

“POST-TRANSPLANT EXTRAMEDULLARY VERSUS MEDULLARY RELAPSE IN ACUTE LEUKEMIA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SYSTEMATIC REVIEW, META-ANALYSIS, AND META-REGRESSION OF OBSERVATIONAL STUDIES”

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Introduction

Extramedullary relapse (EMR) after allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly recognized as a biologically distinct failure of graft-versus-leukemia activity, but evidence remains fragmented across small, inconsistently defined single-institution cohorts, leaving incidence estimates ranging from under 1% to over 30%. We performed the largest synthesis to date comparing extramedullary (EM) versus bone marrow (BM) relapse after allogeneic HSCT.

Methods

We systematically searched PubMed, Embase, Cochrane CENTRAL, and ClinicalTrials.gov, identifying 18 eligible retrospective cohorts (6,802 patients, 1,843 relapse events; Newcastle-Ottawa scores 4–8/9). Random-effects models (REML, Hartung-Knapp-Sidik-Jonkman-adjusted) pooled risk ratios (RR) and mean differences across 27 outcomes, with pre-specified subgroup analysis, meta-regression, sensitivity testing, and GRADE certainty rating.

Results

EM relapse was less frequent than BM relapse (RR 0.36, 95% CI 0.27–0.49; I²=84%, significantly explained by case-definition and region), quantifying, to our knowledge for the first time, how much incidence disagreement across the field is definitional rather than biological. EM relapse carried a post-relapse survival advantage (RR 1.70, 95% CI 1.12–2.58) alongside paradoxically higher second-relapse risk (RR 2.12, 95% CI 1.46–3.08). Prior EM disease (RR 3.71, 95% CI 2.01–6.85) and chronic GVHD (RR 2.01, 95% CI 1.46–2.76) were the strongest predictors of relapse pattern. All findings were rated very-low-to-low certainty (GRADE).

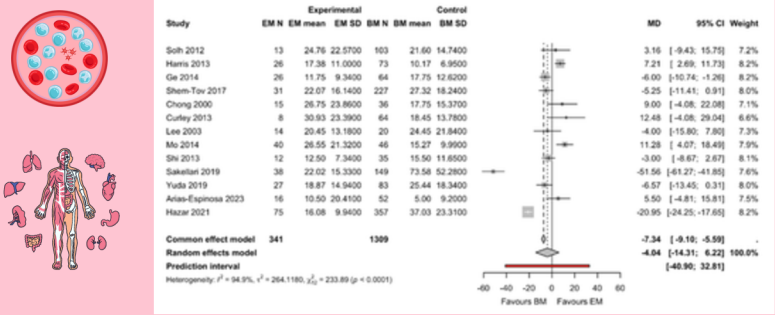
Outcome	Main Result (Extramedullary vs. Bone Marrow)	Effect Size (95% CI)
Relative Frequency	Extramedullary (EM) relapse occurs significantly less frequently than bone marrow (BM) relapse.	RR 0.36 (0.27–0.49)
Time to Relapse	No statistically significant difference was found in how early or late the relapse occurs between compartments.	MD -4.04 months (-14.31 to 6.22)
Early Survival	EM relapse is associated with a 70% higher probability of being alive at follow-up, indicating an early survival advantage.	RR 1.70 (1.12–2.58)
6-Month Mortality	EM relapse is associated with significantly lower mortality at the 6-month mark.	RR 0.49 (0.24–0.97)
Second Relapse Risk	Despite better initial survival, EM relapse does not indicate durable disease control and carries more than twice the risk of a subsequent second relapse.	RR 2.12 (1.46–3.08)
Prior EM Disease	The strongest pre-transplant predictor; patients with prior EM disease are nearly four times more likely to experience an EM relapse phenotype.	RR 3.71 (2.01–6.85)

Literature Search

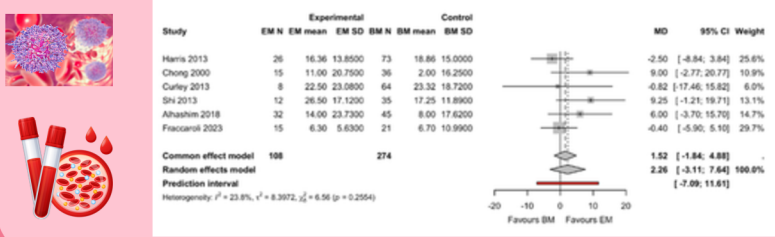


Pooled Results

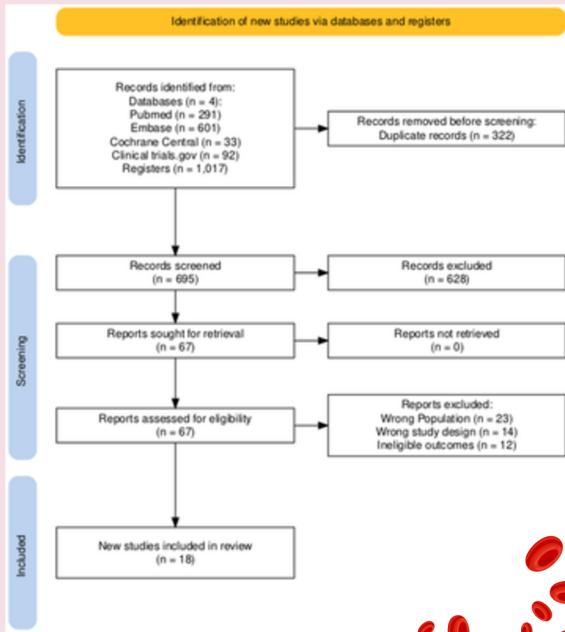
Time to Relapse



Post-relapse Survival



PRISMA Flow sheet



Conclusion

EMR appears to be a rarer, more survivable, yet recurrence-prone relapse pattern with reproducible predictors; standardized definitions and prospective registry validation are needed to confirm these findings and inform risk-adapted surveillance.

References

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