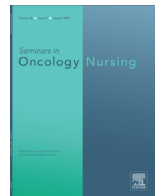




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Factors Associated with Immune Effector Cell-Associated Neurotoxicity Syndrome in Adults with Hematological Malignancies Undergoing Chimeric Antigen Receptor T-Cell Therapy: A Systematic Review

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ABSTRACT

Objectives: We systematically appraised studies investigating factors associated with ICANS development after CAR-T cell therapies in adults with hematological malignancies and estimated ICANS prevalence.

Method: We conducted a systematic review (SR) in 4 databases following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for studies published from 2010 to December 2024. We estimated ICANS prevalence with exact binomial and score test-based 95% confidence intervals. We applied the Freeman-Tukey double arcsine transformation to stabilize variances within random-effects models using the *Metaprop* command in Stata.

Results: Sixteen studies (14 retrospective, n = 135, and 2 prospective, n = 300) were included in this SR. The sample comprised adults with various hematological malignancies who received anti-CD19 anti-BCMA. Some clinical factors seem to be associated with ICANS incidence and severity. In retrospective studies, the pooled prevalence was 41% (95% CI: 31%-51%) for all grades of ICANS and 20% (95% CI: 13%-28%) for grade ≥ 3 ICANS. In prospective studies, the pooled prevalence was 51% (95% CI: 45%-56%).

Conclusions: Approximately half of hematological patients undergoing CAR T therapy develop ICANS. Although some factors may contribute to the development of ICANS, limited studies and samples, the retrospective nature of the majority of studies, and the discordance among the results preclude certain risk factors conclusions.

Implications for Nursing Practice: Nurses play a pivotal role in post-treatment monitoring in the early detection and management of ICANS, given their direct and continuous patient interaction. Increasing nurses' awareness of potential risk factors for ICANS can enhance their vigilance and effectiveness in managing this condition.

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Chimeric antigen receptor (CAR) T cells have demonstrated unparalleled anti-tumor efficacy, resulting in a shift in the treatment paradigm for plasma cell and lymphoid malignancies, including B-cell acute leukemia (B-ALL), large B-cell lymphomas (LBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), multiple myeloma

(MM), and chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL).¹⁻⁶ CAR T cells are T lymphocytes that have been genetically modified to produce synthetic T cell receptors for use in immunotherapy.⁷ These genetically engineered T lymphocytes are designed to recognize and attack specific antigens on cancer cells, providing a targeted and potent treatment option.⁸

The structure of CARs consists of 4 domains, each with a distinct purpose: the antigen recognition domain, the hinge region (also known as the ectodomain), the transmembrane domain, and the intracellular T cell signaling domain, also referred to as the

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Layperson Summary

What we investigated and why

ICANS is the most dangerous and unpredictable toxicity with CAR-T therapy, due to a disruption of the blood-brain barrier. Clinical presentation includes a wide range of neurological signs and symptoms, with aphasia as the most frequently reported. In severe cases, neurotoxicity can progress to encephalopathy and seizures, potentially resulting in death (the risk of death is about 2–3%).

How we did our research

We conducted a systematic review on risk factors and predictors of ICANS in adults with hematological malignancies who underwent CAR-T therapies and a meta-analysis of ICANS prevalence in this population, following a rigorous and recommended methodology.

What we have found

ICANS is a common complication in hematologic patients receiving CAR-T therapy, with a prevalence ranging from 35–47% depending on the study design analysed. Clinical variables and blood chemistry biomarkers may be early indicators of ICANS in hematological patients treated with CAR-T cells. However, more studies on specific populations are needed to examine the impact of these factors under specific conditions and to clarify the discrepancies between studies.

What it means

Despite additional large-scale prospective studies are needed, our results may lay the groundwork for patients' risk stratification and may inform the clinical practice for timely preventive interventions before and during CAR-T therapies.

by a wide spectrum of symptoms and signs, including aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.¹⁷ In severe cases, neurotoxicity progresses to encephalopathy and seizures, potentially resulting in death.^{18,22} Other symptoms and signs, such as headache, tremor, myoclonus, asterixis, hallucinations, weakness, balance problems, and intracranial hemorrhage, are excluded from the definition and diagnosis of ICANS as they are nonspecific.¹⁷

Although CRS is well-characterized and can be effectively managed with IL-6 blockade (e.g., tocilizumab), ICANS remains less predictable and poorly understood.^{23,24} Existing treatments, including corticosteroids and anti-seizure prophylaxis, have shown limited efficacy in severe cases and may compromise the activity of CAR-T cells.²⁵ A higher cumulative dose of corticosteroids was associated with early progression and shorter overall survival after CAR-T therapy.²⁶ Furthermore, the variability in clinical presentation and the rapid onset of severe neurotoxicity highlight a critical need for early identification of at-risk patients.²⁷

Nurses play a pivotal role in post-treatment monitoring in the early detection and management of ICANS,²⁸ given their direct and continuous patient interaction.²⁹ Nurses may facilitate timely intervention by recognizing early signs of encephalopathy and reducing the risk of severe complications.²⁸ Nurses are often the first to observe symptoms of deterioration,³⁰ such as subtle neurological changes,³¹ and are instrumental in implementing monitoring protocols and predicting scores.³² Nurses are essential in correlating patient risk scores with suitable therapeutic interventions through adaptive decision-making processes, playing a crucial role in determining the appropriate clinical activities for patients at risk of deterioration.³² Therefore, increasing nurses' awareness of specific risk factors for ICANS is pivotal to enhance their vigilance and effectiveness in managing this complex condition.³³

Despite these prospects, there is a paucity of robust clinical evidence regarding factors associated with ICANS in adults with hematological malignancies undergoing CAR-T therapies; this creates a significant knowledge gap that limits the development of effective prophylactic and therapeutic strategies. Previous systematic reviews have identified that IL-6, IFN- γ , IL-10, and IL-15,³⁴ endothelial activation and stress indexes, ferritin, and C-reactive protein were associated with both incidence and severity of ICANS.³⁵

Although previous researchers have made important contributions to the current understanding of risk factors associated with CAR-T cell-induced neurotoxicity,^{34,35,36–39} there is, thus far, a limited systematic synthesis of data to guide clinicians in predicting and mitigating this complication. Combining different blood chemical biomarkers with patient clinical factors may offer greater sensitivity in the early identification of patients at risk of neurotoxicity. Implementing these predictors in clinical practice could enhance risk stratification and optimize the management of high-risk patients, thereby preventing neurological condition deterioration and reducing the need for prolonged hospitalization. To address the paucity of literature reviews in this area, this study aims to systematically synthesize evidence on factors associated with ICANS development after CAR-T cell therapies in adults with hematological malignancies. The ultimate goal is to enable the development of evidence-based protocols that improve patient safety, minimize neurotoxicity, and optimize the therapeutic potential of CAR-T cell therapy. These findings will inform clinical practice and support future research designs to optimize CAR-T therapy safety and efficacy.

Methods

Study Design and Research Question

We systematically reviewed factors associated with ICANS in adults with haematological malignancies undergoing CAR-T

endodomain. The antigen recognition domain on the cell's exterior recognizes antigens, while the hinge region and transmembrane domain confer stability. The intracellular domain within the receptor's endodomain is essential for signal transduction, activating the effector functions of CAR T cells.⁹ Advances in CAR-T cell design, such as incorporating co-stimulatory domains to enhance persistence and anti-tumor activity, have significantly improved therapeutic outcomes.^{10–12} Five generations of CAR-T cells have been developed with the same basic structure, differing mainly in their intracellular structural domains and the cytokines and ligands introduced.¹³

Despite these advances, the efficacy of CAR-T therapy is tempered by serious and potentially life-threatening toxicities,¹⁴ particularly cytokine release syndrome (CRS) and neurotoxicity.^{15,16} Neurotoxicity related to CAR-T therapy is defined as immune effector cell-associated neurotoxicity syndrome (ICANS), which has more specific characteristics and unique pathophysiology than other encephalopathies.¹⁷ ICANS's pathophysiology involves endothelial activation and blood-brain barrier (BBB) disruption,¹⁸ high levels of the excitatory N-methyl-D-aspartate (NMDA) receptor agonists glutamate and quinolinic acid in cerebrospinal fluid,¹⁹ and the T cell activation of proinflammatory cytokines and myeloid cells.²⁰ The increased blood-brain barrier permeability facilitates the infiltration of proinflammatory cytokines and CAR-T cells into the central nervous system, triggering neurological symptoms.²¹

ICANS is a disorder characterized by a pathologic process involving the central nervous system that occurs following any immune therapy, resulting in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. It is characterized

therapies. This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024542241) to ensure transparency and rigor in conducting and avoiding redundant literature.^{40,41} The methodology for this review was the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement ([Supplementary File 1](#)),⁴² and the Cochrane Handbook of Systematic Reviews of Interventions.⁴³ The Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidance was utilized to address specific requirements for including observational and etiology studies.⁴⁴

The Population, Exposure, Outcome (PEO) framework was used to pilot this systematic review, with the following components: (P) adults aged ≥ 18 with haematological malignancy, (E) CAR-T cell therapies, and (O) factors associated with nervous system toxicity in CAR-T cell therapies.⁴⁵ This framework is used in systematic analyses of risk factors or etiologic studies; therefore, it was deemed as relevant to our research question, which is: "What are the factors or clinical predictors of ICANS associated with CAR-T cell therapies in adults with hematological malignancies?"

