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Letters to the Editor

Interpreting MRD and Chimerism After Allogeneic Transplantation for Acute Leukemia

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To the editor.

Öksüz and colleagues report a valuable single-center comparison of multiparameter flow cytometry (MFC) measurable residual disease (MRD) and short-tandem-repeat (STR) donor chimerism for relapse prediction after allogeneic transplantation in 264 adults with acute leukemia.[1] Their central message, that month-3 MRD carries independent prognostic weight in acute myeloid leukemia (AML), is consistent with the wider literature.[2] I read the paper with interest and raise four points that fall outside the limitations the authors themselves acknowledge, and that bear on how their findings can be translated into a surveillance protocol.

MRD positivity is defined without a threshold or reported assay sensitivity. The principal claim rests on a dichotomous month-3 MFC-MRD variable (adjusted hazard ratio [HR] 3.69), yet positivity is defined only as "any measurable MRD level," with 100,000 to 500,000 nucleated cells acquired and no reported assay-specific limit of detection (LOD) or limit of quantification (LOQ). The 2021 European LeukemiaNet consensus recommends acquisition of more than 500,000 CD45-expressing cells with at least 100 viable cells in the relevant blast compartment to establish MFC-MRD negativity, together with calculation of assay-specific LOD and LOQ for each panel.[3] The 2025 ELN-DAVID update defines MFC-MRD positivity as ≥0.1%, introduces a low-level category below 0.1% but above the limit of quantification as a warning sign, and requires a minimum of 500,000 CD45-expressing cells to report a negative result.[4] Samples at the lower end of the reported acquisition range therefore do not meet the current denominator for establishing MRD negativity, and a single "any detectable" category may combine results of materially different analytical sensitivity.

This is not a purely technical objection. In the AML cohort, 22 of 100 patients without observed relapse were MRD-positive at month 3. This does not establish false positivity, since follow-up duration and any post-MRD interventions may have influenced outcome; it does show that a binary positive result is not synonymous with impending relapse. Before such a result is used to trigger pre-emptive donor lymphocyte infusion, immunosuppression withdrawal, or hypomethylating therapy, readers need the distribution of MRD values, the assay LOD and LOQ, and analyses using prespecified, assay-supported thresholds. The positive predictive value at clinically relevant time horizons would also be needed to estimate the treatment burden of an MRD-triggered strategy.

Neither "earlier" nor "more sensitive" was established in a paired comparison. The abstract states that MRD detected relapse "earlier and with greater sensitivity than chimerism. Neither claim was demonstrated head-to-head. Among 68 relapsing AML patients, mixed chimerism was detected before overt relapse in 36 (52.9%), whereas MFC-MRD was detected pre-emptively in only 30 (44.1%). MRD reached 55.9% only after adding 8 patients in whom it was first detected at or near overt relapse, which offers little opportunity for pre-emptive intervention. On the authors' own numbers, routine STR chimerism anticipated a larger proportion of AML relapses than MFC-MRD did.

The reported median lead times (177 days for MRD versus 90 days for chimerism) suggest that MRD may provide a longer warning interval when it does become positive. These medians, however, were calculated within different marker-positive subsets and under unequal surveillance schedules, since chimerism was assessed at five timepoints and MFC-MRD at three. They therefore do not establish consistently earlier

detection in the same patients.

In the unadjusted analysis, mixed chimerism had the larger hazard estimate (HR 3.78 vs 2.69), whereas the adjusted estimates were 2.47 and 3.69, respectively. Such changes may legitimately arise from adjustment for correlated prognostic factors, but they illustrate that HR magnitude is model-dependent and should not be interpreted as a direct ranking of diagnostic performance. Reporting the number of patients with both month-3 assays available and entered into the joint model, together with paired sensitivity, specificity, time-dependent discrimination, and the incremental value of each marker, would allow the comparison the abstract asserts. As currently worded, the conclusion risks prompting clinicians to deprioritize chimerism monitoring in a way these data do not support.

The Results text and Table 2 disagree on cytogenetic risk. The Results state that high-risk cytogenetics were more frequent among relapsed AML patients (p = 0.049). Table 2 shows the opposite: high-risk disease was present in 18 of 68 relapsed patients (26.5%) versus 52 of 118 non-relapsed patients (44.1%). The univariate HR (0.61, 95% CI 0.36–1.05) is consistent with the table rather than the text, and the Discussion subsequently states that no association with high-risk classification was found. This directional discrepancy should be corrected; as printed, it will mislead readers.

