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Refining risk within *RUNX1::RUNX1T1*-positive AML: Unmasking a hidden high-risk subgroup

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Precision medicine in oncology is based on a simple expectation: molecular diagnosis should not only define disease subtypes, but also help estimate prognosis and guide treatment. In acute myeloid leukemia (AML), recurrent cytogenetic abnormalities have played this role for many years. One example is t(8;21)(q22;q22.1), which generates the *RUNX1::RUNX1T1* (RR) fusion and defines a biologically distinct subgroup. Patients with this fusion, both children and adults, are usually assigned to a favorable-risk category and are often not considered for hematopoietic stem cell transplantation (HSCT) in first remission. Still, this favorable-risk label does not apply equally to every patient, and some individuals with *RUNX1::RUNX1T1*-positive AML go on to relapse or die despite apparently favorable genetics. In this issue of The Innovation, Xun et al. address this problem by developing a simple model based

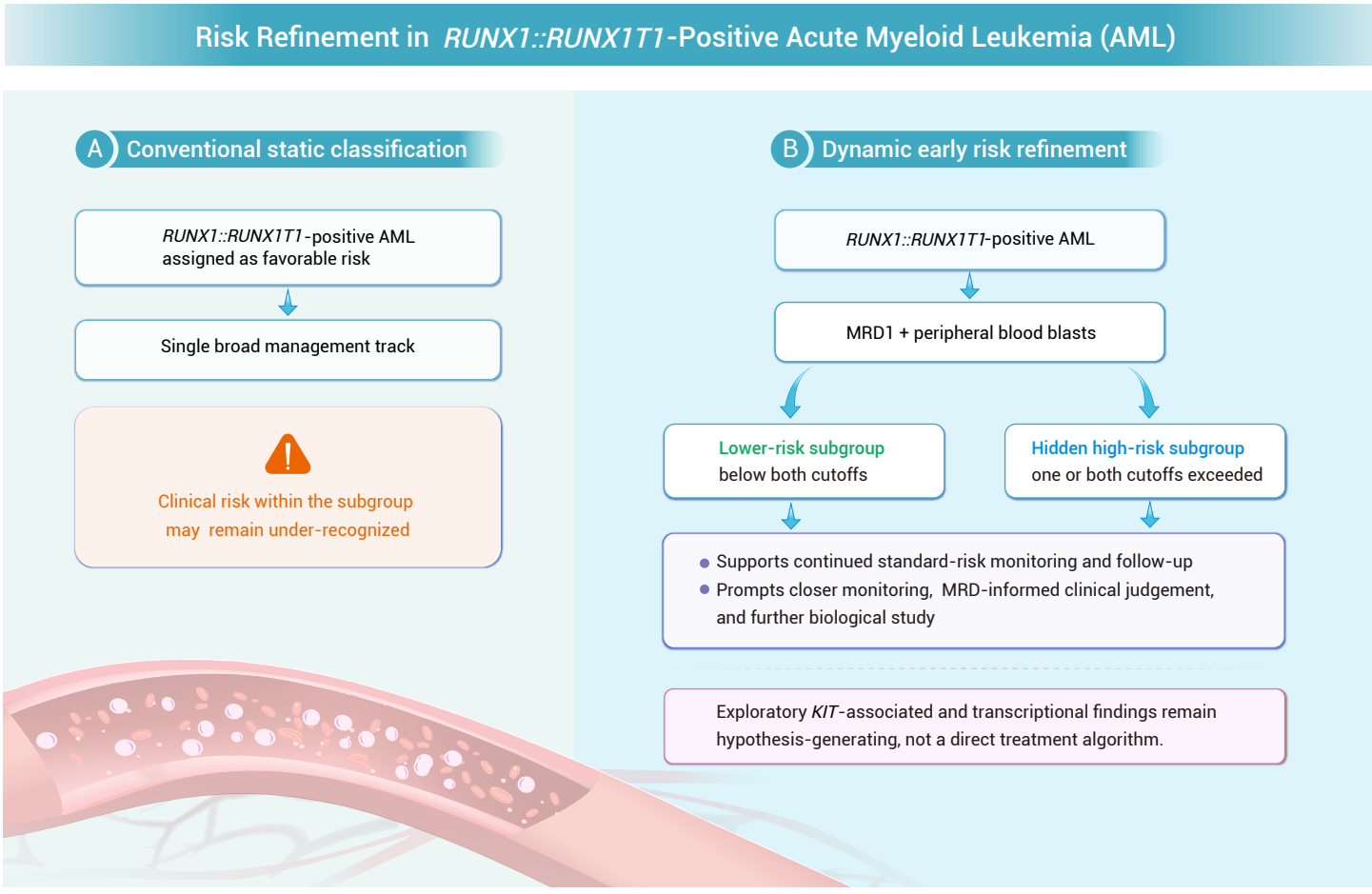

Figure 1. Risk refinement in *RUNX1::RUNX1T1*-positive AML (A) A conventional static risk label based primarily on the presence of the *RUNX1::RUNX1T1* fusion may mask clinically important heterogeneity within this subgroup. (B) A revised framework, inspired by Xun et al., integrates accessible clinical variables—MRD1 and peripheral blood blast percentage—into an early risk model that helps identify a hidden high-risk subgroup. Rather than serving as a stand-alone treatment algorithm, this approach is better understood as a way to refine early risk assessment and to support closer monitoring, MRD-informed clinical judgment, and future investigation of biologically distinct high-risk cases.

on minimal residual disease after induction (MRD1) and peripheral blood blast percentage at diagnosis to identify a hidden high-risk subgroup within pediatric *RUNX1::RUNX1T1*-positive AML.[1]

Xun and colleagues analyzed 284 RR+ pediatric AML cases from public datasets and validated the model externally in 214 patients from three Chinese centers.[1] Rather than relying only on broad cytogenetic classification, their model incorporates two routinely available variables: MRD1 and peripheral blood blast percentage at diagnosis. This is a particular strength of the study, because both measures are already part of routine AML assessment and are readily interpretable in clinical practice.

