# Is it time for age and clinically adjusted minimal residual disease interpretation in acute myeloid leukemia?

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The introduction of sensitive molecular methods enabling the detection of minimal residual disease (MRD) revolutionized decision trees in acute myeloid leukemia (AML). As for any other laboratory tests, even sensitive tests assessing MRD at the level of $10^{-4}$-$10^{-5}$ have false negatives and false positives. In the current issue of *Haematologica*, Mannelli and colleagues retrospectively explored the influence of patients' clinical context, (age, genetic profile, and intensity of pre-MRD testing therapy) on the relapse-free and overall survival predictive value of MRD results.[1] Different methods of MRD evaluation were used: real-time polymerase chain reaction (RT-PCR) MRD testing in patients presenting with core binding factor or *NPM1*-mutated leukemia, and immunophenotype for all other patients. Only patients who achieved morphological complete remission after one induction cycle and completed a second intensive chemotherapy consolidation cycle, with available MRD results after the first and second chemotherapy cycles were included.

In accordance with previously published results, the rate of MRD eradication in the whole group of 194 AML patients was 56.7% and 62.4% following the first and second treatment cycles (MRD2), respectively. A negative result at that point ($MRD2^{neg}$) was most predictive of relapse-free and overall suvival. Notably, in different subgroups, the achievement of a $MRD2^{neg}$ status was associated with different outcomes. For patients younger than 55 who were $MRD2^{neg}$ with standard-dose cytarabine, the 3-year progression-free survival was 86.4% while it was only 46.6% for older adults treated with high-dose cytarabine. The rate of 2017 European LeukemiaNet adverse-risk patients were 16.9% and 2% ($P$=0.014) among those treated with high- or standard-dose cytarabine, respectively. The utilization of allogenic stem cell transplantation was, as expected, higher among high-risk patients and the more sensitive method of MRD evaluation of RT-PCR was only used in standard-risk patients. A study that is powered adequately to evaluate the prognostic value of MRD2 negativity in all potential clinical scenarios would have to be huge and would be very difficult to execute. However, despite the limitations of the study by Mannelli *et al.*, important principles can be learnt.

First and foremost, once again the prognostic power of a $MRD2^{neg}$ status and its role as a desired milestone along AML therapy are being confirmed. Unfortunately, uniformly across all MRD studies in AML patients, rates of false negative (patients who eventually relapse despite being $MRD2^{neg}$) and false positive (patients who remain in remission despite being $MRD^{pos}$) MRD2 results are substantial. Relapse rates despite MRD2 negativity vary between 10-25% in younger, standard-risk AML patients[2,3] to 45-60% in older adults with adverse-risk leukemia.[4,5] Therefore, current guidelines strongly encourage the use of MRD in standard-risk AML and are less determined in poorer risk cases.[6]

The current work by Mannelli and colleagues suggests that adjusting MRD results to patients' clinical context is feasible and makes interpretation more accurate. Since huge studies that could yield statistically powerful MRD survival data for each subgroup segregated by a combination of age, ELN risk, induction/consolidation regimen, transplantation and MRD laboratory test used are not going to happen, a clinically relevant working interpretation paradigm is required. As a general medical rule, the prevalence of faulty results (relapse despite $MRD^{neg}$ or continuous remission despite $MRD^{pos}$ status) is influenced by a test's properties but also by pre-test probability of relapse.[7]

As illustrated in Figure 1, in high-risk leukemia, achievement of a $MRD2^{neg}$ status reduces the risk of relapse, but this risk remains high enough to justify the morbidity and mortality associated with allogeneic stem cell transplantation. In such cases MRD tests are more likely to identify those who are at extreme high risk of relapse ($MRD^{pos}$ high-risk leukemia). In contrast, for patients with standard-risk leukemia, being $MRD2^{neg}$ is reassuring and may justify avoiding allogeneic stem cell transplantation. Mannelli *et al.* demonstrated that age is probably the strongest discriminator of adverse risk. Dose intensity of induction