Data Sources and Search Strategies

We interrogated the databases in December 2024 (PubMed, CINAHL, Web of Science, and EMBASE), searching for articles published from 2013, when these new therapies started to be adopted in practice, until the search date. The search query was grounded in the PEO framework, which constitutes the basis of the principal relevant concepts. The search strategy was first structured for PubMed using MeSH and free-text words and then adapted to the syntax of the other databases. The publication date filter was configured during the search on databases, taking into account the recent history of CAR-T cell therapies.⁴⁶ No language or other restrictions and limits were set in the databases' interface to maximize the research. Additional methods, such as hand-searching and reference checking, were employed to enhance the findings. The search strategy was re-run on the databases before submission to detect additional recent publications. The search strategy for each database, the date of the first search, and the number of records initially found are presented in [Supplementary File 2](#).

Eligibility Criteria

The PEO framework provided the basis for eligibility criteria. Further, the following inclusion criteria were adopted: (1) scientific methodological papers published in peer-reviewed journals, (2) any observational study that analyses the association between CAR-T therapies and baseline risk factors for ICANS, and (3) records with abstract and full-text availability (to be able to perform the studies selection and the quality appraisal appropriately). Case reports, feasibility, and preclinical studies were excluded. Conference abstracts were excluded from the analysis because it was not possible to fully assess the quality of the evidence. No restrictions were placed on haematological malignancies, molecular subtype, setting, disease stage, sex, or ethnicity, as these factors were deemed irrelevant to the study.

Records and Studies Selection

The database search records were loaded into the reference manager software Zotero version 7.0 for Windows to remove duplicates (Center for History and New Media, Fairfax, VA: George Mason University). Once the duplicates were removed, the records were imported into Rayyan to perform the selection.⁴⁷ The PEO framework and the eligibility criteria guided the selection process for the articles. Two authors conducted the selection process independently. A hierarchical stepwise approach was used to standardize the reasons for

exclusion between the 2 authors, in which articles were excluded based on the order reported in the PEO framework and then according to the eligibility criteria reported. A third author was consulted since discrepancies and doubts arose during the selection process to determine the studies' eligibility. The PRISMA 2020 flow diagram for new systematic reviews, encompassing searches of databases, registries, and additional sources, detailed the selection process along with the reasons for the articles' exclusion.⁴²

Data Extraction

An author extracted and entered data independently into a piloted Excel spreadsheet data extraction form. The other 2 authors independently performed this process. Finally, the data were compared to ensure the accuracy of the information abstracted and the structure of the extraction form, guaranteeing that all extracted variables addressed the research question. The following variables were extracted: first author, publication year, country, study design, total sample size, diagnosis, lymphodepletion therapy, CAR-T therapy, outcome definition, and outcome classification. These variables were relevant to frame the results, which we reported separately for greater clarity.

Quality Appraisal

Two reviewers independently used the Newcastle-Ottawa Scale (NOS) to evaluate case-control and cohort studies.⁴⁸ The NOS includes 8 items within 3 domains: subject selection, comparability between groups, and outcome measurement. A star is awarded for each item, except for the comparison domain, which can be rated up to 2 stars. We assigned 1 point if the main confounding variables were detected and 2 points if the main variables were also controlled under the comparability domain. The full score was 9, with scores ranging from 0-4 indicating low quality, 5-6 indicating moderate quality, and 7-9 indicating high quality.^{49,50} Any disagreement regarding data extraction or quality assessment was resolved through a full discussion with a third reviewer.

Data Synthesis

Although the characteristics of the included studies in terms of study design, setting, exposure factor, treatment conditions, outcome assessment, and definition were relatively homogeneous (as shown in [Table 1](#)), the scarcity of available evidence for each analysed factor precluded us from the possibility to perform a meta-analysis to assess the impact of each factor in determine ICANS incidence. Precisely, even in cases where we had at least 2 studies and effect sizes for each variable, differences in study design and logistic regression analysis approaches hindered the adoption of a meta-analytic approach to obtain a quantitative estimate of the overall effect of a particular factor on the defined outcome. Although logistic regression is a powerful analytical method for binary outcomes, the results from the univariate and multiple logistic regressions may be conflicting.⁵ Univariate analysis measures the marginal correlation between covariates and outcomes; therefore, a covariate uncorrelated with the outcome may be significant in multiple regression. Conversely, a covariate may be significant in univariate analysis but not in multiple regression.⁵¹ For these reasons, we synthesized data on risk factors for ICANS using narrative synthesis and displayed the available effect measures in a separate table. This approach allowed us a structured tabulation of results across studies, representing 1 of the acceptable synthesis methods.⁵²

To maximise the research findings, we adopted a meta-analysis of proportions using a random-effects model to assess the pooled prevalence of ICANS.⁵³ We quantitatively pooled the absolute frequencies extracted from the included studies using the `metaprop` command,

the preferred method for conducting a proportion meta-analysis with binomial data.⁵⁴ Metaprop command estimates 95% confidence intervals (CI) using the exact binomial and score test-based CIs by incorporating the Freeman-Tukey double arcsine transformation of proportions.⁵⁴ This method predicts within-study variability using the binomial distribution, providing valid confidence ranges for each study and the pooled prevalence.⁵⁴ Statistical significance was determined as a 2-sided p-value of $< .05$. Given the intrinsic heterogeneity of randomised controlled trials of prevalence, a random-effects model was used for the magnitude estimations.⁵⁵ A funnel plot was designed to examine small-study effects for the outcome: an asymmetrical funnel plot for the line of the summary effect implies disparities between the estimates produced from small and large-size studies.⁵⁶ Data analyses were performed using STATA 17 software (StataCorp. 2019. Stata Statistical Software: Release 17. College Station, TX, USA: StataCorp LLC).

Results

Articles' Screening Results

A total of 2755 results were identified from databases. After removing duplicates, 2321 records remained for screening. Following the evaluation of titles and abstracts, 138 publications were selected for a comprehensive review of their full-texts. In this phase, we excluded 2 studies,^{57,58} which reported data from the FDA Adverse Event Reporting System (FAERS) Public Dashboard.⁵⁹ The basis of this choice lies in the limitations provided by the FAERS website platform: (1) Duplicate and incomplete reports are in the system, (2) Existence of a report does not establish causation (there is no certainty the drug caused the event), (3) Information in reports has not been verified, (4) Rates of occurrence cannot be established with reports.⁵⁹ Further, we

excluded 6 validation studies of scores predicting ICANS,^{36-38,60-62} as it was unfeasible to discern the contribution of each factor to the outcome when a panel of factors was presented. Further, 1 of these studies⁶⁰ shared the same cohort as another included study.²² We also excluded 1 study assessing the outcome as neurocognitive treatment-emergent adverse events (MNTs),⁶³ which include psychiatric symptoms. Finally, 16 studies were included in this systematic review.^{18,64-78} Fig. 1 depicts the PRISMA selection process results and the reasons for exclusions.

Studies Characteristics

To frame the results on factors associated with CAR-T cell therapies, we extracted the main characteristics and summarized them in Table 1. All the included studies analysed potential risk factors of ICANS associated with CAR-T cell therapies as a primary or secondary outcome in adults with various hematological malignancies. Thirteen studies were undertaken in the USA,^{18,64,66,67,69-71,73-78} 2 in Europe,^{65,72} and 1 in Israel.⁶⁸ Fourteen studies have a retrospective design,^{18,64-71,73,74,76-78} and 2 have a prospective design.^{72,75} Among the retrospective studies, 2 were retrospective matched cohort studies,^{67,68} with age as the variable used to create a matched cohort design. In all studies, patients received anti-CD19 CARs, except in 1 study where patients were treated with anti-B-cell maturation antigen (BCMA) therapy,⁶⁷ and in another one where 1 patient was treated with a-fetoprotein-directed CAR T cells for a patient with hepatocellular carcinoma.⁷⁷ Since only 1 patient with hepatocellular carcinoma was involved in Karschnia's study, we decided to include this study in our systematic review as the effect of the disease on the outcome was probably negligible. The outcome definition varied among studies, with 11 assessing the ICANS,^{63-71,73,75} and 5 assessing neurotoxicity (NT).^{18,73,75,77,78}

