

THE GOLDILOCKS ZONE OF ADIPOSITY: A RESTRICTED CUBIC SPLINE META-ANALYSIS OF CONTINUOUS BMI AND THE NON-LINEAR RISK OF SEVERE CRS AND ICANS IN CAR-T CELL THERAPY

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BACKGROUND

- Obesity has emerged as a modifiable risk factor for severe toxicities following chimeric antigen receptor T-cell (CAR-T) therapy, yet the dose-response relationship between body mass index (BMI) and cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) remains poorly characterized.

OBJECTIVE

- To elucidate the continuous, non-linear association between BMI and severe CAR-T toxicities using restricted cubic spline (RCS) meta-analysis.

METHODS



Study Design
Systematic review & meta-analysis



Population
12 studies, 4,218 patients
CD19- or BCMA-directed CAR-T therapy



Statistical Approach



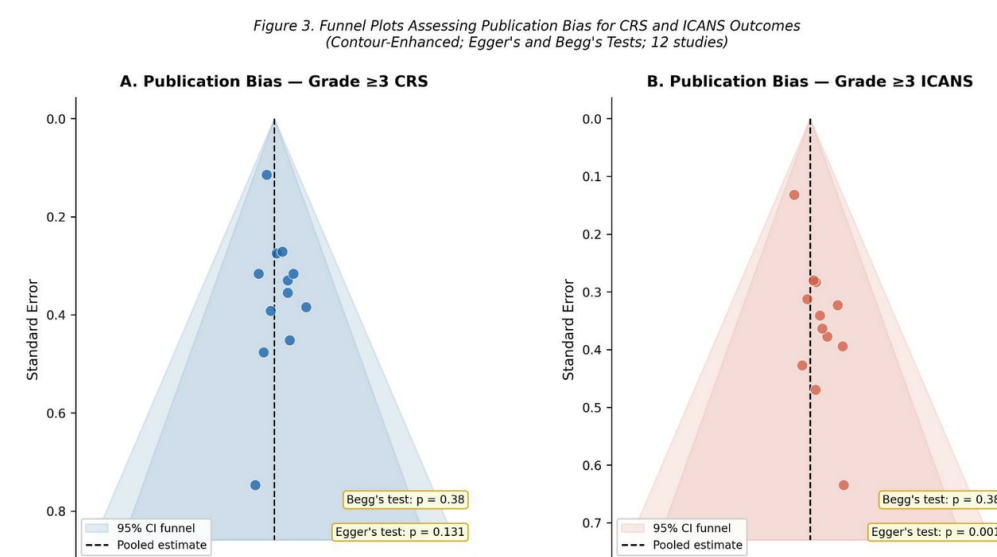
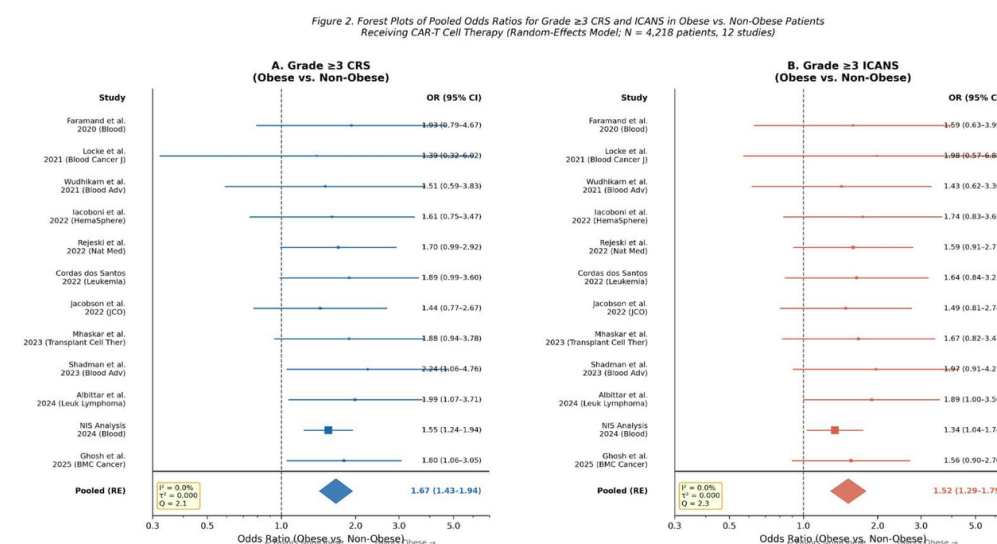
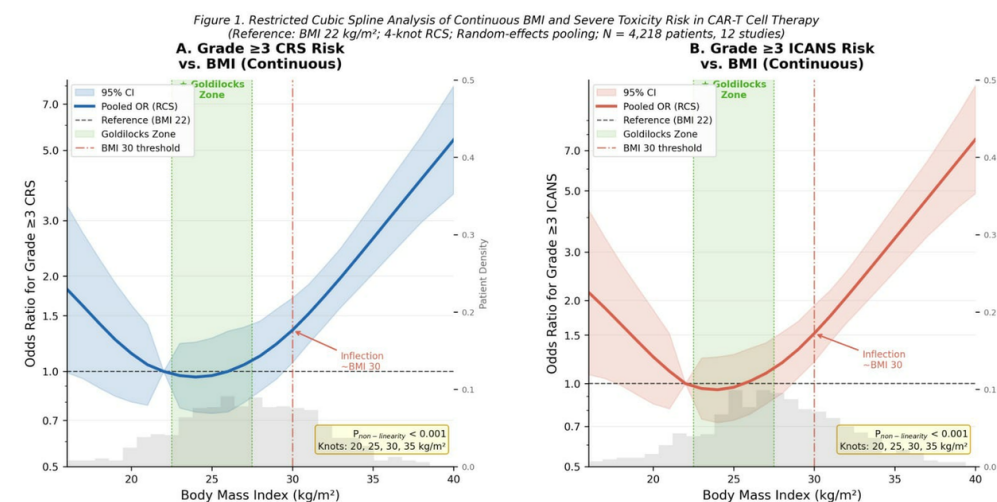
12 Studies 4,218 Patients BMI 22 ref



