IMMUNE EFFECTOR CELL (IEC)–ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS–LIKE SYNDROME (IEC-HS) IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Leen Haj Saleh[1], Marrita Rabadi[1], Motaz Almahmood[5], Aadhila Abbas Manthiri[2], Ayman Dalol[1], Usra Elshaikh[3], Abdulrahman F. Al-Mashdali[4], Mohammed Abdulgayoom[4], Shehab F Mohamed [4]

[1]College of Medicine, Qatar University, Doha, Qatar; [2]College of Pharmacy, Qatar University, Doha, Qatar; [3]Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar; [4]Department of Hematology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar; [5]Tower Health Medical Group, Phoenixville Hospital, Phoenixville, Pennsylvania, USA

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy has achieved high remission rates in relapsed/refractory hematologic malignancies. However, it can trigger immune effector cell–associated HLH-like syndrome (IEC-HS), a severe hyperinflammatory toxicity distinct from classical HLH. We conducted a systematic review and meta-analysis to assess the incidence, outcomes, management, and risk factors of IEC-HS after CAR-T therapy.

METHOD

A comprehensive literature search of PubMed, Scopus, and Embase was performed to identify relevant studies according to PRISMA guidelines. Data on incidence, clinical and laboratory features, management, and survival outcomes were extracted. Pooled incidence estimates were calculated using a random-effects model with Freeman–Tukey double arcsine transformation. Heterogeneity was assessed using the I^2 statistic, and publication bias evaluated with Egger's regression test.

CONCLUSIONS

IEC-HS occurs in a notable proportion of patients after CAR T-cell therapy and is associated with significant morbidity. These findings emphasize the need for standardized diagnostic criteria and validated management strategies to improve recognition and outcomes.

RESULTS

Out of 692 records identified, 35 studies comprising 8,573 patients receiving CAR T-cell therapy for hematologic malignancies were included, of whom 396 developed IEC-HS/HLH. 18 studies were eligible for quantitative synthesis. The pooled incidence of IEC-HS was 10.0% (95% CI: 7.0–14.0), with substantial heterogeneity (I^2 = 92.4%, τ^2 = 0.04), reflecting differences in CAR constructs, disease indications, and diagnostic definitions across studies. Incidence varied by target antigen and clinical setting, with BCMA-directed therapies reporting lower rates (<20%), while higher incidences exceeding 20% were observed in selected CD22-directed trials and pediatric/young adult B-ALL cohorts. CD19-directed therapies demonstrated intermediate and variable incidence across studies. IEC-HS typically developed within 1 to 3 weeks post-infusion, often overlapping with cytokine release syndrome. Reported mortality among HLH cases ranged from 25 to 50% in severe presentations, particularly in patients with multiorgan failure. Egger's test indicated small-study effects (p = 0.004). Subgroup and sensitivity analyses confirmed the robustness of the pooled estimates.

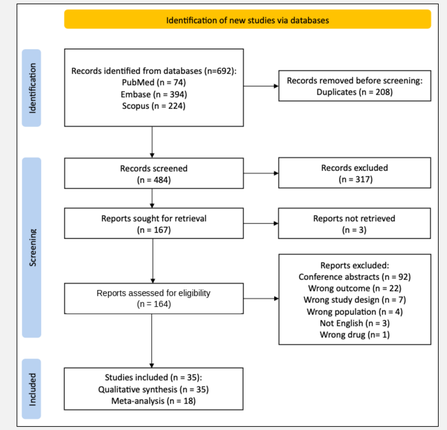

Figure 1: PRISMA Flowchart

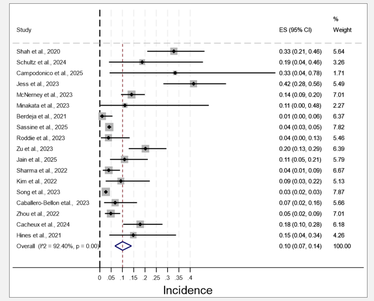

Figure 2: Forest Plot of Pooled HLH Cumulative Incidence

CONTACT INFORMATION

Motaz Almahmood;
Tower Health Medical Group, Phoenixville Hospital, Phoenixville, Pennsylvania, USA
motazodat71@gmail.com

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Qatar National Library for providing open-access funding for this publication.

REFERENCES

[1]Henter J-I, Sieni E, Eriksson J, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. Blood 2024;144:2308–18. https://doi.org/10.1182/blood.2024025077.
[2]Henter J-I, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31. https://doi.org/10.1002/pbc.21039.
[3]Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell Selection Affects Chimeric Antigen Receptor (CAR) T-Cell Potency and Toxicity: Updated Results From a Phase I Anti-CD22 CAR T-Cell Trial. JCO 2020;38:1938–50. https://doi.org/10.1200/JCO.19.03279.