Treatment-related adverse events of chimeric antigen receptor-T therapies for cancers in clinical trials: a systematic review and meta-analysis

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Summary

Background Chimeric antigen receptor (CAR)-T cell therapies are being tested in many ongoing trials against hematologic malignancies and solid tumors. The incidence and profile of treatment-related adverse events are necessary when moving to clinical practice.

Methods Published clinical trials on CAR-T cell therapies were collected from PubMed, Embase, Cochrane, and Web of Science databases between January 1, 2010, and August 27, 2024, with an updated search up to May 1, 2025, to extract tabular data on treatment-related adverse events. A logit-transformed random effects model was used to calculate the incidence and 95% CI of all-grade and grade 3 or higher treatment-related adverse events, with inter-study heterogeneity primarily assessed by I^2 statistics. Differences between different antigen-binder, co-stimulation, cancer types, and specific subgroups were also explored in detail. The study was registered on PROSPERO (ID, CRD42024596383).

Findings This systematic review and meta-analysis included 163 clinical trials involving 6342 patients. Of 4395 patients from 107 trials, 4312 (98.11% [95% CI, 97.65%–98.46%], I^2 = 0.0%) had at least one adverse event of all-grade, and of 4248 patients from 103 trials, 3512 (82.67% [95% CI, 81.50%–83.78%], I^2 = 82.8%) had at least one adverse event of grade 3 or higher. The most common all-grade adverse events and grade 3 or higher adverse events in hematological malignancies were cytokine release syndrome (81.50% [77.04%–85.43%]) and neutropenia (72.30% [62.94%–80.39%]), respectively. The most common all-grade adverse events and grade 3 or higher adverse events in solid tumors was lymphopenia (89.21% [45.31%–99.38%] and 51.96% [8.98%–92.87%]). Ciltacabtagene autoleucel was associated with a lower mean incidence of all-grade adverse events (Risk ratio [RR], 1.00; 95% CI, 0.99–1.01; Rank-score, 0.6341; I^2 = 0.0%) and tisagenlecleucel were associated with lower grade 3 or higher adverse events (RR, 0.93; 95% CI, 0.86–1.02; Rank-score, 0.9738; I^2 = 78.4%) compared with standard care and CAR T-cell therapies. Anti-CD19 CAR-T cells were associated with a lower mean incidence of grade 3 or higher adverse events compared with anti-BCMA CAR-T cells (RR, 0.93; 95% CI, 0.87–0.99; I^2 = 78.4%). CAR-T cells containing 4-1BB costimulation had a lower incidence of grade 3 or higher adverse events than CAR-T cells containing CD28 costimulation (RR, 0.88; 95% CI, 0.81–0.95; I^2 = 78.4%).

Interpretation Our study provides comprehensive data on adverse events associated with different CAR-T cell treatments, maps a complete toxicity profile, and provides an important reference for clinicians to select and manage anti-cancer therapies.

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Keywords: Chimeric antigen receptor T-cell; Targeted; Oncology; Clinical trials; Treatment-related adverse events

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Research in context

Evidence before this study

With the breakthrough of CAR-T cells in the treatment of hematologic malignancies, the focus of research is shifting to solid tumors, which also have initial therapeutic advantages. While the efficacy is significant, safety is also a major concern, and there is an urgent need to fully understand the toxic characteristics of CAR-T cell therapy. We searched Pubmed, Embase, Cochrane, and Web of Science databases for clinical trials investigating CAR-T cell therapy between January 1, 2010, and August 27, 2024, with an updated search up to May 1, 2025, with the search term "Chimeric Antigen Receptor-T". "CAR-T", "Cancer", and "Clinical trials". Eligible studies were limited to prospective trials published in English. If multiple articles from the same study had the most comprehensive adverse event table and fewer than 10 patients were included, the study was excluded.

Added value of this study

In the present study, we conducted a systematic review and meta-analysis of 163 clinical trials with approximately 6342 participants. To our knowledge, our study provides the largest and most comprehensive meta-analysis of treatment-related adverse events based on CAR T-cell therapies. We report a comprehensive overview of common treatment-related adverse events and serious adverse events for CAR-T cells and detailed causes of treatment-related deaths. It is also discussed from many main aspects: different antigen-binder, co-stimulation, cancer types, and specific subgroups. It was found that CAR-T cell therapy had a high incidence of adverse events, and serious adverse events and treatment-related deaths were acceptable. There was a higher incidence of adverse events in hematologic malignancies, anti-BCMA CAR-T cells, and CAR-T cells with CD28 co-stimulation, patients with bulky tumors, prior more than second-line therapies, and previous hematopoietic stem cell transplantation.

Implications of all the available evidence

Due to the increasing advantages of CAR-T cell therapies in recent years, different treatment strategies have different levels of adverse events. Understanding the toxicity profile is a clinical need, which also requires large clinical trials and real-world data support. Therefore, our study provides a comprehensive summary of CAR-T cell therapies, and an overview of treatment-related adverse events in clinical trials, and is intended to serve as a reference for clinicians in clinical practice and may supplement guidelines.

Introduction

The emergence of chimeric antigen receptor (CAR)-T cell therapies has been among the most impactful breakthroughs in the immunotherapeutic management of cancer in recent years, providing an effective means of treating a range of hematological malignancies including leukemia, lymphoma, and multiple myeloma.[1–4] A growing number of clinical trials published in recent years have also yielded promising CAR-T treatment results in patients with various solid tumors including germ cell tumors, gastrointestinal cancers, and neuroblastomas,[5–7] underscoring the impactful nature of this innovative treatment strategy across cancer types. The expanding clinical uptake of CAR-T treatment approaches has led to their widespread testing for a wider range of indications across hundreds of studies published to date. However, there remains a pressing need for further studies aimed at better clarifying the most effective approaches to implementing CAR-T therapies based on a more thorough understanding of the attendant risks.

