

Research Symposium

Clonal Hematopoiesis as a Predictor of Immune Toxicity and Efficacy After Chimeric Antigen Receptor T-cell Therapy: a Systematic Review and Meta-Analysis

Claire Bischel, BSc¹, Adam Bowen, MD, Kristina Golovataya, MD, Claire Russell, DO, Muhammad Saleem, MD, Sarah Gergis, MD, Katlyn Wendel, Lakshmi Thulluri, MD, Stephen Caucci, DO, Sanjay Rao Gergal Gopalkrishna Rao, MD, Kirolos Gergis, MD, Borys Hrinchenko, MD, PhD

¹ McLaren Greater Lansing Hospital

<https://doi.org/10.51894/001c.164015>

Spartan Medical Research Journal

Vol. 11, Issue 2, 2026

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BACKGROUND

Clonal hematopoiesis of indeterminate potential (CHIP), a form of clonal hematopoiesis (CH), is linked to pro-inflammatory myeloid phenotypes and may influence immune toxicity and efficacy after chimeric antigen receptor (CAR) T-cell therapy. We performed a systematic review and meta-analysis to quantify associations between sequencing-defined CH and clinically significant cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and treatment response after CAR T-cell therapy.

METHODS

We searched PubMed, Embase, CENTRAL, and Web of Science from inception to February 2026 for studies reporting sequencing-defined CH in CAR T recipients and pooled outcomes by CH status using random-effects Mantel-Haenszel models. Primary endpoints were severe CRS and severe ICANS (ASTCT grade ≥ 3).

RESULTS

Nine observational cohorts (n=869) were included. CH status was available for 736 patients (84.7%), with prevalence 24%–56% across study-specific variant allele fraction (VAF)

thresholds (most commonly $\geq 2\%$). Risk of bias was moderate in seven studies and serious in two. Across four cohorts (n=360), CH was not associated with severe CRS (RR 0.72, 95% CI 0.24–2.13) or severe ICANS (RR 1.16, 95% CI 0.48–2.81). Secondary toxicity outcomes were also not significantly different for CRS grade ≥ 2 (RR 1.04, 95% CI 0.73–1.48) or any-grade ICANS (RR 0.89, 95% CI 0.45–1.74). In prespecified analyses restricted to CD19-directed products, CH was associated with higher severe ICANS risk (RR 1.66, 95% CI 1.03–2.65), although estimates were sensitive to study-specific CH/CHIP definitions. CH-positive status was associated with modestly higher overall response (RR 1.10, 95% CI 1.01–1.21) and complete response (RR 1.24, 95% CI 1.01–1.52).

CONCLUSIONS

Across this systematic review and meta-analysis of nine observational cohorts, CH was not associated with increased risk of clinically significant CRS or ICANS after CAR T-cell therapy. Prospective, standardized studies incorporating clone size and genotype, uniform CRS/ICANS assessment, and integrated biomarker and CAR expansion profiling are needed before CH can be meaningfully incorporated into clinical risk stratification or treatment decision-making.

Accepted: June 15, 2026 EDT. Published: July 31, 2026 EDT.