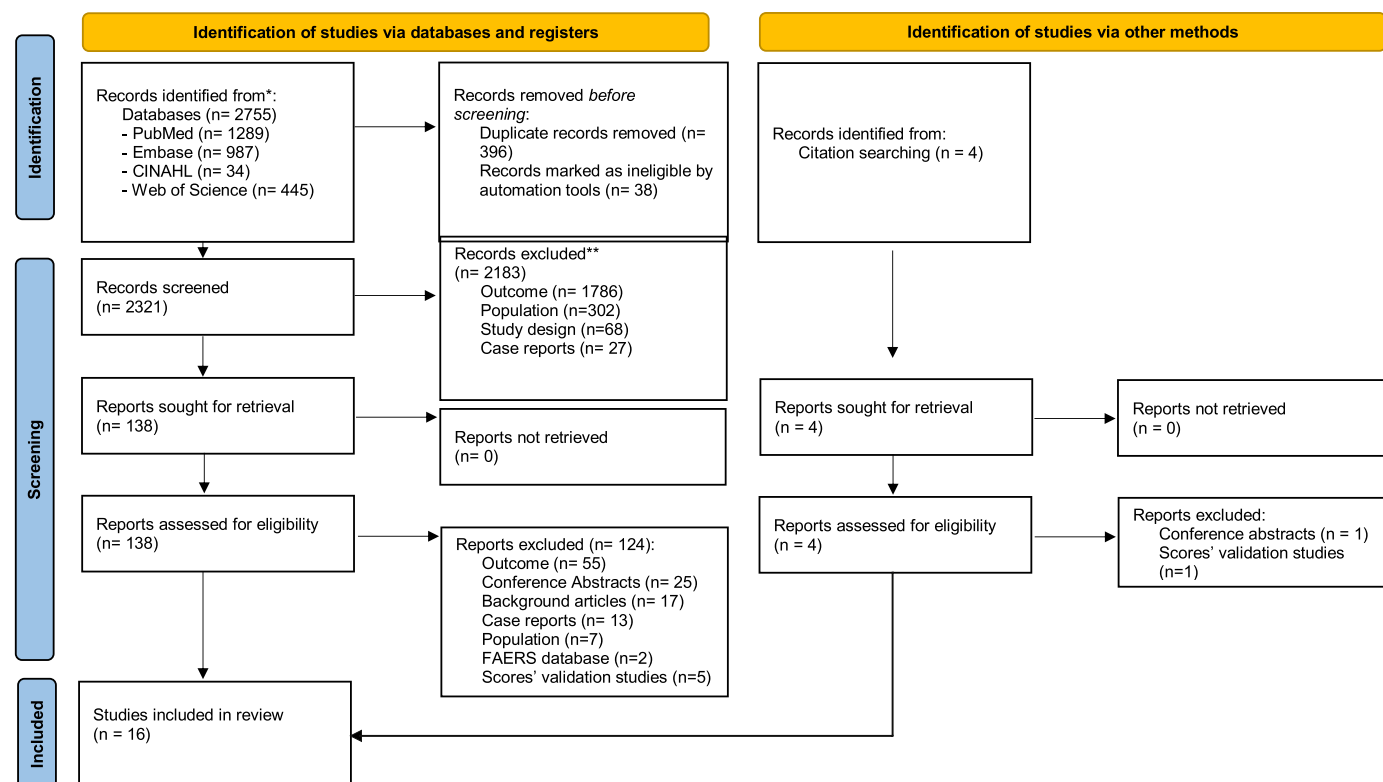


FIG. 1. Flow diagram of the studies' selection process. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. 10.1136/bmj.n71. Available at: <http://www.prisma-statement.org/>

TABLE 1
Characteristics of the Included Studies

First author, year	Country	Study design	Total sample	Diagnosis	Lymphodepletion	CAR-T therapy	Outcome definition	Outcome classification
Faramand et al. ⁶⁴	USA	Retrospective	N = 136 (baseline samples for factors analysis were available only in 51 patients).	R/R DLBCL	Fludarabine 30 mg/m ² /d × 3 days and cyclophosphamide 500 mg/m ² /d × 3 days (with or without bridging treatment).	Anti CD19: Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel).	ICANS	ASTCT
Larue et al. ⁶⁵	France	Retrospective	N = 150	R/R DLBCL, PMBCL, tFL, MCL.	Fludarabine and cyclophosphamide (no data on dosage).	Anti CD19: Axi-cel tisa-cel, and brexucabtagene autoleucel (brexu-cel).	ICANS	ASTCT
Ababneh et al. ⁶⁶	USA	Retrospective	N = 59	DLBCL	N.i.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Reyes et al. ⁶⁷	USA	Retrospective matched cohort study (1 group aged <70 years and another >70 years).	N = 83	MM (n = 61 aged < 70 and n = 22 aged ≥ 70).	Fludarabine below 30 mg/m ² /d × 3 days (with or without bridging treatment).	Anti B-cell maturation antigen (BCMA): vicleucel (ide-cel), autoleucel (cilta-cel).	ICANS	ASTCT
Butt et al. ⁶⁹	USA	Retrospective	N = 30	DLBCL	N.i.	Anti CD19: Axi-cel, tisa-cel, and brexu-cel.	ICANS	ASTCT
Ram et al. ⁶⁸	Israel	Retrospective matched cohort study	N = 82	R/R DLBCL (n = 41 aged >70 in the control group and n = 41 aged ≥70 in the cohort group).	Fludarabine 25-30 mg/m ² /d and cyclophosphamide 250-500 mg/m ² /d × 3 days.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Smith et al. ⁷⁰	USA	Retrospective	N = 228	Two cohorts: ALL (n = 91) and NHL (n = 137).	Fludarabine 30mg/m ² /d and cyclophosphamide 300 mg/m ² /d × 3 days.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Tang et al. ⁷¹	USA	Retrospective	N = 77	LBCL	N.i.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Schoeberl et al. ⁷²	Germany	Prospective	N = 96	DLBCL, BCP-ALL	N.i.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Faramand et al. ⁷³	USA	Retrospective	N = 75	LBCL	Fludarabine 30 mg/m ² /d × 3 days and cyclophosphamide 500 mg/m ² /d × 3 days (with or without bridging treatment).	Anti CD19: Axi-cel and tisa-cel.	NT	CARTOX guidelines.
Holtzman et al. ⁷⁴	USA	Retrospective	N = 45	R/R LBCL	N.i.	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Rubin et al. ⁷⁵	USA	Prospective	N = 204	R/R lymphoma	N.i.	Anti CD19: Axi-cel and tisa-cel.	NT	CTCAE
Strati et al. ⁷⁶	USA	Retrospective	N = 100	R/R LBCL	Fludarabine 30 mg/m ² /day/d × 3 days and cyclophosphamide 500 mg/m ² /d × 3 days (with or without bridging treatment).	Anti CD19: Axi-cel and tisa-cel.	ICANS	ASTCT
Karschnia et al. ⁷⁷	USA	Retrospective	N = 100	Various (CLL/SCLL, ALL, DLBCL, PMBCL).	Fludarabine and cyclophosphamide per standard of care.	Anti CD19 (Axi-cel and tisa-cel) and anti- α -fetoprotein.	NT	CTCAE
Santomasso et al. ⁷⁸	USA	Retrospective	N = 53	R B-ALL	Fludarabine 25 mg/m ² /d × 3 days and cyclophosphamide 1.5-3 g/m ² /d × 1 day (with or without bridging treatment).	Anti CD19: Axi-cel and tisa-cel.	NT	CTCAE
Gust et al. ⁹⁸	USA	Retrospective	N = 133	R B-ALL, NHL, CLL	Fludarabine 25 mg/m ² /d × 3 days and cyclophosphamide 1.5-3 g/m ² /d × 1 day.	Anti-CD19: Tisa-cel, containing a 4-1 BB costimulatory domain.	NT	CTCAE

Hematological diagnoses acronyms: DLBCL, Diffuse Large B-cell lymphoma; R/R DLBCL, Relapsed/Refractory Diffuse Large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; tFL, transformed follicular lymphoma; MCL, mantle cell lymphoma; LBCL, large B-cell lymphoma; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; CLL/SCLL, chronic lymphocytic leukemia/small cell lymphocytic lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; B-ALL, B-cell Acute Lymphoblastic Leukemia; BCP-ALL, B-cell precursor acute lymphoblastic leukemia.

Other acronyms: CAR-T, Chimeric Antigen Receptor Cells-T; NST, Nervous system toxicity; ICANS, Immune effector cell neurotoxicity syndrome; ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; N.i., no information.