The genetically engineered CAR transmembrane receptors are generally introduced into immune cell populations, predominantly T cells, through the use of viral vectors.[8] There are four major domains that comprise the final CAR molecule, including an antigen-binding domain that most commonly consists of a single chain variable fragment from a monoclonal antibody (mAb-scFv), an IgG or CD8α/CD28-based hinge domain, a transmembrane (TM) domain, and an intracellular domain that can consist of co-stimulatory (most commonly 4-1BB and CD28) and signal transduction (predominantly CD3ζ) domains.[9] CAR antigen specificity is the primary factor that determines the safety and efficacy profile of the resultant CAR-T cells.[9] The tuning of CAR affinity, epitope locations, and the features of the hinge, TM, and signal domains can all improve CAR-T cell-mediated tumor recognition.[9] The two most characteristic and common toxic reactions associated with CAR-T therapy are cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS). These disorders are mediated by activated T-cells and cytokines released by bystander immune cells (primarily IL-6) and activated by initial CAR-T/tumor target interactions.[10] In solid tumors, the most prominent form of toxicity associated with CAR-T treatment consists of on-target extratemporal effects mediated by the recognition of the target antigens of the engineered CAR-T cells in off-tumor tissues. Upon target engagement, these CAR-T cells form immune synapses with the target cell that trigger the release of effector factors that ultimately lead to target cell killing.[11]

To date, the U.S. Food and Drug Administration (FDA) has approved two CAR-T products targeting B cell maturation antigen (BCMA) (Abecma® [idecabtagene vicleucel; ide-cel] and Carvykti® [cabtagene autoleucel; cilta-cell]), as well as four targeting CD19 (Breyanzi® [lisocabtagene maraleucel; iso-cel], Kymriah® [tisagenlecleucel; tisa-cel],

Tecartus® [brexucabtagene autoleucel; brexu-cel], and Yescarta® [axicabtagene ciloleuce; axi-cel]). Despite consistent evidence that these CAR-T therapies can provide promising efficacy when used for cancer treatment, their tolerability remains a topic of active concern to both patients and clinicians, particularly given the risk of severe, sometimes life-threatening adverse events. A few meta-analyses conducted to date have explored the clinical toxicity associated with CAR-T treatment, revealing relatively high incidence of CRS incidence and generally high adverse events incidence associated with both anti-CD19 and anti-BCMA CAR-T products.[12–14] However, most of these studies focused on the incidence of CRS and neurotoxicity associated with hematologic malignancies, and only one study looked at the incidence of non-CRS and neurotoxicity. In this study, all adverse events related to the treatment of hematologic malignancies and solid tumors were discussed in detail, with a particular focus on CRS and neurotoxicity. There remains a pressing need for quantitative analyses aimed at surveying different adverse events associated with a range of CAR-T therapies, providing a broader view of the full spectrum of treatment-related toxicity. Comprehensive toxicity profiles are vital to fully assess treatment-related risks to enable the more effective clinical application of these therapies.

The goal of this study was to systematically explore the incidence and characteristics of all treatment-related adverse events associated with CAR-T therapies based on data published in clinical trials. These analyses included summaries of adverse events associated with different antigen-binding domains, co-stimulatory domains, and target tumor types, thus offering a detailed survey that can aid the appropriate selection of CAR-T regimens while addressing current gaps in the international guidelines for CAR-T therapy management. Data from large-scale phase III randomized controlled trials (RCTs) were further used to compare treatment-related adverse events incidence across drugs and domains.

Methods

This meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, which was registered on PROSPERO (ID, CRD42024596383).[15]

Search strategy and study selection

The PubMed, Cochrane, Embase, and Web of Science databases were searched for relevant articles published between January 1, 2010, and August 27, 2024, with an updated search up to May 1, 2025, using the following search terms: "Chimeric antigen receptor-T", "CAR-T", "Cancer", and "Clinical Trials" (Supplementary Table S1). Studies were eligible for inclusion if they[1] focused on cancer patients undergoing CAR-T treatment,[2] provided details and supporting tabular data related to treatment-related adverse events incidence,[3] were prospective clinical trials published before August 27, 2024, and[4] were published in English. Studies were excluded if[1] non-cancer patients were included,[2] the primary treatment did not consist of CAR-T cell therapy,[3] the studies were not prospective clinical trials,[4] they were meeting abstracts, or[5] they enrolled fewer than 10 patients. If multiple articles were associated with the same study, the most comprehensive dataset with the most complete adverse events-related data or the most recent study was retained for analysis.

Data extraction

Two investigators (YW Zhu and K Liu) independently completed the process of study selection, with a third investigator (H Zhu) helping to resolve any discrepancies. These investigators extracted author names, publication year, trial name, trial stage, cancer type, CAR-T name, and structural features, the number of patients that underwent CAR-T treatment, the number of adverse events, and associated references, compiling these in an independent table (Supplementary Table S2). Safety data were additionally extracted for treatment-related adverse events of all grades (Common Terminology Standard for Adverse Events [CTCAE] grade 1 to 5), serious treatment-related adverse events (serious threat to the patient's health or death), treatment-related mortality (CTCAE grade 5), and second primary malignancy. Adverse events coding was performed as per the Medical Dictionary of Regulatory Activities (MedDRA).

Statistical analyses

Overall adverse events incidence and adverse events profiles were analyzed based on the number of events relative to the number of patients, with logit-transformation random-effects models being used to compute the final risk and corresponding 95% confidence intervals (CIs).[16] These models were fitted with restricted maximum likelihood estimates and the addition of 0.5, a simple form of Firth penalization, for each cell.[16] In the case that different clinical trials may report incomplete adverse events at different specific cutoff thresholds, cumulative binomial probabilities were used for left-censoring adverse events to maintain the possibility of consistent parameter estimation by Bayesian meta-analysis of adverse drug effects with censored data (MAGEC) modeling framework.[17–19] The primary aggregate measures for this study were the incidence and associated profiles for all-grade and grade 3 or higher adverse events. Treatment-related mortality profiles were established by comparing the number of deaths to the total number of treatment patients. Given

the complex structural features of CAR-T cells, subgroup analyses for adverse events incidence were performed for different CAR-T cell antigen targets (>20 in total) and co-stimulatory domains (4-1BB and CD28). Adverse event incidence were also established for different types of cancers (hematologic malignancies and solid tumors). In addition, factors that might influence the incidence of adverse events were also explored (tumors bulk, number of lines of prior therapy, prior autologous or allogeneic stem cell transplantation [SCT], baseline lactate dehydrogenase [LDH], and baseline C-reactive protein [CRP]). The one-way ANOVAs were used to detect differences in incidence between groups in these subgroup analyses, with $P < 0.05$ being indicative of significant differences. Before this, Shapiro–Wilk W and Levene's tests are required to determine whether normality and homogeneity of variance are satisfied. If these hypotheses are not valid, the non-parametric test is performed (Kruskal–Wallis H-test [$P \leq 0.050$ is considered a significant difference between groups]). After multiple testing adjustments, the Bonferroni correction method was used.