The reason for the unexpected direction cannot be determined from the data presented and may reflect coding, selection, risk-category definitions, sampling variation, or competing mortality. Separately, 42 AML patients died without documented relapse. A cause-specific Cox model validly addresses etiologic association, but it does not provide the absolute probability of relapse that surveillance and intervention decisions require. Reporting the cumulative incidence of relapse with non-relapse mortality as a competing event, alongside cause-specific and subdistribution hazard estimates, would let clinicians translate a month-3 biomarker result into an interpretable relapse probability.[5,6] Such an analysis might clarify the risk-classification result, though it cannot be assumed to explain it.

Chronic GVHD appears to have been modeled as a fixed covariate. Chronic graft-versus-host disease (GVHD) is reported as protective against relapse in univariate analysis (HR 0.51) and is described as protective in the Discussion. Chronic GVHD, however, is a post-transplant, time-dependent exposure whose status is not known at baseline and may become established before or after the month-3 landmark. Patients who relapse or die before developing chronic GVHD cannot become exposed, so analyzing eventual GVHD status as an ordinary fixed covariate introduces guarantee-time bias favoring the relapse-free group.[7] The authors appropriately landmarked MRD and chimerism to address precisely this problem. Chronic GVHD should be handled the same way, either as a time-dependent covariate or in a prespecified landmark analysis based only on GVHD status established by that landmark. The attenuated and non-significant adjusted estimate (HR 0.72, p = 0.446) does not remove the design concern. As analyzed, the study cannot establish that chronic GVHD itself conferred a protective graft-versus-leukemia effect.

None of these points detracts from the study's core contribution. The dataset is a good one and the question it addresses is clinically pressing. Reporting the assay thresholds, framing the MRD-versus-chimerism comparison as unpaired, correcting the cytogenetic discrepancy, and accounting for competing risk would allow other centers to translate these findings into a genuinely risk-adapted surveillance strategy. I thank the authors for a valuable contribution.

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Competing interests: The authors declare no competing interest.

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References:

1. Öksüz SBT, Seval GC, Dalva K, Toprak SK. Post-transplant relapse in acute leukemia: comparative value of MRD and chimerism. Mediterr J Hematol Infect Dis. 2026;18(1):e2026028. https://doi.org/10.4084/MJHID.2026.028
2. Loke J, McCarthy N, Jackson A, Siddique S, Hodgkinson A, Mason J, Crawley C, Gilleece M, Peniket A, Protheroe R, Kirkland K, Craddock C. Posttransplant MRD and T-cell chimerism status predict outcomes in patients who received allografts for AML/MDS. Blood Adv. 2023;7(14):3666-3676. https://doi.org/10.1182/bloodadvances.2022009493
3. Heuser M, Freeman SD, Ossenkoppele GJ, Buccisano F, Hourigan CS, Ngai LL, Tettero JM, Bachas C, Baer C, Béné MC, Bücklein V, Czyz A, Denys B, Dillon R, Feuring-Buske M, Guzman ML, Haferlach T, Jorgensen JL, Kern W, Lacombe F, Maurillo L, Preudhomme C, van der Reijden BA, Thiede C, Venditti A, Vyas P, Wood BL, Walter RB, Döhner K, Roboz GJ, Cloos J. 2021 update on MRD in acute myeloid leukemia:

a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753-2767. https://doi.org/10.1182/blood.2021013626
4. Cloos J, Valk PJM, Thiede C, Döhner K, Roboz GJ, Wood BL, Walter RB, Wang S, Wierzbowska A, Wei AH, Wu D, Vergez F, Venditti A, van der Reijden BA, van de Loosdrecht AA, Tiong IS, Thol FR, Subklewe M, Roumier C, Reuvekamp T, Ravandi F, Preudhomme C, Plesa A, Othman J, Ossenkoppele GJ, Ofran Y, Mimoun A, Maurillo L, Majchrzak A, de Leeuw D, Kern W, Kim DDH, Ikoma-Colturato MRV, Haaksma LH, Guzman ML, Feuring M, Depreter B, Czyz A, Bücklein V, Baer C, Bachas C, Freeman SD, Buccisano F, Hourigan CS, Dillon R, Heuser M. 2025 update on MRD in acute myeloid leukemia: a consensus document from the ELN-DAVID MRD Working Party. Blood. 2026;147(11):1147-1167. https://doi.org/10.1182/blood.2025031480
5. Iacobelli S; EBMT Statistical Committee. Suggestions on the use of statistical methodologies in studies of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48(Suppl 1):S1-S37. https://doi.org/10.1038/bmt.2012.282
6. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol. 2013;66(6):648-653. https://doi.org/10.1016/j.jclinepi.2012.09.017
7. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31(23):2963-2969. https://doi.org/10.1200/JCO.2013.49.5283