TABLE 2
Results from Logistic Regression Analyses of Primary Studies

	Univariate logistic regression	Multivariate logistic regression	Sample	Study design	Description of association
Sociodemographic variables					
Age					
Faramand et al. ⁶⁴	/	OR = 1.02 (0.99-1.05); <i>P</i> = .23	N = 136	Prospective	With grade ≥2 ICANS
Rubin et al. ⁷⁵	OR = 1.05 (1.01-1.09); <i>P</i> < .001	/	n = 204	Prospective	With the onset of NT
Sex					
Rubin et al. ⁷⁵	OR = 1.06 (0.47-2.38); <i>P</i> = .88	/	n = 204	Prospective	With the onset of NT
Hematological parameters					
High fibrinogen					
Holtzman et al. ⁷⁴	OR = 2.68 (1.36-6.33); <i>P</i> = .01	/	n = 45	Retrospective	With all grades ICANS
Holtzman et al. ⁷⁴	OR = 3.27 (1.60-8.27); <i>P</i> < .001	/	n = 45	Retrospective	With grade ≥2 ICANS
Therapeutic aspects					
No. of doses of Tocilizumab					
Rubin et al. ⁷⁵	OR = 5.42 (2.42-12.13); <i>P</i> < .001	/	n = 204	Prospective	With the onset of NT
CAR with CD28 domain					
Larue et al. ⁶⁵	OR = 9.7 (2.18 to 43.13); <i>P</i> = .003	OR = 9.77 (1.99-47.91); <i>P</i> = .005	n = 150	Retrospective	With grade ≥2 ICANS
Bridging therapy					
Faramand et al. 2024 ⁶⁴	/	OR = 1.47 (0.62-3.56); <i>P</i> = .38	n = 136	Prospective	With grade ≥2 ICANS
Blood chemistry and biomarkers					
C-reactive protein ≥4 mg/dL					
Faramand et al. ⁶⁴	OR = 1.4 (1.2-1.6); <i>P</i> < .05	OR = 1.3 (1.0-1.6); <i>P</i> < .05	n = 136	Prospective	With grade ≥2 ICANS
Ferritin ≥400 ng/mL					
Faramand et al. ⁶⁴	OR = 1.3 (1.1-1.6); <i>P</i> < .05	OR = 1.2 (0.89-1.52); <i>P</i> = .28	n = 136	Prospective	With grade ≥2 ICANS
Larue et al. ⁶⁵	OR = 2.72 (1.08-6.87); <i>P</i> = .034	OR = 2.23 (0.71-6.99); <i>P</i> = .171	n = 150	Retrospective	With grade ≥2 ICANS
Low albumin <35 g/L					
Larue et al. ⁶⁵	OR = 3.36 (1.27-8.88); <i>P</i> = .014	OR = 1.42 (0.37-5.52); <i>P</i> = .610	n = 150	Retrospective	With grade ≥2 ICANS
Neurofilament light chain >58 pg/mL					
Laure et al. ⁶⁵	OR = 4.01 (1.54-10.49); <i>P</i> = .005	OR = 3.52 (1-12.4); <i>P</i> = .050	n = 150	Retrospective	With grade ≥2 ICANS
Hypophosphatemia					
Tang et al. ⁷¹	/	OR = 1.9 (18.9-19.1); <i>P</i> = .02	n = 77	Retrospective	With all grades ICANS
Metabolic tumors parameters					
Metabolic tumor volume					
Ababneh et al. ⁶⁶	OR = 4.3; <i>P</i> = .01	/	n = 59	Retrospective	With all grades ICANS
Standardized uptake value					
Ababneh et al. ⁶⁶	OR = 12; <i>P</i> = .01	/	n = 59	Retrospective	With grades 3-4 ICANS
Other clinical conditions					
History of vascular disease					
Ram et al. ⁶⁸	OR = 1.2 (0.78-1.81); <i>P</i> = .45	/	n = 82	Retrospective	With all grades ICANS
Dementia					
Ram et al. ⁶⁸	OR = 1.4 (0.81-1.63); <i>P</i> = .38	/	n = 82	Retrospective	With all grades ICANS
ECOG 2-3					
Faramand et al. ⁶⁴	/	OR = 0.75 (0.29-1.8); <i>P</i> = .54	n = 136	Prospective	With grade ≥2 ICANS
Larue et al. ⁶⁵	OR = 5.29 (1.92-14.62); <i>P</i> = .001	OR = 3.34 (0.83-13.36); <i>P</i> = .088	n = 150	Retrospective	With grade 2-4 ICANS
Fever					
Rubin et al. ⁷⁵	OR = 3.86 (2.14-6.94); <i>P</i> < .001	/	n = 204	Prospective	With the onset of NT
Histologic subtype (aggressive vs indolent)					
Rubin et al. ⁷⁵	OR = 4.55 (1.46-14.18); <i>P</i> < .001	/	n = 204	Prospective	With the onset of NT
Cytokine release syndrome (CRS)					
Rubin et al. ⁷⁵	OR = 0.65 (0.52-0.81); <i>P</i> < .001	/	n = 204	Prospective	With the onset of NT
Santomasso et al. ⁷⁸	OR = 52.5 (8.66-1027); <i>P</i> < .001	/	n = 53	Retrospective	With severe NT

Immune effector cell-associated neurotoxicity syndrome (ICANS); Neurotoxicity (NT); 95% CI for all results.

However, the scale used for assessing ICANS and NT severity was equal in all the studies: The American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for ICANS¹⁷ and the Common Terminology Criteria for Adverse Events (CTCAE) for NT.⁷⁹ Only Faramand's 2020⁷³ used the CAR-TOX guidelines to grade NT.⁸⁰

Risk Factors for ICANS

Our systematic review sought to summarize baseline factors associated with ICANS in adults with hematological malignancies who received CAR-T cell therapies. To provide evidence of the risk factors, we reported the results of linear regression analyses in a designated table whenever feasible (Table 2). In instances where the authors did not evaluate the associations that yielded an effect measure, we provided a narrative description of the findings in the subsequent subsections based on the type of parameters. All the presented results refer to values at baseline, before lymphodepletion or CAR-T infusion. In the following sections, we retain the terms used by the authors to define the outcomes and results, thereby preserving the original data.

Sociodemographic Variables

Two studies used a retrospective matched cohort study to analyse the variable age and found no statistically significant difference between the elderly and the young groups in all grades of ICANS incidence (*P* = .48; *P* = 1.0)^{67,68} and grades 3, 4 (*P* = .54).⁶⁸ Conversely, Rubin's study found that age is significantly associated with the onset of neurotoxicity (OR: 1.05; 95% CI: 1.01-1.09; *P* < .001).⁷⁵ Gust's study found that neurotoxicity of any grade was more frequent in younger patients (*P* = .094) and those with B-ALL (*P* = .084) in univariate analysis.¹⁸ Sex was not significantly associated with NT in Rubin's study.⁷⁵ Ethnicity did not show a significant association with ICANS incidence.⁷⁴ Faramand et al. found no significant association between age (OR 1.02; 95% CI: 0.99-1.05; *P* = .23) and ≥2 ICANS in a multivariate analysis.⁶⁴

Haematological Parameters

No differences between patients with low or high-grade neurotoxicity were retrospectively found for the hematologic parameters of white blood cell counts or absolute neutrophil counts.^{76,77} Platelet counts were significantly lower at baseline in individuals who later

developed high-grade neurotoxicity compared to patients who developed low-grade neurotoxicity (74.6 ± 16 vs $166.8 \pm 36 \times 10^9/L$; $P = .030$).^{77,78} Low baseline platelet count ($\leq 50,000/\mu l$) and presence of fever ($\geq 38.0^\circ C$) on day 3 of CAR T cell infusion identified 17 of 23 patients (73.9%) who proceeded to develop severe neurotoxicity.⁷⁸ Conversely, Holtzman's study did not find a significant statistical association between platelet count and ICANS.⁷⁴

Patients with severe neurotoxicity had a significantly higher incidence of laboratory markers of disseminated intravascular coagulation (DIC).^{18,78} Prothrombin time (PT), activated PTT, and D-dimer were more elevated in patients with severe neurotoxicity.^{18,78} Elevated fibrinogen (517 vs 403 mg/dL, ULN 438 mg/dL, $P = .003$) was associated with the development of ICANS.⁷⁴ Precisely, elevated fibrinogen on the day of CAR-T infusion was predictive of ICANS with an ROC curve (AUC 0.724 , 95% CI: $0.5642-0.88438$).⁷⁴ Logistic regression showed that elevated fibrinogen was predictive of any grade of ICANS (OR = 2.68 , 95% CI: $1.36-6.33$, $P = .01$) and of severe ICANS (OR 3.27 ; 95% CI: $1.60-8.27$, $p < 0.001$).⁷⁴

Therapeutic aspects

Previous cancer treatments were not associated with a higher frequency of grade 3-4 ICANS compared with grade 0-2 ICANS,⁷⁶ as well as bridging therapy ($P = .33$).⁷⁴ Accordingly, Faramand found no significant association between bridging therapy with grade ≥ 2 ICANS in a multivariate analysis (OR = 1.47 ; 95% CI: $0.62-3.56$; $P = .38$).⁶⁴ Exposure to piperacillin/tazobactam, meropenem, or imipenem (P-I-M) in the 4 weeks before CD19 CAR T cells seem to be associated with increased ICANS in NHL ($P = .013$) and the mixed cohort of NHL and ALL patients ($P = .023$), despite divergent results when selecting specific populations with different haematological diagnosis and specific antibiotic therapy.⁷⁰ In particular, P-I-M exposure in patients with NHL was associated with a higher rate of ICANS regardless of the co-stimulatory domain used (CD28: $P = .043$; 4-1BB: $P = .038$).⁷⁰ Tocilizumab use was associated with the development of ICANS ($P < .01$) and severe ICANS ($P = .02$).⁷⁴ The number of doses of tocilizumab was significantly associated with NT in Rubin's study.⁷⁵

The type of Infused T-cell products had no significant association with the development of ICANS or neurotoxicity in 2 studies.^{71,78} However, Larue et al. demonstrated that CAR with CD28 domain was a strong predictor of grade 2-4 ICANS in both univariate (OR = 9.7 ; 95% CI: $2.18-43.13$; $P = .003$) and multivariate (OR = 9.77 ; 95% CI: $1.99-47.91$; $P = .005$) regression analyses.⁶⁵ Furthermore, Gust et al. found that a high CAR-T cell dose was significantly associated with neurotoxicity in univariate ($P < .0001$) and multivariate analysis ($P = .0009$).¹⁸ In particular, the infused CAR-T cell dose was the only factor associated with more severe neurotoxicity (grade ≥ 3 versus grade 1-2, $P = .014$).¹⁸

