IMPACT OF CLONAL HEMATOPOIESIS ON OUTCOMES AFTER HEMATOPOIETIC CELL TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

Clonal hematopoiesis (CH) — a recurrent somatic mutation in hematopoietic cells — is enriched by prior cytotoxic therapy. Its role as a modifier of outcomes after hematopoietic cell transplantation (HCT) is increasingly recognized, yet its gene-specific impact across autologous (auto-HCT) and allogeneic (allo-HCT) transplantation has not been systematically quantified.

AIM

To evaluate, via systematic review and meta-analysis, the association between CH and:

- Therapy-related myeloid neoplasms (t-MN)
- Overall survival (OS)
- Non-relapse mortality (NRM)
- Relapse

— *across auto-HCT and allo-HCT recipients.*

METHOD

- Primary outcome: t-MN after auto-HCT. Secondary: OS, NRM, relapse
- risk-of-bias assessment (Newcastle-Ottawa Scale)
- Random-effects (DerSimonian-Laird) models pooled hazard ratios (HR) with 95% CI; heterogeneity via I^2 and Cochran's Q
- Prespecified subgroups: gene (DNMT3A, TET2, TP53, PPM1D) and VAF (2–10% vs ≥ 10%)
- Sensitivity analyses excluded studies with < 5 t-MN events

CONCLUSIONS

CH exerts gene-specific and VAF-dependent effects that diverge across transplant platforms.

- Auto-HCT: TP53/PPM1D-CH is strongly linked to t-MN, inferior survival, and higher NRM; DNMT3A-CH appears clinically neutral
- Allo-HCT: donor DNMT3A-CH is associated with reduced relapse — consistent with a graft-versus-leukemia effect — without a clear survival detriment

These findings support incorporating gene-specific, VAF-informed CH profiling into pre-transplant risk stratification.

RESULTS

Fifteen studies (>15,000 patients) were included.

Auto-HCT (n>10,000): CH was associated with markedly increased t-MN risk (HR 4.85, 95% CI 2.39–9.82; I^2=28%), driven largely by TP53/PPM1D-mutated clones (aHR 7.29, 95% CI 1.72–30.94); DNMT3A-CH was not associated with increased risk. CH also predicted inferior OS (HR 1.34, 95% CI 1.21–1.49) and higher NRM (HR 2.97, 95% CI 1.90–4.64), with a consistent VAF-dependent gradient across outcomes.

Allo-HCT: Donor-derived CH was associated with lower relapse risk (HR 0.79, 95% CI 0.67–0.93), driven primarily by DNMT3A clones (sHR 0.59, 95% CI 0.39–0.90), alongside higher chronic GVHD rates. The effect on OS (HR 0.91, 95% CI 0.75–1.11) was not statistically significant.

See Figure 1 and Table 1 for full effect estimates →

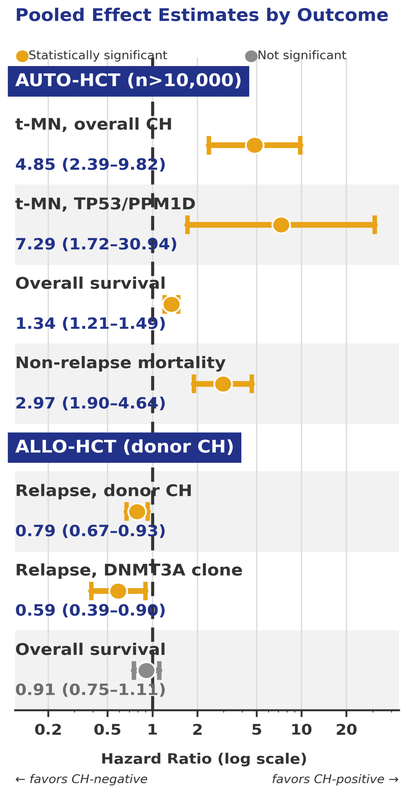

Figure 1. Pooled hazard ratios (HR) with 95% CI for CH-associated outcomes across auto-HCT and allo-HCT. Dasahed line = HR 1.0 (no effect).

Population	Outcome	Effect	95% CI	I^2
Auto-HCT	t-MN, overall CH	HR 4.85	2.39–9.82	28%
Auto-HCT	t-MN, TP53/PPM1D	aHR 7.29	1.72–30.94	—
Auto-HCT	t-MN, DNMT3A	NS	—	—
Auto-HCT	Overall survival	HR 1.34	1.21–1.49	45%
Auto-HCT	Non-relapse mortality	HR 2.97	1.90–4.64	—
Allo-HCT	Relapse, donor CH	HR 0.79	0.67–0.93	—
Allo-HCT	Relapse, DNMT3A clone	sHR 0.59	0.39–0.90	—
Allo-HCT	Overall survival (NS)	HR 0.91	0.75–1.11	—

Table 1. Pooled effect estimates for CH-associated outcomes after HCT.