemostatic resuscitation of major bleeding: a multicenter study. Ann Surg. 2022;276(4):579–88.
4. Aoki M, Katsura M, Matsushima K. Association between whole blood transfusion and mortality among injured pediatric patients. Ann Surg. 2024;279(5):880–4.
5. Yadav K, Lewis RJ. Immortal time bias in observational studies. JAMA. 2021;325(7):686–7.
6. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550–60.
7. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. Stat Med. 2002;21(12):1689–709.

Publisher's Note