Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

Cytokine Release Syndrome after Haploidentical Transplantation is Associated with Improved Survival Without Increasing Transplant-Related Mortality

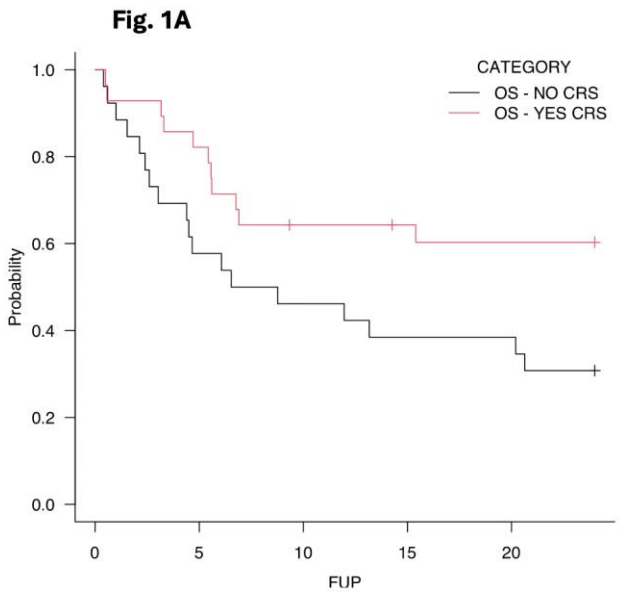
Keywords: Haploidentical HSCT; CRS; TRM.

Published: July 01, 2026 **Received: May 07, 2026** **Accepted: June 18, 2026**

Citation: Avenoso D., Difrancesco N., Morello E., Magliano G., Farina M., Radici V., Hanmantgad S., Bernardi S., Re F., Leoni A., Russo D., Malagola M. Cytokine release syndrome after haploidentical transplantation is associated with improved survival without increasing transplant-related mortality. Mediterr J Hematol Infect Dis 2026, 18(1): e2026059, DOI: http://dx.doi.org/10.4084/MJHID.2026.059

Dear Editor.

Cytokine release syndrome (CRS) following haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is frequent but poorly characterized, and its prognostic significance remains controversial.[1,2,3,4] In this single-center study, we show that CRS is associated with improved overall survival, particularly in patients transplanted beyond first complete remission (CR1), without increasing transplant-related mortality (TRM). Haploidentical HSCT with post-transplant cyclophosphamide (PTCy) is increasingly used in patients lacking matched donors.[5] Early post-infusion inflammatory syndromes resembling CRS are commonly observed and share clinical and biological features with immune effector cell-associated CRS.[2] However, whether CRS reflects beneficial immune activation (graft-versus-leukemia, GVL) or harmful toxicity remains unclear. We retrospectively analyzed 104 consecutive patients undergoing haplo-HSCT between July 2008 and September 2024. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for transplantation procedures and for the use of anonymized clinical data for research purposes, in accordance with institutional policy. All patients received GVHD prophylaxis with PTCy, mycophenolate mofetil and tacrolimus as previously described.[6] After excluding 18 patients with early-documented infections during the early post-transplant period, 86 patients were evaluable for CRS assessment. This exclusion was intended to reduce potential misclassification between infectious fever and CRS, although it may have introduced some selection bias. CRS was defined according to ASTCT criteria in the absence of alternative causes.[7] The primary endpoint was overall survival (OS); secondary endpoints included relapse-free survival (RFS), GVHD/relapse-free survival (GRFS), cumulative incidence of relapse (CIR), and TRM. Relapse and TRM were analyzed using a competing risk framework. Given the sample size, the analysis focused on unadjusted comparisons. Most CRS events were grade 1–2 according to ASTCT criteria (43 out of 44), while high-grade CRS was uncommon (1 out of 44). Owing to the limited number of severe CRS events, a stratified analysis according to CRS grade was not feasible and should be considered a limitation of the study. In the overall cohort, OS was numerically higher in patients with CRS, although this did not reach statistical significance (median not reached vs 24 months; $p = 0.10$). Similarly, no significant differences were observed in GRFS or RFS between groups. In contrast, in patients transplanted beyond CR1 (62.5% of the cohort), CRS was significantly associated with improved OS (median not reached vs 7.6 months; $p = 0.02$ – **Figure 1A**). In this subgroup, RFS (median not reached vs 6.7 months; $p = 0.06$) and GRFS (median 39.9 vs 6.9 months; $p = 0.09$) also showed consistent trends in favor of CRS, although these differences did not reach statistical significance. When relapse was analyzed using a competing-risk approach, the cumulative incidence of relapse was numerically lower in patients with CRS in both the overall cohort and the advanced-disease subgroup; however, these differences were not statistically significant. TRM was comparable between groups ($p > 0.5$ – **Figure 1B**), with no evidence of increased early mortality in patients developing CRS. No significant differences were observed in the incidence or severity of acute and chronic GVHD. These findings may suggest that early inflammatory activation associated with CRS does not necessarily translate into increased clinically significant alloreactivity.[8] From a biological perspective, CRS may represent the clinical correlate of early donor immune activation, characterized by cytokine release and expansion of T and natural killer cells. This early alloimmune activation could potentially contribute to disease control, particularly in patients with residual disease at transplant, although this hypothesis remains speculative.