Data from corresponding RCTs were extracted and used to perform indirect comparisons of the safety profiles of five different CAR-T regimens, standard of care, anti-CD19 CAR-T therapies, anti-BCMA CAR-T therapies, and CAR-T therapies with differing co-stimulatory domains. A frequentist network meta-analysis method was conducted with the corresponding effect model to summarize risk ratios (RRs) and 95% CIs when assessing safety, together with rank-scores (*p*-scores), with higher scores being indicative of a better safety profile.[20,21] An I^2 statistic >50% was considered indicative of significant heterogeneity (random-effects model) and the source of heterogeneity should be evaluated using meta-regression analysis by STATA (v 18.0) with the *metareg* packages (the Restricted Maximum Likelihood [REML] algorithm).[22] Cochrane collaborative guidelines were used to assess the risk of bias for clinical trials.[23] Analyses of the risk of bias were performed using funnel plots, with symmetry being indicative of the absence of bias, and Egger's tests, with $P > 0.050$ being indicative of the absence of publication bias.[24,25] R (v 4.4.0) with the *meta and netmeta* packages and Shiny-MAGEC were used to analyze data.[26]

Ethics statement

This protocol was not submitted for ethical review because it was a systematic review and meta-analysis of CAR-T treatment-related adverse events, not patients or personal health information.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Eligible trials and characteristics

The selected search strategy returned 1104 records, ultimately leading to the inclusion of 163 trials enrolling 6342 patients with various cancer types in the present meta-analysis (Fig. 1 and Supplementary Table S2). All trials were evaluated for risk of bias (Supplementary Table S3). In total, 25 CAR-T therapy types targeting different tumor-associated antigens were identified among these trials, including therapies targeting CD19 (n = 79), BCMA (n = 18), mixed targets (n = 18), CD22 (n = 5), CD30 (n = 5), disialoganglioside (GD2, n = 4), human epidermal growth factor receptor 2 (HER-2, n = 4), CD7 (n = 3), class C group 5 member D (GPRC5D, n = 3), epidermal growth factor receptor (EGFR, n = 3), mesothelin (n = 3), carcinoembryonic antigen (CEA, n = 2), claudin18.2 (CLND18.2, n = 2), natural killer group 2D (NKG2D, n = 2), carboxyanhydrase-IX (CAIX, n = 1), CD20 (n = 1), CD70 (n = 1), CD133 (n = 1), C-type lectin-like molecule 1 (CLL-1, n = 1), glypican-3 (GPC3, n = 1), human papillomavirus (HPV, n = 1), interleukin-13 receptor alpha 2 (IL-13Rα2, n = 1), prostate stem cell antigen (PSCA, n = 1), claudin 6 (CLDN6, n = 1), prostate-specific membrane antigen (PSMA, n = 1), and tumor-associated glycoprotein-72 (TAG-72, n = 1). These trials enrolled patients undergoing treatment for lymphoma (n = 49), multiple cancers (n = 46), leukemia (n = 45), gastrointestinal cancers (n = 9), neurological cancers (n = 5), genitourinary cancers (n = 4), sarcomas (n = 2), epithelial cancers (n = 1), lung cancer (n = 1), and pleural mesothelioma (n = 1).

Overall incidence of treatment-related adverse events

At least one all-grade adverse event was reported for 4312 of 4395 patients (98.11% [95% CI, 97.65%–98.46%]; $I^2 = 0\%$) across 107 trials, while 3512 of 4248 patients (82.67% [95% CI, 81.50%–83.78%]; $I^2 = 82.8\%$) across 103 trials experienced at least one grade 3 or higher adverse events. Of 4312 hematologic malignancies, 4031 reported at least one all-grade adverse event (98.40% [97.96%–98.74%]), and among 3217 of 3820 patients (84.21% [83.01%–85.33%]) experienced at least one grade 3 or higher adverse event. When overall adverse events incidence was summarized by CAR-T antigen-binding domain, the CAR-T therapy types most commonly associated with all-grade adverse events and grade 3 or higher adverse events were anti-BCMA (99.78% [99.23%–99.93%]) and anti-GPRC5D (99.18% [88.21%–99.95%]) therapies, respectively (Fig. 2).

Of 364 solid tumours, 345 reported at least one all-grade adverse event (94.66% [91.82%–96.55%]), and among 295 of 428 patients (68.88% [64.34%–73.09%]) experienced at least one grade 3 or higher adverse event. When overall adverse events incidence was summarized by CAR-T antigen-binding domain, the CAR-T therapy types most commonly associated with all-grade adverse events and grade 3 or higher adverse events were

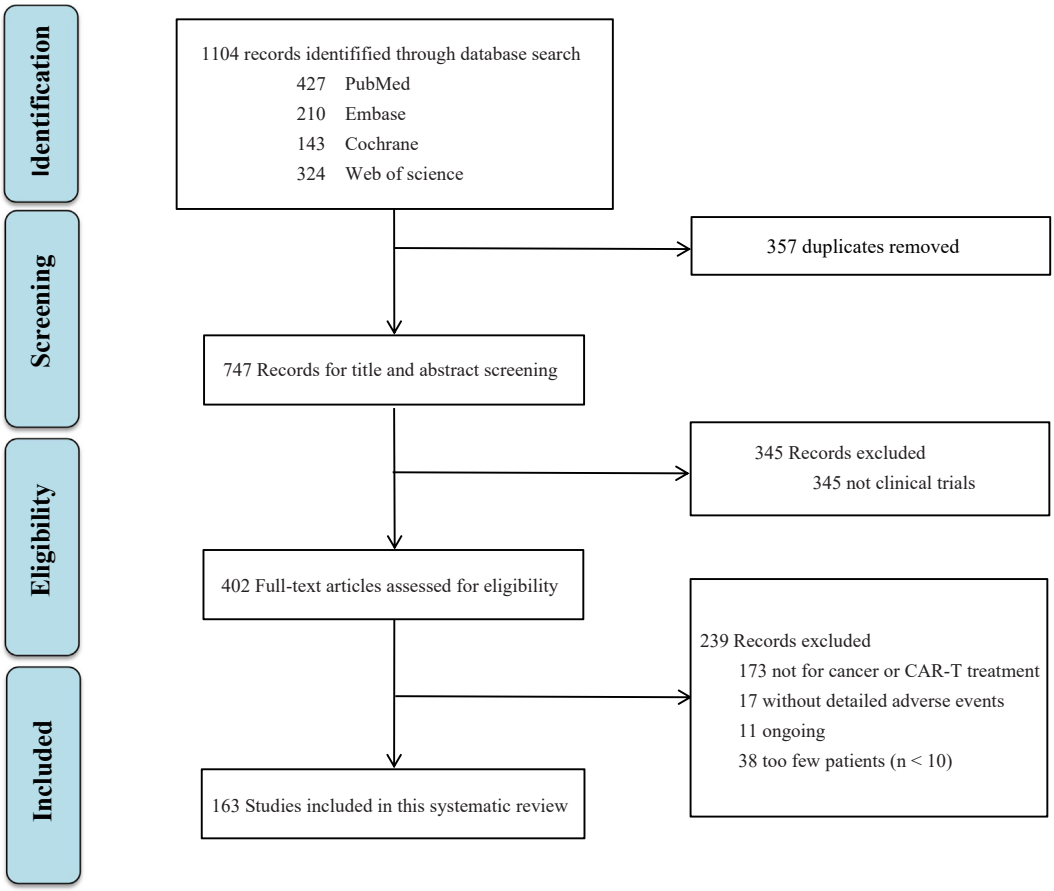

Fig. 1: Study selection process.