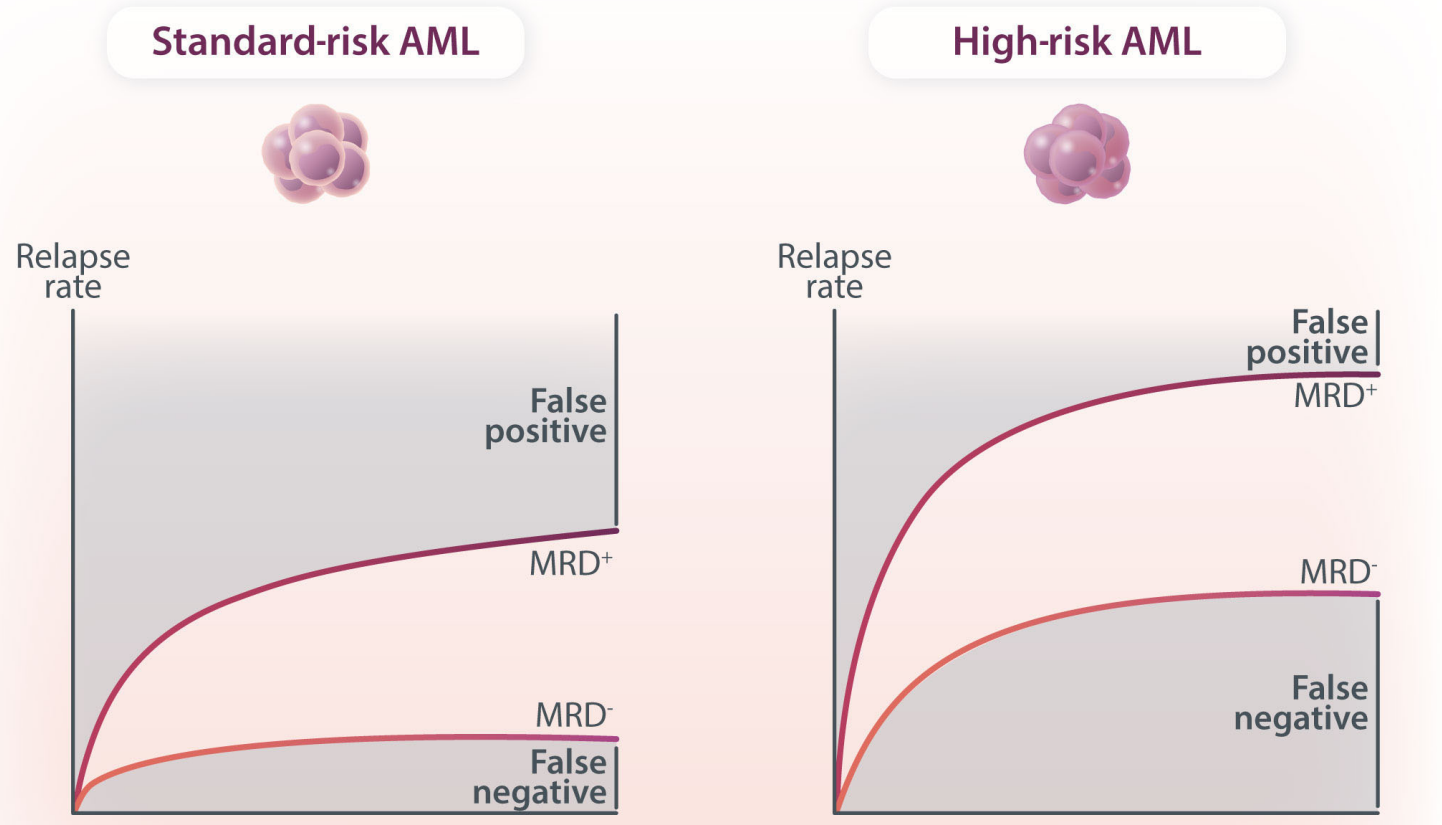


**Figure 1. The clinical impact of minimal residual disease in different clinical scenarios.** AML: acute myeloid leukemia; MRD: minimal residual disease.

(by cytarabine dose) also emerged as an important factor in their study, although in another study, when intensive and non-intensive regimens were compared, the pre-MRD testing therapy effect was not statistically significant.[8] Due to the retrospective nature of the work and the fact that groups divided by cytarabine doses were imbalanced I would vote for European LeukemiaNet risk as the second factor to be considered after age. In conclusion, assessing MRD is fundamental during AML therapy, but results should be interpreted completely differently in high- and standard-risk situations.

**Disclosures**

*No conflicts of interests to disclose.*

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