Persistent DNMT3A Mutations Predicting Relapse After Acute Myeloid Leukemia Remission: A Systematic Review of Molecular Persistence and Circulating DNA Dynamics

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Background

- **DNMT3A** is one of the most common mutations in Acute Myeloid Leukemia (AML).
- It is also frequently detected in age-related clonal hematopoiesis (CHIP).
- Persistent DNMT3A during remission creates uncertainty in distinguishing benign clones from true measurable residual disease (MRD).
- Accurate differentiation is essential for predicting relapse and guiding treatment.

Methods

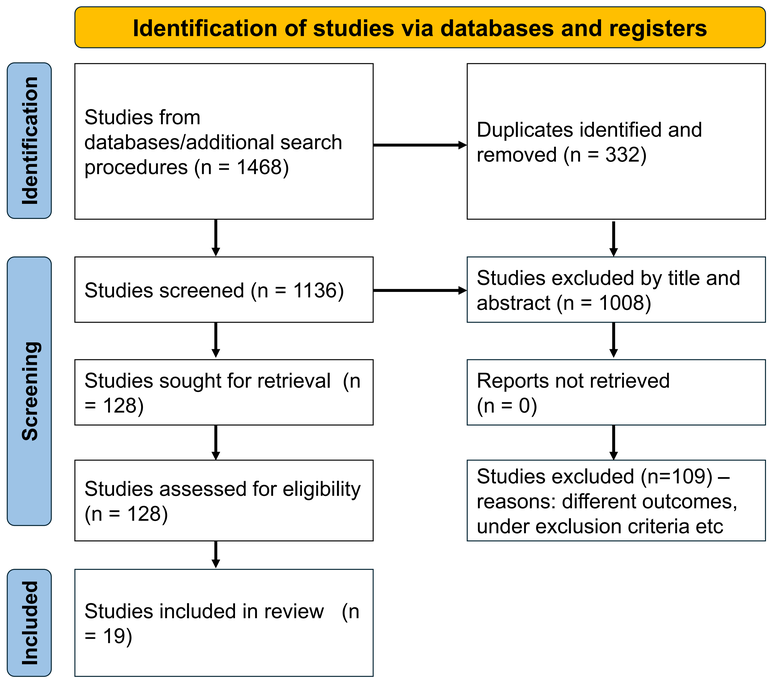
PRISMA 2020 systematic review.

Searched PubMed, Embase, Cochrane Library, and Web of Science

Included adults with DNMT3A-mutated AML in first complete remission.

MRD assessed using ultra-sensitive NGS and plasma cfDNA.

Evaluated Relapse-Free Survival, Overall Survival, cfDNA kinetics, and co-mutation status.



Objectives

- Evaluate whether persistent DNMT3A mutations independently predict AML relapse.
- Assess the role of plasma cell-free DNA (cfDNA) kinetics in distinguishing residual leukemia from CHIP.
- Examine the prognostic impact of co-mutation clearance on relapse risk.

Results

Key Findings:

- 19 studies involving 3,298 patients were included.
- Persistent DNMT3A alone did not independently predict relapse.
- Driver mutation co-persistence was associated with a substantially higher relapse risk.
- Rising plasma cfDNA DNMT3A levels strongly predicted impending relapse (>90% PPV).
- Co-mutation clearance (e.g., *NPM1*, *FLT3-ITD*) was the strongest favorable prognostic factor.

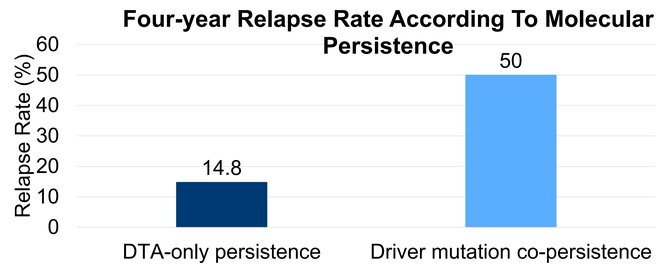


Figure 1. Comparison of the 4-year relapse rate between patients with isolated DTA (DNMT3A/TET2/ASXL1) persistence and those with persistent driver mutations. Co-persistence of driver mutations was associated with a substantially higher risk of relapse.

Table 1. Summary of Major Findings

Parameter	Finding	Clinical Significance
Bone marrow DNMT3A persistence	Did not independently predict relapse	Poor standalone MRD marker
DTA-only persistence	14.8% relapse rate	Lower relapse risk
Driver mutation co-persistence	50% relapse rate	Higher relapse risk
Rising plasma cfDNA DNMT3A	PPV >90%	Strong predictor of impending relapse
Co-mutation clearance	Best protective factor	Favorable prognosis

Key Clinical Message

- Persistent DNMT3A alone does not predict relapse. Integrating plasma cfDNA kinetics with co-mutation clearance offers a more accurate strategy for measurable residual disease assessment and relapse prediction in AML..

Conclusion

- Persistent DNMT3A mutations should **not** be used as a standalone MRD marker.
- Plasma cfDNA kinetics provide superior discrimination between CHIP and residual leukemia.
- Clearance of co-occurring driver mutations remains the strongest predictor of favourable outcome.
- Integrating cfDNA dynamics with co-mutation analysis enables more accurate relapse prediction and personalized risk assessment.

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