anti-CLND18.2 (99.59% [93.84%–99.97%]) and anti-CLND18.2 (99.59% [93.84%–99.97%]) therapies, respectively (Fig. 2).

Over 150 different treatment-related adverse event types were reported across the 163 trials included in this study. To focus on the adverse events with the greatest clinical relevance, those reported in fewer than three studies were excluded from the analysis and 116 adverse events were included eventually. In patients with hematologic malignancies, the most commonly reported all-grade adverse events included CRS (81.50% [77.04%–85.43%]), neutropenia (76.89% [68.28%–84.13%]), and fever/pyrexia (74.39% [64.53%–82.65%]). In patients with hematologic malignancies, the most commonly reported grade 3 or higher adverse events included neutropenia (72.30% [62.94%–80.39%]), lymphopenia (49.44% [26.42%–73.76%]), and leukopenia (42.20% [24.79%–59.96%]) (Fig. 3). In patients with solid tumours, the most commonly reported all-grade and grade 3 or higher adverse events included lymphopenia (89.21% [45.31%–99.38%] and 51.96% [8.98%–92.87%]), leukopenia (88.18% [1.40%–99.99%] and 42.28% [11.01%–79.86%]), and neutropenia (66.60% [31.67%–91.13%] and 24.55% [0.81%–77.83%]) (Fig. 3).

In addition, generic CAR-T-related adverse events were also explored in greater detail (Fig. 4). In patients with hematologic malignancies, the incidence of all-grade and grade 3 or higher CRS was 81.50% (77.04%–85.43%) and 9.78% (7.84%–11.86%), respectively; the incidence of all-grade and grade 3 or higher ICANS was 18.76% (14.38%–23.75%) and 4.84% (3.32%–6.65%), respectively; the incidence of all-grade and grade 3 or higher infection was 25.35% (16.03%–36.13%) and 12.26% (9.22%–15.36%), respectively. In patients with solid tumours, the incidence of all-grade and grade 3 or higher CRS was 54.27% (30.40%–75.83%) and 1.79% (0.19%–6.03%), respectively; the incidence of all-grade and grade 3 or higher ICANS was 1.86% (0.01%–15.31%) and 0.00% (0.00%–0.00%), respectively; the incidence of all-grade and grade 3 or higher infection was 4.09% (0.03%–12.85%) and 1.58% (0.01%–15.26%), respectively. In addition to the general adverse event analysis of the CAR-T products that have