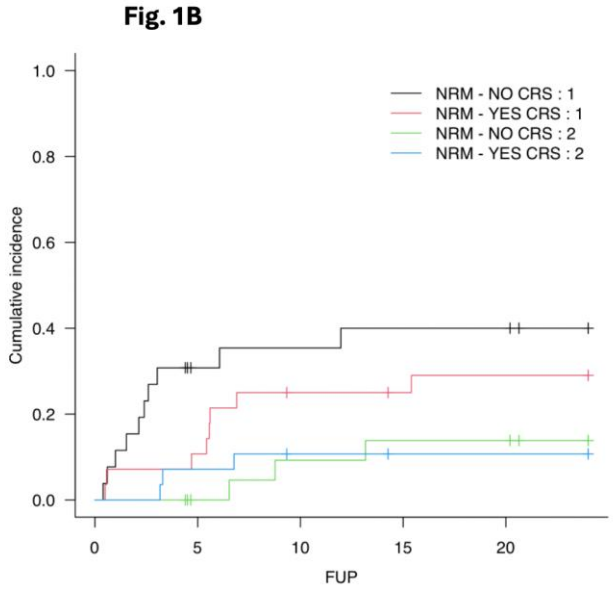


Figure 1A. overall survival in patients undergoing transplant in CR>1 according to the presence of CRS.
Figure 1B. non-relapse mortality and incidence of relapse death according to the presence of CRS in patients undergoing transplant in CR>1. 1=non-relapse mortality; 2=relapse.

Table 1. Patients characteristics. AML= acute myeloid leukaemia, MF= myelofibrosis, MDS= myelodysplastic syndrome, ALL= acute lymphoblastic leukaemia, HL= Hodgkin Lymphoma, NHL= non-Hodgkin Lymphoma, GZL= grey zone lymphoma, BPDCN= blastic plasmacytoid dendritic cell neoplasm, DLBCL= diffuse large B-cell lymphoma, PLL= prolymphocytic leukaemia, MDS/MPN-U= myelodysplasia/myeloproliferative neoplasm unspecified, MPAL= mixed phenotype leukaemia, CML= chronic myeloid leukaemia, CRS= cytokine release syndrome.

Patients' characteristics	**N (%)**
Total	104 (100)
Male	66 (63)
Female	38 (37)
Median age (range)	55 (16–76)
Diagnosis	
AML	45 (43,3)
MF	10 (9,6)
MDS	10 (9,6)
B-ALL	8 (7,7)
T-ALL	6 (5,7)
HL	6 (5,7)
NHL T	4 (3,8)
GZL	3 (2,9)
BPDCN	3 (2,9)
DLBCL	2 (1,9)
T-PLL	2 (1,9)
MDS/MPN U	1 (1)
T/HRBCL	1 (1)
MPAL	1 (1)
NHL B	1 (1)
CML	1 (1)
Disease Status at transplant	
First Complete Remission	39 (37,5)
Advanced disease	65 (62,5)
Donor relationship	
Brother/Sister	34 (32,7)
Son/Daughter	54 (51,9)
Parents	15 (14,4)
Other	1 (1)
Female donor for male recipient	24 (23)
HCT-CI	
<3	46 (44,2)
≥3	58 (55,8)
CRS	
YES	44 (51)
NO	42 (49)
Months of median follow up (range)	17 (0–115)

Notably, no patients received specific treatment for CRS, and clinical manifestations resolved after post-transplant cyclophosphamide administration. This observation supports the hypothesis that CRS in this setting is driven by early alloimmune activation, subsequently modulated by PTCy, as suggested by other groups.[9-11]

This study has several limitations, including its retrospective design, single-center setting, and limited sample size, particularly for subgroup analyses. In addition, the cohort was heterogeneous and included different hematologic malignancies with distinct relapse risks and potentially different sensitivities to graft-versus-leukemia effects. The relatively small number of severe CRS cases also precluded a meaningful analysis

according to CRS grade. Finally, the exclusion of patients with early documented infections, although intended to improve diagnostic specificity for CRS, may have introduced selection bias. In conclusion, CRS after haplo-HSCT was associated with improved survival in patients with advanced disease, without evidence of increased TRM. These findings suggest that CRS may reflect early alloimmune activation after transplantation; however, the retrospective design, limited sample size, and cohort heterogeneity preclude definitive conclusions regarding a graft-versus-tumor effect. Larger prospective studies are needed to validate these observations.

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Competing interests: The authors declare no competing interest.

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