Blood Chemistry and Serum Biomarkers

Low albumin levels (3.7 vs 3.9 g/dL, $P = .04$) at baseline were associated with a higher frequency of grade 3-4 ICANS compared with grade 0-2 ICANS in Strati's study.⁷⁶ Accordingly, Larue observed that low albumin levels (< 35 g/L) were associated with grade 2-4 ICANS in univariate analysis (OR = 3.36 ; 95% CI: $1.27-8.88$; $P = .014$);⁶⁵ no significant association was found in a multivariate analysis (OR = 1.42 ; 95% CI: $0.37-5.52$; $P = .610$).⁶⁵ Similarly, Santomasso noticed that serum protein and albumin concentrations were decreased in patients with severe neurotoxicity.⁷⁸

Absolute levels of the acute-phase proteins C-reactive protein (CRP) and ferritin at the time of CAR T-cell infusion did not significantly differ between patients who later developed low- or high-grade neurotoxicity in large B-cell lymphoma (LBCL) patients^{26,74} and a mixed sample.⁷⁷ Faramand's study found that baseline levels of CRP (≥ 4 mg/dL) were associated with ICANS ≥ 2 in both univariate (OR = 1.4 ; 95% CI: $1.2-1.6$; $P < .05$) and multivariate (OR = 1.3 95% CI: $1.0-1.6$); $P < .05$) models.⁶⁴ High ferritin levels were significantly

associated with ICANS ≥ 2 in univariate logistic regression models in both Faramand's study (OR = 1.4 ; 95% CI: $1.2-1.6$; $P < .05$; ferritin ≥ 400 ng/mL)⁶⁴ and Larue's study (OR = 2.72 ; 95% CI: $1.08-6.87$; $P = .034$; ferritin > 803 ng/L).⁶⁵ No significant association was found between high ferritin levels and ICANS ≥ 2 in both Faramand (OR = 1.2 ; 95% CI: $0.89-1.52$; $P = .28$)⁶⁴ and Larue (OR = 2.23 ; 95% CI: $0.71-6.99$; $P = .171$)⁶⁵ studies with multivariate logistic regression analyses.

Renal function indexes and electrolytes were not associated with a higher frequency of grade 3-4 ICANS compared with grade 0-2 ICANS.⁷⁶ Hypophosphatemia, defined as serum phosphorus level < 2.0 mg/dL, was significantly associated with the onset of ICANS, representing a risk factor (OR = 1.90 , SE = 0.83 , $P = .0217$) in a multivariate logistic regression model.⁷¹ ICANS grade was negatively associated with serum phosphorus, with each unit increase in ICANS grade associated with a 0.29 mg/dL decrease in phosphorus ($P < .0001$).⁷¹ Faramand's study analyzed the association between noradrenaline (NAD) peak levels and NT using a univariate logistic regression,⁷³ however, no significant associations were detected.⁷³

Serum neurofilament light chain (NfL) levels (> 58 pg/mL) were significantly associated with grade 2-4 ICANS in both univariate (OR = 4.01 ; 95% CI: $1.54-10.49$; $P = .005$) and multivariate (OR = 3.52 ; 95% CI: $1-12.4$; $P = .050$) regression models of Larue's study.⁶⁵ Accordingly, Butt et al. observed that patients who developed any grade ICANS, low-grade (grade 1-2) ICANS, and grade 3 or higher ICANS had significant increases in NfL levels (mean, 87.6 pg/mL, 115.3 pg/mL, and 71.7 pg/mL, respectively) compared with the grade 0 group (29.4 pg/mL).⁶⁹ In particular, baseline NfL levels predicted ICANS with high accuracy (area under the ROC curve, 0.96), sensitivity (0.91), and specificity (0.95).⁶⁹ Similar results were supported by Shoebel's study where patients with moderate to severe ICANS (ICANS grade 2-4) had significantly higher NfL-post levels than those with no to mild ICANS (ICANS grade 0-1) (ICANS grade 0-1: 27.9 pg/mL [IQR, $20.1-54.3$ pg/mL] vs ICANS grade 2-4: 75.3 pg/mL [IQR, $32.4-183.0$ pg/mL]; $P < .01$).⁷² As a result, the multivariable logistic regression found a significant correlation between higher NfL-post levels and the severity of ICANS ($P < .001$).⁷²

Proinflammatory Cytokines and Syndromes

Patients with severe neurotoxicity had higher levels of *IL1 α* , *IL2*, *IL3*, *IL5*, *IL6*, *IL10*, *IL15*, *IP10*, *INF γ* , *GCSF* ($P = .0009$), *GM-CSF*, and *MCP1* by day 3, suggesting that early rise and higher peak of these serum cytokines were associated with severe neurotoxicity.^{18,78} Low epidermal growth factor (EGF) levels are also correlated with neurotoxicity.⁷⁸ Specifically, patients with low IL15 (< 50 pg/mL) or high EGF (> 120 pg/mL) have a low risk of severe neurotoxicity ($3/27$; 11% ; 95% CI: $2-29$). Patients with high IL15, low EGF, and low IL10 (< 200 pg/mL) have an intermediate risk ($9/15$; 60% ; 95% CI $32-84$), and patients with high IL15, low EGF and high IL10 have a high risk of severe neurotoxicity ($10/10$; 100% ; 95% CI $69-100$).⁷⁸ Accordingly, Faramand's study found that baseline IL6 ($P = .036$) and *ANG2/ANG1* ($P = .004$) were associated with severe ≥ 3 ICANS.⁶⁴ The same results were obtained in Faramand's previous study, where baseline levels of IL6 ($P = .013$), *ANG2/ANG1* ($P = .0056$), and *ANG2* ($P = .0190$) were associated with severe NT.⁷³ In particular, peak levels of *IL6* ($P = .0128$), *ANG2/ANG1* ($P = .0016$), *IFN γ* ($P = .0064$), and *IL15* ($P = .0006$) and lower peak levels of *ANG1* ($P = .028$) were associated with severe NT.⁷³ Gust's study found that within the first 6 days after CAR-T cell infusion, 100% of patients with an IL-6 concentration ≥ 501 pg/mL developed grade ≥ 4 neurotoxicity.¹⁸ Specifically, Gust et al. found that serum *ANG2* concentration ($P = .0003$) and *ANG2/ANG1* ($P = .0014$) were higher in patients with grade ≥ 4 neurotoxicity compared to those with grade ≤ 3 neurotoxicity.¹⁸ Multivariate logistic regression confirmed the significant role of *ANG2/ANG1* for severe NT ($P = .0154$).⁷³

NT was highly correlated with the manifestation of Severity of Cytokine Release Syndrome (CRS), with fever $\geq 38^{\circ}\text{C}$ as an early sign.^{18,77,65} In Rubin's study, fever was significantly associated with NT (OR= 3.86; 95% CI: 2.14-6.94; $P < .001$).⁷⁵ Gust's study found that patients who developed grade ≥ 3 neurotoxicity had more severe CRS ($P < .0001$).¹⁸ These data were confirmed by Santomasso's study⁷⁸, which found a strong correlation between severe neurotoxicity and severe CRS (OR= 52.5, 95% CI: 8.66-1027.2, $P < .001$) and between severe neurotoxicity and any grade of CRS (OR= 5.36, 95% CI: 2.52-15.74, $P < .001$). Gust's study found that patients who developed grade ≥ 3 neurotoxicity had more severe CRS ($P < .0001$).¹⁸ Accordingly, Rubin's study found a significant association between CRS and NT (OR= 0.65; 95% CI: 0.52-0.81; $P < .001$).⁷⁵ Conversely, in Holtzman's study,⁷⁴ no relationship between CRS high (3-4) versus low (0-2) grade and the development of severe ICANS ($P = .25$) was found.

