Clinical Predictors of Severe Cytokine Release Syndrome in CAR T Cell Therapy for B Cell Malignancies: A Systematic Review and Meta-Analysis

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1 Context

Cytokine release syndrome (CRS) is the most frequent and potentially life-threatening complication of chimeric antigen receptor (CAR) T cell therapy for B cell malignancies. Early identification of patients at high risk for severe CRS (sCRS) is essential for timely intervention and safe clinical management as CAR T therapy continues to expand worldwide, across both academic and community treatment settings.

2 Objective

To systematically evaluate and quantify clinical and laboratory predictors associated with severe CRS after CAR T therapy for B cell malignancies, with the goal of informing risk-stratified monitoring and prophylactic strategies.

3 Design

A systematic review and meta-analysis was conducted following PRISMA guidelines. PubMed, Embase, Web of Science, and Cochrane databases were searched from January 2018 to March 2026. Random-effects models pooled odds ratios (ORs) and 95% confidence intervals (CIs) for predictors of grade ≥3 CRS according to ASTCT consensus criteria, with heterogeneity assessed using the I^2 statistic.

4 Setting

Data were gathered from clinical trials and institutional series across major tertiary cancer centers in North America, Europe, and Asia, reflecting real-world CAR T delivery across diverse practice settings.

5 Participants

Twenty-nine studies including 4,612 patients with relapsed or refractory B cell malignancies were analysed. Study populations encompassed both pediatric and adult patients treated with anti-CD19 or dual-target CAR constructs across a range of disease subtypes.

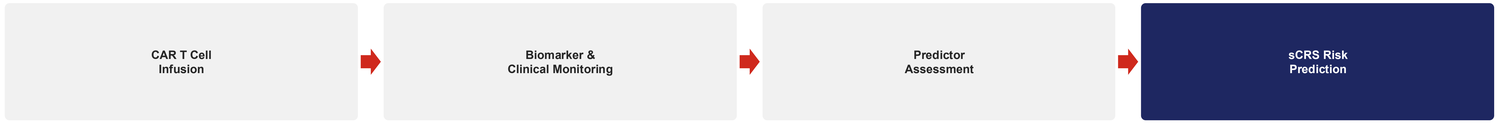
6 Interventions

Standard CAR T cell therapies, including axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel, administered per institutional protocols, were included — reflecting the range of commercially available CD19-directed products.

7 Main Outcome Measures

Incidence and predictors of severe CRS across included studies, with predictors evaluated individually and within composite clinical-biomarker models.

Results



11.8%

pooled incidence of severe CRS (95% CI 9.4–14.1)

AUC 0.85

predictive accuracy of composite clinical + biomarker models

OR 3.41

for severe CRS with an early post-infusion IL-6 surge (95% CI 2.28–5.02)

- High baseline tumor burden increased the odds of severe CRS more than threefold (OR 3.25; 95% CI 2.12–4.99).
- Elevated pre-infusion ferritin >3,000 ng/mL nearly tripled the odds of severe CRS (OR 2.87; 95% CI 1.76–4.65).
- An early post-infusion IL-6 surge was the strongest predictor identified (OR 3.41; 95% CI 2.28–5.02).
- Day 7 cytopenias were independently associated with severe CRS (OR 1.94; 95% CI 1.25–3.03).
- Composite models integrating clinical and inflammatory markers achieved strong predictive accuracy (AUC ≈ 0.85).

Conclusions

Severe CRS occurs in approximately one in nine patients receiving CAR T therapy for B cell malignancies. High tumor burden, elevated inflammatory biomarkers, and early hematologic toxicity reliably predict sCRS.

Standardized, prospectively validated scoring systems are needed to guide prophylactic and therapeutic strategies — improving the safety and precision of CAR T cell therapy as its use continues to expand.

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