RCS Knots
BMI 20, 25, 30, and 35 kg/m²;
reference BMI 22 kg/m²



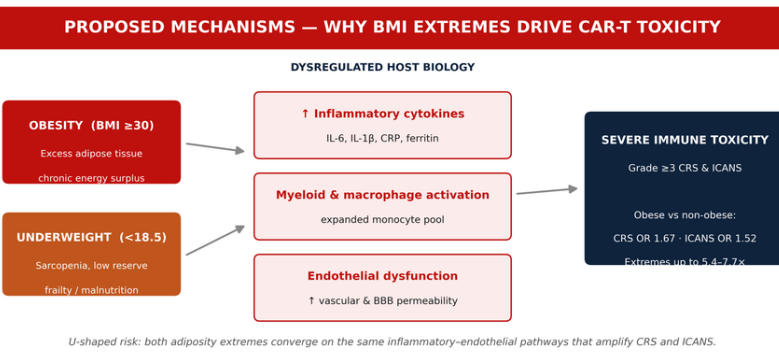
Statistical Analysis
DerSimonian-Laird random-effects models
Restricted cubic spline modeling
Continuous BMI per 5 kg/m² increment
Outcomes: grade ≥3 CRS and ICANS
Egger's and Begg's tests for publication bias



CLINICAL INTERPRETATION BY BMI PATTERN

BMI pattern	Interpretation	Evidence
Underweight	Higher risk of severe toxicity	CRS OR 1.82; ICANS OR 2.14
BMI 22.5–27.5	Lowest-risk 'Goldilocks Zone'	Non-linear U-shaped association; p < 0.001
Obesity	Higher risk of severe toxicity	CRS OR 1.67; ICANS OR 1.52
BMI 40	Markedly elevated predicted risk	CRS OR 5.39; ICANS OR 7.67

Outcome	OR per 5 kg/m ² BMI increase (95% CI)	P value	Obese-group rate	Normal-BMI rate	OR at BMI 40
Grade ≥3 CRS	1.67 (1.43–1.94)	<0.001	34.8%	15.3%	5.39
Grade ≥3 ICANS	1.52 (1.29–1.79)	<0.001	31.2%	12.8%	7.67



RESULTS

OR 1.67

Grade ≥3 CRS —
obese vs. non-
obese (95% CI
1.43–1.94)

OR 1.52

Grade ≥3 ICANS —
obese vs. non-
obese (95% CI
1.29–1.79)

BMI 22.5–27.5

Goldilocks Zone —
lowest-risk
adiposity range

p < 0.001

Non-linearity — U-
shaped curve for
both toxicities

• Per 5 kg/m² BMI: CRS OR 1.41 (1.28–1.55), ICANS OR 1.38 (1.24–1.53) — GRADE High.

• Both extremes raise risk → underweight OR 1.82 (CRS) / 2.14 (ICANS); BMI 40 OR 5.39 (CRS) / 7.67 (ICANS).

• Robust → I²=0%, consistent across all CAR-T products (p=0.71), no CRS publication bias (Egger's p=0.131).

CONCLUSION

- This meta-analysis establishes a robust, non-linear relationship between BMI and severe CAR-T toxicities, with both underweight and obese phenotypes conferring substantially elevated risk. The Goldilocks Zone (BMI 22.5–27.5 kg/m²) represents an optimal adiposity range for toxicity mitigation, supporting pre-treatment weight optimization strategies in CAR-T candidates.

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