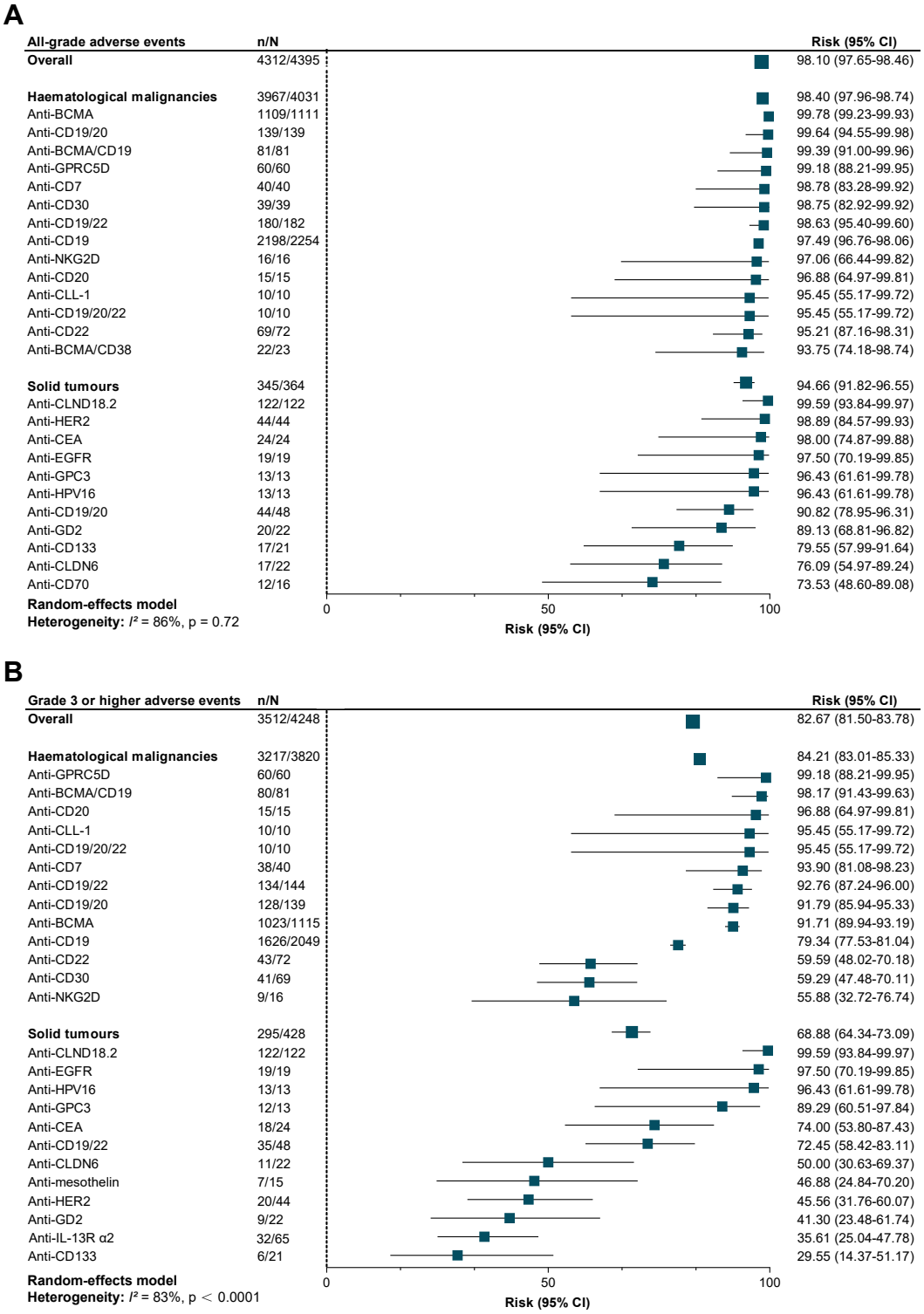

Fig. 2: The overall incidence of adverse events in different antigen-binder classes. Note: A. All-grade adverse event; B. Grade 3 or higher adverse events. Abbreviations: BCMA, B cell maturation antigen; CLND18.2, Claudin18.2; GPRC5D, class C group 5 member D; HER2, Human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; NKG2D, the natural killer group 2D; CEACAM5, carcinoembryonic antigen; GPC3, Glypican-3; HPV, Human papillomavirus; CEA, carcinoembryonic antigen; CLL-1, C-type lectin-like molecule 1; GD2, disialoganglioside; CLDN6, The oncofetal antigen claudin 6; IL-13Rα2, interleukin-13 receptor alpha 2.

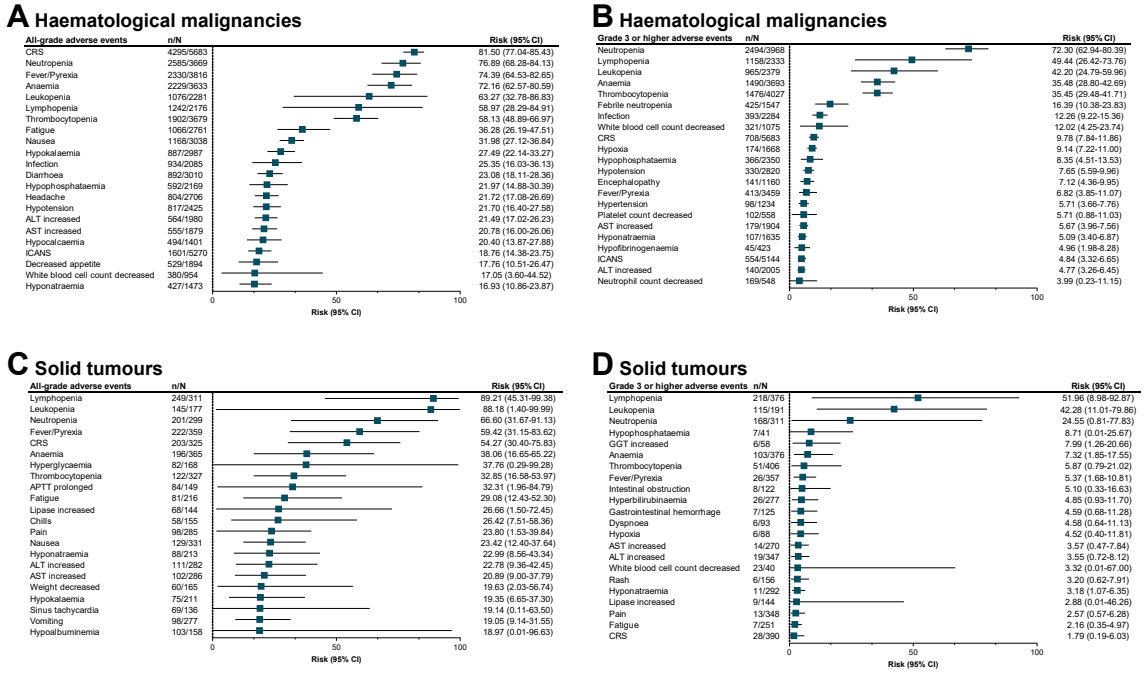

Fig. 3: Incidences of the most common adverse events. Note: A. All-grade adverse events in hematological malignancies; B. Grade 3 or higher adverse events in hematological malignancies; C. All-grade adverse events in solid tumors; D. Grade 3 or higher adverse events in solid tumors. Abbreviations: n/N, reported events/corresponding total; CRS, Cytokine release syndrome; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ICANS, Immune cell-associated neurotoxicity syndrome; APTT, Activated partial thromboplastin time; GGT, Gamma-glutamyltransferase.

been produced, the results showed satricabtagene autoleucel (94.79% [22.88%–99.92%]) and brexucabtagene autoleucel (17.24% [5.10%–44.78%]) had higher all-grade and grade 3 or higher CRS; Axicabtagene ciloleucel (77.09% [47.00%–94.84%]) and brexucabtagene autoleucel (31.44% [21.75%–42.86%]) have higher all-grade and grade 3 or higher ICANS; Tisagenlecleucel (43.54% [0.19%–99.80%]) and idecabtagene vicleucel (16.91% [0.16%–68.50%]) had higher all-grade and grade 3 or higher infection (Fig. 4).

Incidence of treatment-related serious adverse events, death, and second primary malignancy

In 27 trials enrolling 1418 patients, 690 of these patients (48.66% [46.06%–51.26%]; I^2 = 71.6%) experienced serious treatment-related adverse events. Of these adverse events, the most commonly reported were infection (17.33% [13.61%–21.80%]), prolonged cytopenia (16.67% [5.47%–40.86%]), pyrexia (10.00% [8.24%–12.09%]), tumor lysis syndrome (8.70% [2.18%–28.88%]), hypotension (8.39% [6.09%–11.47%]), and CRS (8.19% [6.28%–10.61%]) (Supplementary Table S4 and Figure S1).

In 99 trials enrolling 4574 patients, 146 of these patients (3.19% [2.72%–3.74%]; I^2 = 0%) experienced treatment-related mortality. The most commonly reported causes of treatment-related death included infections (n = 50 [34.3%]), CRS (n = 32 [21.9%]), pneumonia (12 [8.2%]), multisystem organ failure (6 [4.1%]), and cerebral hemorrhage (5 [3.4%]) (Table 1).

In 16 trials enrolling 1677 patients, 127 of these patients (7.57% [6.40%–8.94%]; I^2 = 56.2%) experienced second primary malignancy. The most commonly reported second primary malignancy was myelodysplastic syndrome (n = 30 [1.8%]), Basal cell carcinoma (n = 15 [9.0%]), squamous cell carcinoma (14 [8.4%]), Acute myeloid leukemia (12 [7.2%]), and malignant melanoma (8 [4.8%]) (Supplementary Table S5).

