

Response to Comment on: "Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia"

by Jochen J. Frietsch, Sarah Flossdorf and Inken Hilgendorf

Received: September 22, 2026.

Accepted: September 25, 2026.

Citation: Jochen J. Frietsch, Sarah Flossdorf and Inken Hilgendorf. Response to Comment on: "Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia". Haematologica. 2026 Oct 1. doi: 10.3324/haematol.2026.302050 [Epub ahead of print]

Publisher's Disclaimer.

E-publishing ahead of print is increasingly important for the rapid dissemination of science.

Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.

E-publishing of this PDF file has been approved by the authors.

After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval, the final version of the manuscript will then appear in a regular issue of the journal.

All legal disclaimers that apply to the journal also pertain to this production process.

Response to Comment on: “Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia”

Jochen J Frietsch ^{1,2}, Sarah Flossdorf ^{3,4}, Inken Hilgendorf ¹

¹ Klinik für Innere Medizin II, Abteilung für Hämatologie und Internistische Onkologie, Universitätsklinikum Jena, Am Klinikum 1, 07747 Jena, Germany

² Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany

³ Deutsches Register für hämatopoetische Stammzelltransplantation und Zelltherapie e.V., DRST, Jörg-Syrlin-Straße 141, 89081 Ulm, Germany

⁴ Institut für Medizinische Informatik, Biometrie und Epidemiologie, Universitätsklinikum Essen, Universität Duisburg-Essen, Hufelandstraße 55, 54147 Essen, Germany

Corresponding author: Jochen Frietsch, Frietsch_J@ukw.de

Author contributions: J.J.F. conceived the comment and drafted the manuscript; S.F. and I.H.

critically reviewed and revised the manuscript. All authors approved the final version for submission.

Conflicts of interest: The authors declare no conflicts of interest.

Response to Comment:

In their commentary on our article, “Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia”¹, Jaing and Wang argue that our statements regarding children are overly general and want a more detailed analysis ².

There is no doubt that a five-year-old child may face a greater lifetime burden of complications following allogeneic hematopoietic stem cell transplantation, given their longer life expectancy. In a recently published paper, we provided a detailed analysis of differences in non-relapse-related mortality across the age groups 0–12, 13–17, 18–39, 40–59 and 60–72 years, stratified by underlying disease, acute myeloid leukemia or acute lymphocytic leukemia, based on the same dataset that is discussed in the commentary by Jaing and Wang ^{2,3}.

A five-year follow-up period would provide a more reliable assessment of the long-term effects in children. Although the analyses presented here are based on data from the German Pediatric Registry for Stem Cell Transplants and Cell Therapies (PRSZT) and the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST), the available data are insufficient to provide statistically robust estimates for longer follow-up periods. As noted by Jaing and Wang, this limitation is largely attributable to the steadily decreasing number of patients at risk over time. With regard to causes of death, we have previously shown that, particularly among patients aged 0–12 years, relapse or progression of leukemia is the leading cause of death compared with the other age groups ³.

Although concerns regarding survivor bias are valid, they should be distinguished from immortal-time bias. Survivor bias can arise when an analysis is restricted to individuals who have survived or otherwise remained eligible up to a predefined time point, thereby necessarily excluding those who experienced the outcome before that point. In the present analysis, however, such conditioning is intentional and directly reflects the research question:

we are specifically interested in the long-term health and mortality risk of cancer survivors who have already reached a defined time point (e.g. five years) after diagnosis or treatment. Accordingly, the analyses are explicitly conditional on survival to that time point and should therefore not be interpreted as estimates of the mortality risk among all patients from the time of initial cancer diagnosis.

This conditional approach also avoids a potential source of immortal-time bias. Immortal-time bias occurs when a period of follow-up during which an individual must remain alive and event-free to be classified into a particular exposure or survivor group is incorrectly attributed to that group. In our analyses, the period preceding the defined time point is not included in the subsequent risk period. Instead, follow-up begins at the predefined time point and includes only individuals who are alive and otherwise eligible at that time. Thus, the time required to reach the predefined time point is not incorrectly counted as event-free survival time during follow-up. The resulting estimates therefore describe mortality and health risks conditional on survival to the respective time point and should be interpreted accordingly.

Importantly, this distinction does not imply that the exclusion of patients who die before the predefined time point is inconsequential. Rather, it defines the target population and estimand of the analysis. The relevant comparison is therefore not between all individuals initially diagnosed with cancer and the general population, but between cancer survivors who have reached the specified time point and individuals from the corresponding general population who are also alive at that time point. This approach allows the analysis to address whether, conditional on survival to the specified time point following cancer diagnosis or treatment, the subsequent mortality risk of cancer survivors remains elevated compared with that of the general population.

In summary, the approach we have chosen is conceptually related to Dal Maso's concept ⁴. By comparing the survival curve for relapse-free survival from five years onward in patients with acute leukemia with that of the general population, the analysis suggests that excess mortality during this period approaches zero, which is consistent with the underlying concept of cure models. However, explicit estimates of the cure rate or a model-based decomposition

of residual mortality risk are not performed in our analysis and cannot be derived from the available data.

Jaing and Wand also note that the estimates provided are unadjusted and that no multivariable analyses were performed. In this context, however, it is important to recognize that our analysis compares a cohort of patients with acute leukemia with the general population. Characteristics such as disease type, disease status, donor type, and intensity of conditioning are specific to the cancer patient population and are not applicable to the general population. Consequently, these disease- and treatment-related factors cannot be directly accounted for, when comparing the two populations. For the corresponding estimates, we refer readers to Frietsch et al. ³.

References:

1. Frietsch JJ, Flossdorf S, Ahmadian A, et al. Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia. *Haematologica*. xxx
2. Jaing TH, Wang YL. Excess mortality convergence after paediatric allogeneic transplantation: a caveat for the right to be forgotten. Comment on: "Decreasing excess mortality after allogeneic stem cell transplantation for acute leukemia". *Haematologica*. xxx
3. Frietsch JJ, Flossdorf S, Ahmadian A, et al. Survival trends in young adults with acute leukaemia after AHSCT in Germany: comparisons with younger and older patients. *Transplant Cell Ther*. 2026;32(8):962.e961-962 e915.
4. Dal Maso L, Serraino D, Guzzinati S. Is survivorship an endless experience? *Cancer*. 2022;128(20):3597-3598.