Metabolic tumour parameters and progression

Patients with high disease burden, defined as bone marrow blasts $\geq 5\%$ or radiographically evident extramedullary disease in patients with leukemia, were more likely to develop severe neurotoxicity.⁷⁸ Accordingly, Gust's study found that, with univariate analysis, neurotoxicity of any grade was more frequent in patients with a high tumour burden ($P = .072$).¹⁸ Bone marrow involvement by biopsy (12% vs 29%, $P = .05$) was associated with a higher frequency of grade 3-4 ICANS compared to grade 0-2 ICANS.⁷⁶ Accordingly, Gust's study found that neurotoxicity of any grade was more frequent in patients with CD19+ cells in bone marrow in both univariate ($P = .062$) and multivariate analysis ($P = .0165$).¹⁸ High metabolic tumour volume (MTV) pre-CAR T was correlated with developing ICANS events (OR= 4.3, $P = .01$), and high maximum standardised uptake value (SUV) pre-CAR T was associated with grade 3-4 neurological events (OR= 12, $P = .01$) in univariate logistic regression on DLBCL patients.⁶⁶ High total lesion glycolysis was not significantly correlated with developing any grade ICANS or high-grade ICANS in DLBCL patients.⁶⁶ Tumour metabolic volume was not statistically associated with ICANS in Ababneh's study ($P = .93$).⁶⁶

Karschnia's study⁷⁷ found that 69% and 50% of lymphoma patients with high-grade and low-grade neurotoxicity, respectively, had pre-treatment LDH levels of 400 U/L ($P = .473$). In Holtzman's study,⁷⁴ LDH (618 vs 506 units/L, ULN 618 units/L, $P = .04$) was associated with the development of ICANS, as well as in Faramand's study ($P = .028$) for ≥ 3 ICANS in LBCL patients.⁶⁴ Conversely, Strati's study found no statistically significant association between LDH levels and a higher frequency of grade 3-4 ICANS compared with grade 0-2 ICANS.⁷⁶

Other Clinical Characteristics

History of vascular disease or dementia did not predict the occurrence of ICANS in the elderly group (≥ 70 years) (OR= 1.2, 95% CI: 0.78-1.81, $P = .45$ and OR= 1.4, 95% CI: 0.81-1.63, $P = .38$, respectively).⁶⁸ Other prior neurologic and psychiatric disorders were not associated with ICANS incidence.⁷⁶ Conversely, Gust's study found that any pre-existing neurologic comorbidities were associated with neurotoxicity in univariate ($P = .0059$) and multivariate analysis ($P = .0023$).¹⁸ Eastern Cooperative Oncology Group (ECOG) performance status > 0 (80% vs 61%, $P = .05$) was associated with a higher frequency of grade 3-4 ICANS compared with grade 0-2 ICANS.⁷⁶ Precisely, Larue et al. found a significant association between ECOG performance status and ≥ 2 ICANS in univariate analysis: OR= 5.29; 95% CI: 1.92-14.62; $P = .001$. No significant association was found between ECOG performance status and ≥ 2 ICANS by Faramand (OR 0.75; 95% CI: 0.29-1.8; $P = .54$)⁶⁴ and Larue (OR = 3.34; 95% CI: 0.83-13.36; $P = .088$) in a multivariate analysis.⁶⁵ Lymphoma type and subtype were not statistically associated with ICANS.⁷⁴ In contrast, Rubin's study found that the histologic lymphoma subtype (aggressive vs indolent) was significantly associated with NT (OR= 4.55, 95% CI: 1.46-14.18); $P < .001$.⁷⁵

Pooled Prevalence of ICANS: Meta-Analysis Results

In retrospective studies the pooled prevalence was 41% (95% CI: 31-51%, $P < .001$, $I^2 = 94.40$) for all grades ICANS ($n = 14$ studies and $n = 1351$ individuals total),^{18,64-71,73,74,76-78} (Fig. 2), 23% (95% CI: 17-29, $P < .001$, $I^2 = 77.85$) for grade 1-2 ICANS (with missing

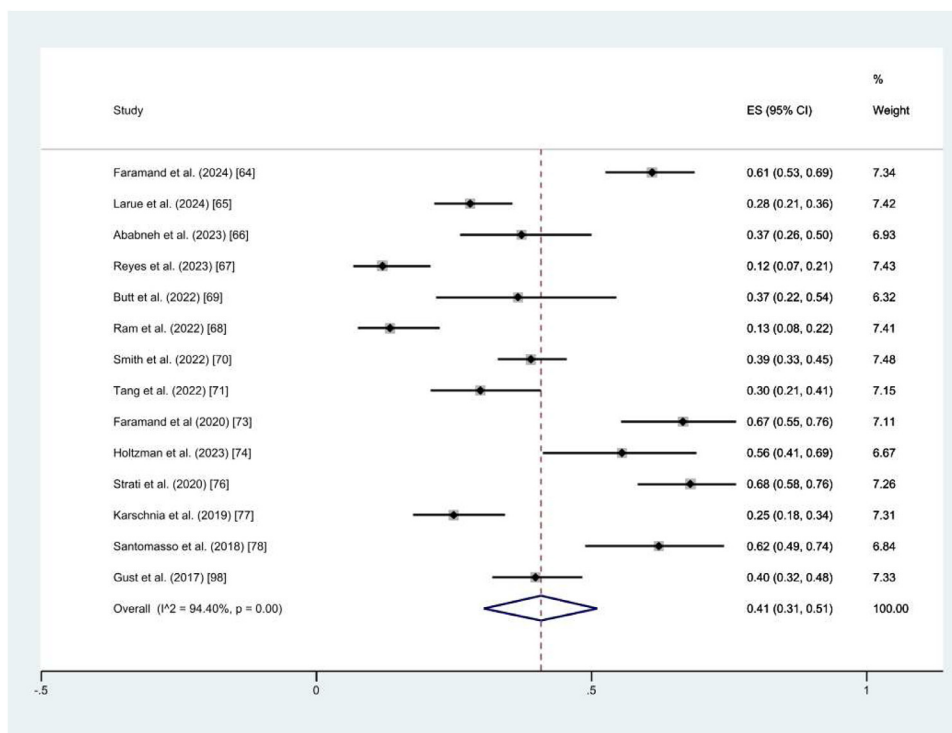


FIG. 2. ICANS prevalence for all grades in retrospective studies.

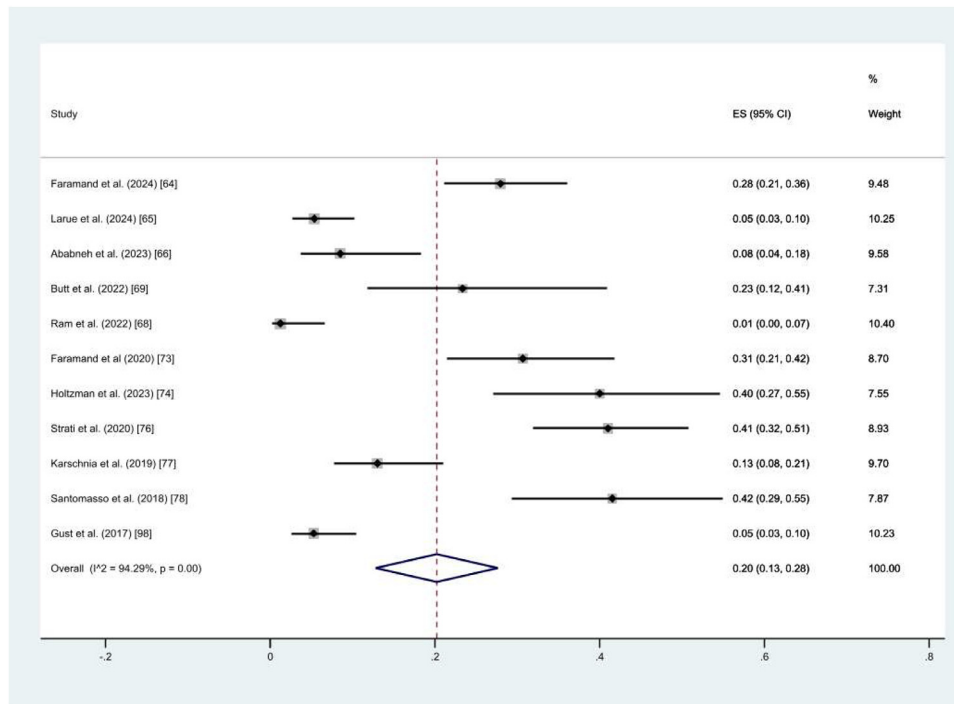


FIG. 3. ICANS prevalence for grade 3–4 ICANS in retrospective studies.

information in 3 studies)^{67,70,71} (Supplementary File 3), and 20% (95% CI: 13–28, $P < .001$, $I^2 = 94.29$) for grade 3–4 ICANS (with missing information in 3 studies)^{67,70,71} (Fig. 3). The sample comprised individuals aged between 19 and 90 years with diverse haematological malignancies. The mean time to ICANS was 5.2 days, with this data reported only in 7 studies.^{18,68,71,73,74,77,78}

In prospective studies (n=2 studies and n=300 individuals total),^{72,75} the pooled prevalence was 51% (95% CI: 45–56%, $P < .001$, $I^2 = 0\%$) (Supplementary File 4). The sample comprised individuals aged 19–83 years with B-cell precursor acute lymphoblastic leukemia and diffuse large B-cell lymphoma who underwent treatment with axi-cel and tisa-cel. Only 1 of these 2 studies reported data regarding ICANS grade;⁷⁵ therefore, we could not calculate the prevalence based on the ICANS severity.

The asymmetric-shaped funnel plot (Supplementary File 5) suggested a risk of publication bias, in particular for studies with small sample sizes. This might suggest that smaller studies with unfavorable results were not published. The regression-based Egger’s test for

small-study effects was performed to regress the effect estimate on its standard error, weighted by its inverse variance. Despite the qualitative apparent asymmetry, Egger’s test for publication bias was not statistically significant ($P = .0735$). However, the power of Egger’s test is considerably lower when there is substantial heterogeneity, and then the visual inspection may be preferable to Egger’s test in cases of high heterogeneity.⁸¹

Risk of Bias of the Included studies

The quality assessment results are summarized in Table 3. Of the 16 studies, 10 were rated as high quality,^{18,66–69,71,72,74,75,78} and 6 as medium quality,^{64,65,70,73,76,77} with an overall average score of 6.7. The overall quality of the studies was good. All included studies received the maximum score in the exposure domain, as exposure assessment was consistently conducted using objective and validated methods, such as medical records, biomarker quantification, or standardized clinical criteria. These rigorous methodologies reduce the risk of misclassification and enhance the reliability of exposure assessment across studies.