Subgroup analyses of incidence of treatment-related adverse events

Next, the overall incidence of adverse events and associated adverse events profiles were evaluated for these 25 different CAR-T therapies across 163 clinical trials based on their target antigens (Fig. 2 and Supplementary Figure S2). The most commonly reported all-grade adverse events associated with anti-CD19 CAR-T therapies included CRS (77.98% [76.39%–79.50%]), pyrexia (67.11% [64.60%–69.52%]), and neutropenia (57.10% [54.48%–59.68%]), while the most common grade 3 or higher adverse events were neutropenia (48.70% [46.20%–51.20%]), lymphopenia (36.11% [31.88%–40.57%]), and anaemia (31.51% [29.09%–34.04%]). Among patients who underwent anti-BCMA CAR-T therapy, the most commonly reported all-grade adverse events included white blood

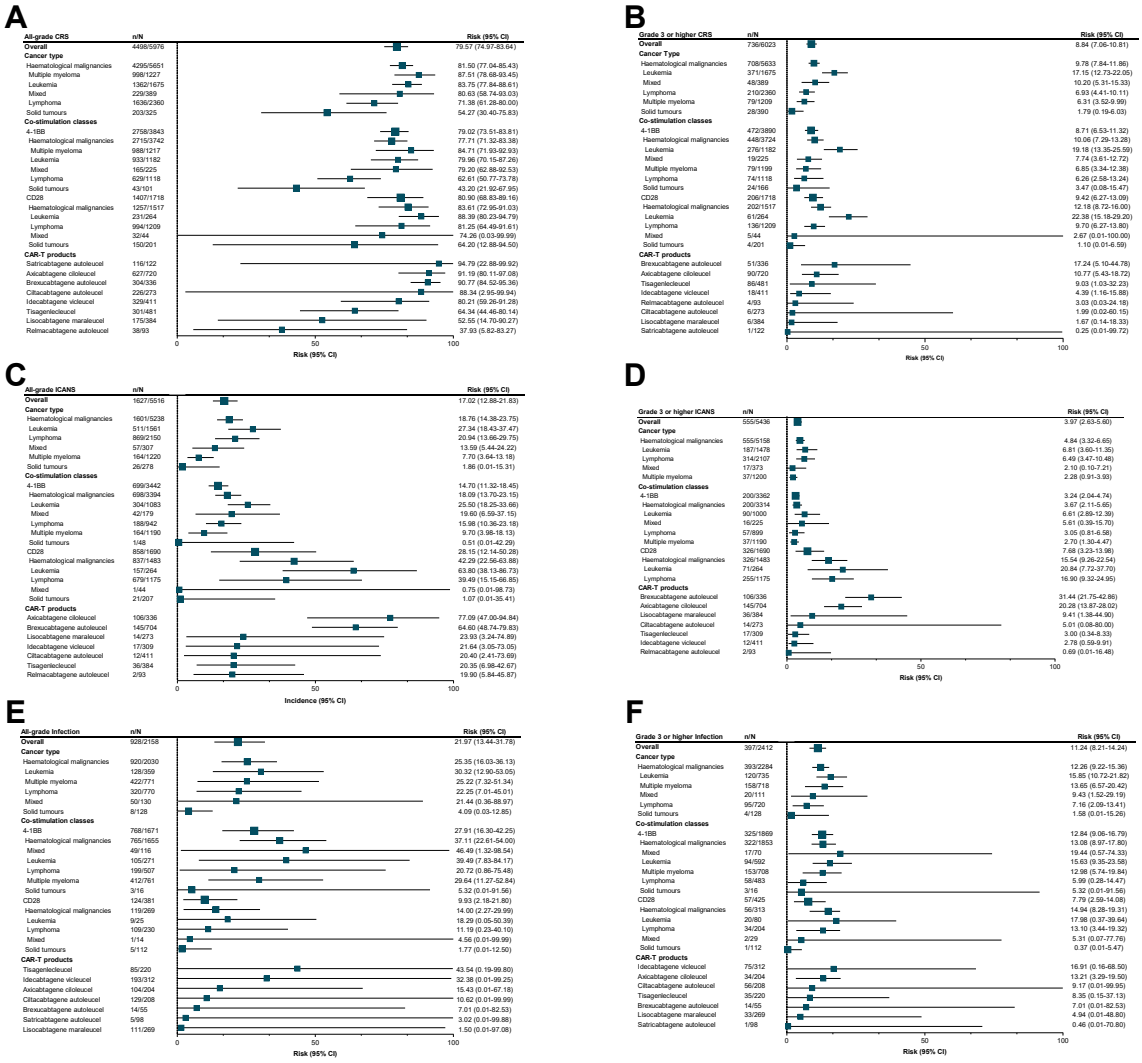

Fig. 4: Generic CAR-T Toxicities. Note: A. All-grade CRS; B. Grade 3 or higher CRS; C. All-grade ICANS; D. Grade 3 or higher ICANS; E. All-grade infection; F. Grade 3 or higher infection. Abbreviations: n/N, reported events/corresponding total; CRS, Cytokine release syndrome; ICANS, Immune cell-associated neurotoxicity syndrome.

cell (WBC) count decreased (86.21% [68.51%–94.73%]), neutropenia (86.15% [83.88%–88.15%]), and CRS (81.16% [78.72%–83.38%]), while the most commonly reported grade 3 or higher adverse events included WBC count decreased (88.00% [68.70%–96.08%]), neutropenia (84.15% [81.80%–86.24%]), and prolonged activated partial thromboplastin time (APTT) (54.55% [43.38%–65.27%]). Treatment-related adverse events for other CAR-T antigen-binding domains are summarized in Table S6 and Figure S2 in the supplementary materials.