The model uses a limited number of variables, but its stratification result is clinically relevant. Patients were classified as RR+ low risk only when both peripheral blood blast percentage and MRD1 were below the prespecified cutoffs; the remaining patients were assigned to the RR+ high-risk group. In the training cohort, peripheral blood blasts ≥67.5% and MRD1 ≥0.015 were independently associated with poorer overall survival. Based on these two

variables, 37.4% of evaluable patients were classified as high risk. This group showed inferior OS and EFS, with a 5-year OS of 73.0%, compared with 91.0% in the low-risk group. Together, these findings show that clinically meaningful heterogeneity persists within *RUNX1::RUNX1T1*-positive AML, despite its usual classification as favorable-risk disease.

KIT mutations were detected in 107 of 298 patients in the combined RR+ cohorts, accounting for 35.9% of cases, and exon 17 mutations were the most common subtype. *KIT*-mutated patients had worse OS and EFS, with exon 17 mutations showing the strongest adverse association. Among RR+ high-risk patients with *KIT* mutations, dasatinib was associated with improved OS and EFS, whereas this benefit was not observed in the low-risk group.[1-2] These findings are noteworthy, but they should be interpreted with caution. Because the study was retrospective, the observations related to *KIT* mutations and dasatinib are better viewed as exploratory than practice-changing. At present, their main value is to suggest directions for future prospective study rather than to support immediate changes in routine management. Accordingly, these observations are better understood as signals for future investigation than as the basis for a ready-to-use therapeutic pathway. The main clinical message of the study, however, lies in earlier recognition of high-risk disease through MRD1 and peripheral blood blast percentage rather than in immediate therapeutic redirection. In that sense, the main contribution of the work is to refine early risk assessment in *RUNX1::RUNX1T1*-positive AML. Such refinement may support closer monitoring and MRD-informed clinical judgment. In appropriate clinical settings, it may also prompt more careful consideration of treatment intensification or transplantation strategies.[3]

The model proposed by Xun et al. follows a similar logic in *RUNX1::RUNX1T1*-positive AML. It does not discard the importance of the fusion, but adds early clinical information to identify patients whose outcomes may differ from what the conventional favorable-risk label would suggest. More generally, the study underscores a familiar problem in AML risk assessment: molecular classification alone does not fully capture clinical outcome.[4] Existing prognostic systems are therefore best viewed as a foundation rather than a final answer. They provide the initial structure for risk assignment, but additional clinical and biological information is often needed to refine that assessment. In this context, the study by Xun et al. supports a more dynamic approach to risk stratification, in which the initial diagnosis is continually reassessed using peripheral blood findings, treatment response, MRD status, and other relevant data.

This study may also inform the design of future clinical trials. Instead of using a single molecular marker as the main basis for enrollment, trials could consider a more refined risk profile that combines baseline disease biology with early treatment response. In high-risk, *KIT*-negative RR-AML patients, Xun et al. further performed transcriptional profiling and identified several potential therapeutic directions, including changes related to CD200 and TLR3. These observations are noteworthy but should be interpreted cautiously. Because the study was retrospective, the *KIT*- and dasatinib-related findings are better viewed as exploratory than practice-changing.

Before such an approach can be widely used, several practical issues need to be addressed. Although the model relies on variables that are generally available in clinical practice, MRD testing still varies across laboratories, particularly with respect to assay platform, sensitivity, gating strategy, and reporting format. Whether MRD is measured by flow cytometry or RT-qPCR, broader application of this model will require more consistent methodology and standardized interpretation, as emphasized by the European LeukemiaNet MRD Working Party.[5] The validation of the model in patients older than 28 years is also noteworthy, but it should be interpreted as a reason for further study rather than immediate extension to all adult patients. Future work should evaluate this framework across different age groups, treatment regimens, and clinical settings. Such work will be important in clarifying how broadly this model can be applied and whether it can meaningfully improve risk-adapted management in *RUNX1::RUNX1T1*-positive AML. At the same time, the study remains retrospective, and its predictive performance is moderate rather than definitive; broader clinical adoption and treatment implications will require prospective validation.

By identifying a substantial proportion of *RUNX1::RUNX1T1*-positive patients with poorer outcomes, the model refines a category that may otherwise be applied too broadly. Its main strength is that it uses simple clinical variables that are already available in routine care, while also pointing to areas that warrant further biological and clinical investigation. For patients whose disease does not follow the expected favorable-risk course, earlier recognition could support closer monitoring, more appropriate risk-adapted therapy, and enrollment in clinical studies better matched to their risk profile. Overall, this work supports a stepwise approach to AML risk assessment: established genetic categories remain the starting point, but they should be refined over time using treatment response, residual disease, and other clinically relevant biological information. Importantly, this framework is best viewed as a tool for earlier risk recognition rather than as a stand-alone therapeutic algorithm.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.