Regarding representativeness, none of the studies included a sample that could be considered fully representative of the entire population undergoing CAR T-cell therapy. In several cases, patient recruitment was limited to specific medical centers, often specialized in cellular therapy, which may introduce selection bias. Further, the majority of these studies focused on populations treated with tisa-genelecleucel and axicabtagene ciloleucel, the first 2 medications approved by the FDA and EMA and, for many years, the only ones accessible for the treatment of particular haematological illnesses. This limitation reduces the external validity of the findings, as the characteristics of the included populations may not reflect those of all patients receiving CAR T-cell therapy in broader clinical settings.

Additionally, 5 studies did not include a control group,^{64,65,73,76,77} preventing an evaluation of comparability. The absence of a reference population without the exposure of interest limits the ability to infer causal relationships, as potential confounders could not be accounted for through direct comparison. Among the remaining studies, 7 implemented comprehensive comparability analyses,^{14,18,67–69,74,78}

TABLE 3
Risk of Bias of the included studies

	Selection	Comparability	Exposure	TOT
Faramand et al. ⁶⁴	*	*	*	5
Larue et al. ⁶⁵	*	*	*	5
Ababneh et al. ⁶⁶	*	*	*	7
Reyes et al. ⁶⁷	*	*	**	8
Butt et al. ⁶⁹	*	*	*	8
Ram et al. ⁶⁸	*	*	**	7
Smith et al. ⁷⁰	*	*	*	6
Tang et al. ⁷¹	*	*	*	8
Schoeberl et al. ⁷²	*	*	*	7
Faramand et al. ⁷³	*	*	*	5
Holtzman et al. ⁷⁴	*	*	**	8
Rubin et al. ⁷⁵	*	*	*	7
Strati et al. ⁷⁶	*	*	*	5
Karschnia et al. ⁷⁷	*	*	*	5
Santomasso et al. ⁷⁸	*	*	**	8
Gust et al. ⁹⁸	*	*	**	8

Risk of bias interpretation: 0–4 (low quality), 5–6 (moderate quality), 7–9 (high quality).

incorporating multivariable statistical adjustments to control for key confounding factors such as age, sex, tumor burden, prior neurological conditions, and previous exposure to neurotoxic therapies. These studies provide stronger internal validity as they attempt to isolate the effect of the exposure from other influencing variables.

Overall, while the exposure assessment was consistently rigorous, limitations in representativeness and the absence of control groups in some studies introduce potential biases that should be considered when interpreting the results.

Discussions

CAR-T cells represent a highly effective therapy for managing relapsed or refractory B cell-derived haematological malignancies, including lymphoma, leukaemia, and multiple myeloma.⁸² Notwithstanding the remarkable potential of CAR-T cells, specific therapy-related toxicities have been reported,¹⁶ with ICANS as the most unpredictable and life-threatening.⁸ In light of the limited systematic evidence to guide clinicians in predicting and mitigating this complication, this review systematically summarized observational studies analyzing factors associated with ICANS development after CAR-T, providing evidence to improve patients' risk assessment and monitoring.

Overall Characteristics of the Included Studies

As also reflected in our summary, the USA is the leading country in CAR-T cell products.⁸³ Currently, 6 FDA-approved second-generation CAR-T therapies are available in the USA for the treatment of haematological malignancies, depending on disease stage, type, and population age: Tisagenlecleucel (tisa-cel), ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel), lisocabtagene maraleucel (liso-cel), targeting the CD19 antigen, and Idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), targeting the BCMA antigen.⁸² However, the number of approved CAR-T cell products varies worldwide, with 11 countries (USA, Canada, Germany, France, Spain, the United Kingdom, Italy, ISRAEL, Australia, Singapore, and China) benefiting.⁸³ Although the FDA approved 6 CAR-Ts, our analysis did not uncover the results of lisocabtagene maraleucel (liso-cel). However, liso-cel was the fourth commercially available autologous CD19-directed CAR T-cell product approved as a second-line treatment option for refractory or relapsed (RR) LBCL in 2022.⁸² The included studies on individuals with R/R LBCL, which utilised axi-cel and tisa-cel (approved by the FDA in 2017), date back to 2020, when liso-cel was not still approved.

Overall, the outcome definition and classification were quite homogeneous among studies, although some still utilized neurotoxicity and the Common Terminology Criteria for Adverse Events (CTCAE) for the assessment. There are several definitions and scores to grade these toxicities, such as the CTCAE and the CARTOX guidelines;^{80,84} however, these definitions and gradings were not specifically designed for CAR-T cell therapies and were accurate enough for capturing the severity, timing, and spectrum of neurological manifestations.^{23,85} Thus, the American Society for Transplantation and Cellular Therapy (ASTCT) has proposed the ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells to clearly define the neurotoxicity related to CAR-T cell therapies (or any immune effector cell engaging therapy) and its grading.¹⁷

Prevalence and Risk Factors for ICANS

Approximately half of the haematological patients undergoing CAR T therapy experience ICANS, with variable proportions depending on the study design and ICANS grade. Our results fall within the range reported by a recent narrative review, which describes an

ICANS's prevalence ranging from 37.5%-77%.²⁷ In addition, a recent meta-analysis on ICANS incidence reported a proportion of 26.9% (95% CI, 21.7%-32.7%) for all grades and 10.5% (95% CI, 8.1%-13.6%) for high-grade ICANS.⁸⁶ However, this meta-analysis included data from all the available clinical trials and real-world studies, and the authors adopted a different statistical approach to perform the meta-analysis. Since our primary aim was to investigate potential predictors of ICANS, additional data on ICANS incidence reported in other non-eligible studies were not considered in our meta-analysis. As a result, none of the studies included in this published meta-analysis were selected.

The results on factors associated with ICANS development after CAR-T cell therapies were highly discordant, and unfortunately, our review failed to give a clear understanding of risk factors associated with ICANS after CAR-T therapies. The type of CAR-T product used in the selected studies may be 1 of the key factors determining discordances among the results for each variable, since researchers found that CAR-T structure and composition may contribute to toxicity patterns.^{39,87} In this regard, a recent meta-analysis including clinical trials and real-world studies found that cohorts with anti-CD19 drugs had significantly higher ICANS incidences and high-grade ICANS than cohorts with other agents (OR = 4.6).⁸⁶ However, CAR-T cells are a recent therapy, with the first approved drug in 2017,⁸³ and both efficacy and safety remain to be further demonstrated outside clinical trials with real-world data.⁸⁸

Among sociodemographic variables, age may contribute to ICANS in a selected prospective study of 204 participants. However, highly discordant results were found in our selected studies and the excluded prediction score studies that investigated potential variables to be included in these scores.³⁶⁻³⁸ Precisely, it is unclear if younger or older individuals are at more risk of developing ICANS.^{67,68,75}

Considering the haematological parameters, elevated levels of fibrinogen, a blood coagulation protein, at baseline seem to play a significant role in the development of ICANS as well as its severity. In several neurological disorders, fibrinogen accumulates in the brain after the BBB disruption since it contains multiple binding sites for cellular receptors, and proteins are expressed in the nervous system.⁸⁹ The fibrinogen retention activates central nervous system inflammation, scar formation in the brain, promotes cognitive decline, and inhibits repair.⁸⁹ BBB permeability is altered in CD19 CAR-t therapy, although the causes are still unclear.⁹⁰

Results on therapeutic aspects suggested a significant role of tocilizumab in determining ICANS and its severity. Tocilizumab is a humanized monoclonal antibody targeting the IL-6 receptor and is commonly used to manage CAR T cell-related CRS.⁹¹ Accordingly, a recent retrospective multicenter study suggested caution in using tocilizumab for patients with a potentially high risk of ICANS, as up to 75% of ICANS and 87.5% of grade ≥ 3 ICANS occurred in the tocilizumab group patients.⁹² Although the type of infused T-cell products had no significant association with the development of ICANS or neurotoxicity in 2 studies, Larue et. al demonstrated that receiving CD28-equipped CAR T cells was the strongest predictor of grade 2-4 ICANS. Interestingly, real-world data results exhibited that grade 1-2 and grade ≥ 3 ICANS were significantly more frequent with axi-cel than with tisa-cel.⁹³ In practice, while axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) use the same CAR with costimulation domains derived from CD28, tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) use transmembrane domains derived from the 4-1BB co-stimulation domain.⁹⁴ Further, our included univariate and multivariate analyses significantly associated high CAR-T cell doses with neurotoxicity. A recent systematic review suggested that administering dose fractions of CAR-T cells over 2-3 days instead of a single-dose infusion may reduce the toxicity of CAR-T cell therapy, including CRS and neurotoxicity, especially in patients with high tumour burden.⁹⁵