When focusing on adverse events associated with CAR-T patients with 4-1BB and CD28 co-stimulatory domains, 4067 of 4141 patients (98.21% [97.76%–98.57%]); I^2 = 0%) across 99 studies experienced at least one all-grade adverse event, while 3335 of 4015 patients (83.06% [81.87%–84.19%]); I^2 = 82.9%) across 96 studies experienced at least one grade 3 or higher adverse events. Next, the adverse events profiles of CAR-T patients with 4-1BB and CD28 co-stimulatory domains were explored in greater detail, pooling the adverse events profiles from 105 (4059 patients) and 45 (1856 patients) trials, respectively (Supplementary Table S7). Among patients who underwent CAR-T treatment with 4-1BB co-stimulation, the most commonly reported all-grade and grade 3 or higher adverse events was CRS (79.13% [73.80%–83.95%] and neutropenia (68.15% [66.38%–69.86%]). In addition, the incidence of all-grade and grade 3 or higher CRS was 79.13% (73.80%–83.95%) and 8.91% (6.60%–11.49%), respectively; the incidence of all-grade and grade 3 or higher ICANS was 15.26% (11.79%–19.13%)

Cause of death	CAR-T cell therapy (N = 4574) Patients-no. (%)
Overall	**146 (3.2)**
Immune system disorders	**36 (24.7)**
Cytokine release syndrome	32 (21.9)
Immune cell-associated neurotoxicity syndrome	3 (2.1)
Haemophagocytic lymphohistiocytosis	1 (0.7)
Infections and infestations	**50 (34.3)**
Sepsis	17 (11.6)
Bacteremia	5 (3.4)
Septic shock	5 (3.4)
Infection (Unknown[a])	5 (3.4)
Aspergillosis	3 (2.1)
Candidemia	2 (1.4)
Klebsiella	2 (1.4)
Septicaemia	2 (1.4)
Pulmonary infection	2 (1.4)
Cytomegalovirus	1 (0.7)
Escherichia coli	1 (0.7)
Herpes simplex virus	1 (0.7)
Mucormycosis	1 (0.7)
Staphylococcus	1 (0.7)
Intestinal infection	1 (0.7)
Perineal infection	1 (0.7)
Respiratory	**24 (16.4)**
Pneumonia	12 (8.2)
Pulmonary hemorrhage	4 (2.7)
Bronchopneumonia	2 (1.4)
Respiratory failure	2 (1.4)
Acute respiratory distress syndrome	1 (0.7)
Diffuse alveolar damage	1 (0.7)
Hypoxia	1 (0.7)
Lung abscess	1 (0.7)
Neurologic	**10 (6.9)**
Cerebral hemorrhage	5 (3.4)
Encephalopathy syndrome	3 (2.1)
Brain herniation	1 (0.7)
Progressive multifocal leukoencephalopathy	1 (0.7)
Gastrointestinal	**8 (5.5)**
Gastrointestinal hemorrhage	3 (2.1)
Hepatic failure	2 (1.4)
Alimentary tract hemorrhage	1 (0.7)
Mesenteric infarction	1 (0.7)
Pseudomembranous colitis	1 (0.7)
Cardiovascular	**7 (4.8)**
Cardiac arrest	2 (1.4)
Refractory hypotension	2 (1.4)
Cardiac arrhythmia	1 (0.7)
Cardiomyopathy	1 (0.7)
Veno-occlusive disease	1 (0.7)
Hematologic	**3 (2.1)**
Neutropenia	3 (2.1)
Other	**8 (5.5)**
Multisystem organ failure	6 (4.1)
Therapy-related acute myeloid leukaemia	1 (0.7)
Therapy-related myelodysplastic syndrome	1 (0.7)

[a]No details were given on the species of infected organism.

Table 1: **Causes of 146 treatment-related deaths of CAR-T cell therapies.**

and 3.31% (2.09%–4.83%), respectively; the incidence of all-grade and grade 3 or higher infection was 45.14% (32.49%–58.72%) and 15.24% (11.11%–19.96%), respectively (Fig. 4). Among patients who underwent CAR-T treatment with CD28 co-stimulation, the most commonly reported all-grade adverse events were pyrexia (85.27% [82.96%–87.31%]) and lymphopenia (71.09% [66.78%–75.05%]), respectively. The incidence of all-grade and grade 3 or higher CRS was 81.07% (69.62%–89.08%) and 9.62% (6.45%–13.28%), respectively; the incidence of all-grade and grade 3 or higher ICANS was 31.78% (14.37%–53.46%) and 8.30% (3.55%–14.78%), respectively; the incidence of all-grade and grade 3 or higher infection was 21.26% (5.12%–51.93%) and 9.69% (3.01%–20.61%), respectively (Fig. 4). The incidence of generic CAR-T-related adverse events of CD28 and 41BB in different cancer types was also shown in Fig. 4.

In addition, factors that might influence the incidence of adverse events were also explored (tumors bulk [105 studies], number of lines of prior therapy [111 studies], prior autologous or allogeneic SCT [113 studies], baseline LDH [38 studies], and baseline CRP [38 studies]). All-grade Adverse events in patients with bulky tumors (98.48% [97.96%–98.87%]), prior first-line therapy (99.25% [97.87%–99.74%]), prior autologous or allogeneic SCT (94.93% [94.09%–95.66%]), baseline normal LDH (97.63% [96.29%–98.49%]), and baseline normal CRP (99.84% [97.48%–99.99%]); Grade 3 or higher adverse events in patients with bulky tumors (81.71% [80.24%–83.10%]), more than second-line of prior therapy (84.30% [83.10%–85.44%]), prior autologous or allogeneic SCT (80.66% [79.16%–82.08%]), baseline normal LDH (83.87% [81.16%–86.26%]), and baseline normal CRP (92.77% [89.30%–95.17%]) (Fig. 5). In multivariable meta-regression analyses, factors associated with a higher incidence of grade 3 or higher AEs included hematologic malignancies, more than second-line of prior therapy, and bulky tumors; Factors associated with a higher incidence of CRS include hematologic malignancies and bulky tumors; And factors associated with a lower incidence of ICANS included CAR-T with 4-1BB co-stimulatory and anti-CD19 (Supplementary Table S8 and Figure S3). The highest mean all-grade adverse events (ANOVA, $P = 0.0014$) and grade 3 or higher adverse events (ANOVA, $P = 0.043$) incidence were evident in multiple myeloma (99.71% [99.19%–99.90%] and 92.33% [90.71%–93.68%]). ANOVA and nonparametric tests found significant differences in the incidence of adverse events across cancer type, antigen-binder, number of lines of prior therapy, tumors bulk, and prior autologous or allogeneic SCT (Supplementary Table S9).