Divergent results were noticed when comparing the conclusions of certain authors with the findings on univariate and multivariate models on the role of specific blood chemistry biomarkers in predicting ICANS. However, high levels of CRP, ferritin, and circulating enzyme lactate dehydrogenase, and low albumin levels, serum protein, and phosphate before CAR-T infusion seem to be significantly associated with both ICANS frequency and severity in the majority of the studies. In particular, ferritin and CRP serum levels peaked with the onset of neurologic symptoms, and increased ferritin levels were associated with higher neurotoxicity grade.^{18,77} In particular, patients who developed severe neurotoxicity had significantly higher concentrations of C-reactive protein at day 3 compared to those with mild neurotoxicity in B-cell Acute Lymphoblastic Leukemia patients.⁷⁸ Implementing these baseline and routine blood chemistry biomarkers in machine learning-based models may be able to risk-stratify patients receiving CAR-T therapy to identify those who may benefit from close monitoring and/or early therapeutic intervention to prevent or mitigate the severity of ICANS.^{96,97}

The current analysis supports an association between high levels of specific proinflammatory cytokines, such as IL1 α , IL2, IL3, IL5, IL6, IL10, IL15, IP10, INF γ , GCSF, GM-CSF, MCP1, ANG2/ANG1, and ANG2 at baseline and ICANS, including its severity. The interaction between cytokines and the components of the neurovascular unit, including endothelial cells, pericytes, astrocytes, microglia, and neurons, modulates the central nervous system inflammation and then the neurological dysfunction.⁹⁸

Our study underlines the role of NfL as a potential biomarker for predicting the risk of ICANS. The NfL is a cytoskeletal protein released into the cerebrospinal fluid (CSF) and blood following damage to central and peripheral neurons.⁹⁹ The exact mechanism by which NfL is released from damaged neurons remains incompletely elucidated; nonetheless, it is likely a direct result of compromised cell membrane integrity.^{100,101} Nonetheless, the measurement of blood NfL introduces a novel blood biomarker for neurological disorders, circumventing the invasiveness of cerebrospinal fluid samples that limited the therapeutic utility of NfL.¹⁰⁰ However, the blood NfL is not disease-specific and physiological processes, including body mass index, diabetes, and hypertension,^{99,100} may trigger its release. In order to appropriately evaluate the contribution of NfL as a surrogate for sub-clinical neurological damage, excluding patients with neurological history could be an effective strategy, as Larue et al. suggested.⁶⁵

All the studies (except 1) confirmed CRS as a risk factor for ICANS, with fever as an early sign. Fever occurred with a median of 2 \pm 3 days (range, 0–4 days) after infusion of CAR T cells in low-grade neurotoxicity patients.⁷⁷ CRS is a systemic inflammatory response caused by cytokines released by infused CAR T cells that may lead to widespread organ dysfunction along with a constellation of symptoms.¹⁰² CRS consistently preceded the onset of neurologic symptoms, and the median time between the first fever and first neurologic symptoms was 3 \pm 1.5 days (range, 1–19 days).⁷⁷ Early-onset fever may, therefore, raise suspicion for impending CAR T-cell neurotoxicity.⁷⁷ CRS lasts for a median of 5 \pm 0.9 days (1–11 days) and is sometimes entirely resolved before low-grade neurotoxicity occurs. The median onset of severe neurotoxicity from the beginning of CRS was 8 days (range, 1–11 days). Neurotoxicity sometimes occurs after CRS has entirely resolved, although it is always preceded by fever.⁷⁸ CRS represents the most frequently observed immune-mediated toxicities along with ICANS, and their strong association may suggest common biological pathways and biomarkers mediation.³⁴ However, the standard treatment for CRS, tocilizumab, does not seem to improve ICANS and might exacerbate symptoms in some cases.^{18,77,103}

Some pretreatment metabolic tumour parameters such as high metabolic tumour volume, high maximum standardised uptake value, and high tumour burden as bone marrow involvement (defined as the percentage of blast cells in a patient's bone marrow)

have been significantly associated with ICANS and severity in all the included studies and may be considered promising prognostic markers in predicting ICANS. According to a recent systematic analysis, dose fractionation of CAR-T cells in patients with a high tumour burden is thought to result in regulated expansion and tumour destruction, leading to lower peaks of inflammatory cytokines that determine neurological damage and toxicity.⁹⁵ Elevated levels of circulating enzyme lactate dehydrogenase (LDH) have been historically considered in oncology as a marker of bad prognosis, usually attributed to elevated tumour burden and cancer metabolism.¹⁰⁴ Although we found that both tumour burden and LDH are potential biomarkers for ICANS, recent evidence suggests that elevated LDH levels could be independent of tumour burden and contain a negative predictive value.¹⁰⁴ This independent relationship could help to guide future research in the definition of prognostic score for predicting ICANS.

Evidence on additional clinical characteristics, such as a history of vascular disease, ECOG performance status, and histologic molecular subtype, are scarce and heterogeneous, with some studies and analyses supporting their potential role in increasing the risk of ICANS, whereas others found no significant associations. However, before focusing on these elements as potential risk factors, some of these aspects require particular attention from healthcare professionals since recent research highlighted high variability of performance status (PS) assessment between patients with hematologic malignancies and their physicians.¹⁰⁵ Precisely, age, disease stage, and disease subtype were significant predictors of PS disagreement between patients and physicians: patients who were older or had more advanced disease and/or more aggressive disease subtypes were more likely to disagree with their physician's PS evaluation (with some additional co-existing factors such as depression and well-being contributing).^{105–107}

Limitations

The results of this systematic review should be interpreted in light of several limitations. First, our systematic review yielded a considerable number of retrospective studies with a limited sample size. Retrospective studies reported data from charts and medical records that were not originally designed to collect specific research data, and therefore, some information could be missing.¹⁰⁸ Further, retrospective studies are subjected to selection bias in how controls in a case-control study are identified.¹⁰⁸ The limited oversight of predictor variable quality and the potential omission of significant variables complicate the demonstration of confounding variables and causality.¹⁰⁸ For these reasons, the generalization of results should be cautious in determining cause-effect relationships in these investigations.¹⁰⁸ However, in our analysis, the quality of evidence ranged from medium to high, and some authors used appropriate statistical techniques (e.g. multiple regression analysis) to control for potential confounders and account for missing data (e.g. multiple imputation). Second, our search was conducted on 4 databases without including additional web search engines such as Google Scholar, which allow searching for academic resources and scholarly literature; this choice may have precluded some results. However, reference checking was performed as an additional method. Third, we conducted a meta-analysis on ICANS prevalence with limited results. However, conducting a meta-analysis about ICANS prevalence was not our primary aim, and the choice of conducting a meta-analysis was to maximize the selected research findings. Therefore, meta-analysis results should be interpreted with caution as additional primary data are available in the literature to estimate ICANS incidence. However, to be as accurate as possible, we performed a proportional meta-analysis, which is the preferred method for conducting a proportion meta-analysis with binomial data, and we based the analyses on the study

design. Further, we assessed the publication bias. Finally, although the studies' characteristics were homogeneous, the studies' results on potential predictors of ICANS were limited and highly discordant; this precluded us from quantifying the impact of each factor on the outcome and giving clear recommendations on predictors.

Implications for Nursing Practice

Nurses have a crucial role in post-treatment monitoring in the early detection of neurological deterioration, given their continuous patient interaction. These results will increase nurses' awareness of potential risk factors for ICANS and enable their vigilance in managing patients undergoing CAR-T therapies. Nurses may enable individualized pathways for at-risk patients by acknowledging clinical predictors, connecting diagnostic and expert services, and delivering targeted information to patients and caregivers. Their active participation in the multidisciplinary team is essential for optimizing resource allocation and supporting good clinical decisions, ultimately enhancing patient health outcomes.

Conclusion

This review systematically synthesized current evidence on socio-demographic and clinical factors associated with ICANS in adults with hematological malignancies undergoing CAR-T cell therapy. The emerging epidemiological overview of ICANS prevalence, along with the analysis of a broad range of potential predictors, helps to enhance clinical understanding and facilitate early risk identification for this severe complication. ICANS remains a frequent and unpredictable toxicity, affecting approximately half of patients receiving CAR-T therapy. While certain baseline variables appear to be associated with ICANS development and severity, the predominance of retrospective studies, small sample sizes, and inconsistent findings across studies limit the ability to draw definitive conclusions. Our findings underscore a pressing need for high-quality, prospective, and large-scale studies to assess the predictive value of identified factors and inform the development of robust prognostic models. Translating these predictors into clinical practice may improve patient risk stratification, facilitate timely interventions, and ultimately reduce ICANS-related morbidity and hospitalization.

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CRediT authorship contribution statement

Silvia Belloni: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Chiara Giacon:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Arianna Magon:** Writing – review & editing, Supervision, Data curation. **Daniele Girardi:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Marco Alfredo Arcidiacono:** Writing – review & editing, Supervision, Data curation. **Greta Ghizzardi:** Writing – review & editing, Methodology, Data curation. **Gianluca Conte:** Writing – review & editing, Supervision, Methodology. **Rosario Caruso:** Writing – review & editing, Supervision, Methodology. **Cristina**

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.soncn.2025.151944.

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