Indirect comparisons of treatment-related adverse events

Using five RCTs enrolling 882 patients, indirect comparisons of treatment-related adverse events were

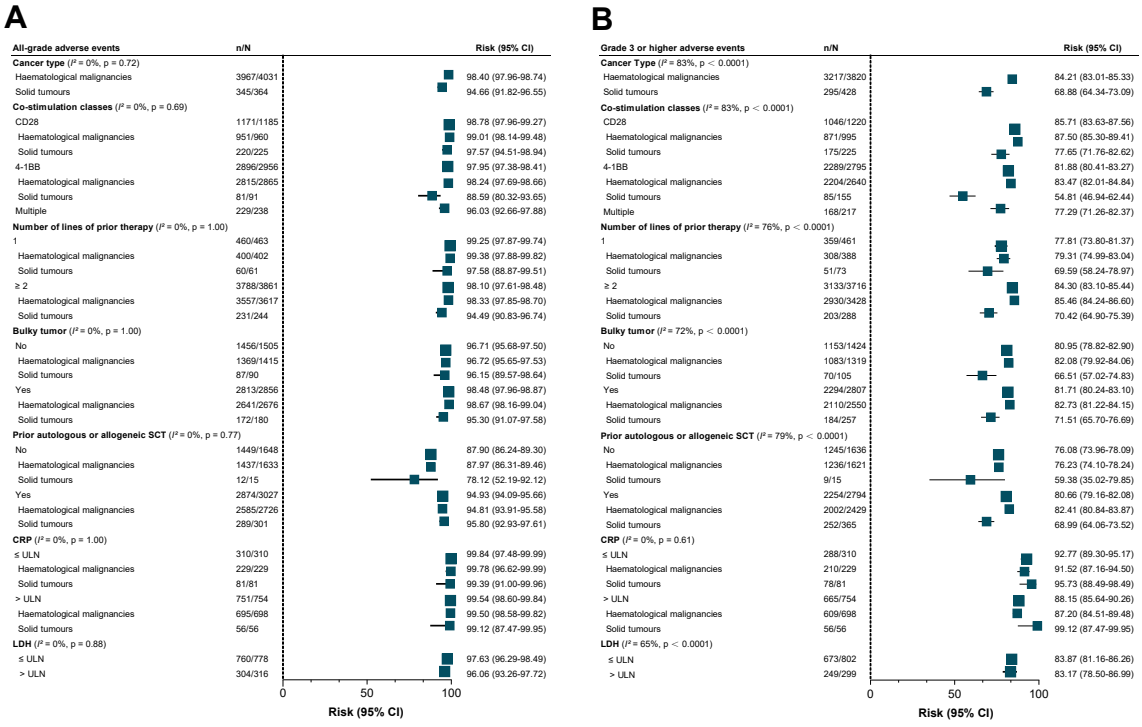

Fig. 5: Incidences of adverse events in subgroups. Note: A. All-grade adverse events; B. Grade 3 or higher adverse events. Abbreviations: n/N, reported events/corresponding total; SCT, stem cell transplantation; CRP, C-reactive protein; LDH. lactate dehydrogenase.

performed focusing on different CAR-T therapies (5 types), standard of care (platinum-based chemo-immunotherapy regimens), target antigens (2 types), and co-stimulatory domains (2 types). It was found to be transitive and similar based on the baseline features of RCTs, and therefore comparable between treatments (Supplementary Figure S4 and Table S10). Among the approved drugs included in this analysis, ciltacabtagene autoleucel was associated with a lower mean all-grade adverse event incidence (RR, 1.00 [0.99–1.01]; *p-score* = 0.6341) while tsagenlecleucel was associated with a lower mean incidence of grade 3 or higher adverse events (0.93 [0.86–1.02]; *p-score* = 0.9738) relative to standard therapies. With respect to antigen targets, anti-CD19 CAR-T therapies were associated with lower mean incidence for both all-grade (0.99 [0.98–1.01]; *p-score* = 0.4646) and grade 3 or higher adverse events (0.93 [0.87–0.99]; *p-score* = 0.6097) relative to anti-BCMA CAR-T therapies. As to the CAR-T costimulatory domains, 4-1BB CAR-T cells were associated with lower incidence of all-grade (0.99 [0.98–1.01]; *p-score* = 0.3714) and grade 3 or higher adverse events (0.88 [0.81–0.95]; *p-score* = 0.9995) relative to treatment outcomes when using CD28 CAR-T cells (Supplementary Table S11).

Study heterogeneity and publication bias

The sources of heterogeneity found by meta-regression analysis were detailed in Supplementary Table S8. Study heterogeneity was defined by an I^2 statistic was >50% and the Cochran Q test P-value. No heterogeneity was observed concerning all-grade treatment-related adverse events (I^2, 0.0%; P-value range, 0.66–1.0), grade 3 or higher treatment-related in the CRP group (I^2, 0.0%; P-value, 0.61), or treatment-related death (I^2, 0.0%; P-value, 0.97) among the studies included here, while varying levels of heterogeneity were observed for grade 3 or higher treatment-related (I^2, range, 65.3%–89.2%; P-value, <0.0001), serious adverse events (I^2, 71.6%; P-value, <0.0001), and second primary malignancy (I^2, 56.2%; P-value, 0.0031) (Supplementary Table S12). No significant publication bias was detected in this study, as evidenced by a funnel plot (roughly symmetric) and Egger's test (P > 0.05) (Supplementary Table S11 and Figure S5).

Discussion

CAR-T therapies have recently emerged as promising anticancer treatment strategies that have been approved for the treatment of hematologic malignancies under various national guidelines. This initial success has prompted further exploration of the value of CAR-T therapies for non-hematological malignancies, and there have been a growing number of clinical trials focused on this topic and a range of different cancer-specific targets. However, the lack of safety data for

these therapies remains a persistent detriment to their wider uptake. The present study represents the largest and most comprehensive systematic review and meta-analysis of CAR-T treatment-related adverse events to date, compiling research data from 163 published trials. Previously published meta-analyses have included far fewer studies (80 or less) and were primarily focused on particular adverse events including CRS, neurological symptoms, cardiovascular toxicity, and hematological toxicity.[12–14,27] These studies also noted different degrees of concern for different targets when assessing CAR-T treatment-related adverse events, but did not conduct in-depth analyses of solid tumors or co-stimulatory domains. Comprehensive analyses of all potential treatment-related adverse events commonly encountered in the course of CAR-T therapy are vital to provide clinicians with a valuable reference. A global profile of CAR-T-related adverse event incidence will provide complementary support for the formulation of international guidelines aimed at managing these complications, in addition to informing clinical practice.

Several factors should be considered when obtaining informed consent from patients undergoing CAR-T therapy, and careful monitoring together with early recognition of adverse events-related signs and symptoms can aid in the post-treatment care of these patients. In this meta-analysis, CAR-T therapies were associated with a high incidence of treatment-related adverse events, with 98.10% and 82.67% of patients respectively experiencing all-grade and grade 3 or higher adverse events. Notably, CRS was the most common all-grade adverse event (79.659%) and the most common grade 3 or higher immune-related adverse event (8.94%). CRS also consistently emerged as the second most common serious (approximately 3.6% chance) and fatal (approximately 0.7% chance) events, which need to be disclosed to patients. The second most common immune-related adverse event of any grade was ICANS, impacting approximately 3 of every 10 CAR-T patients, while HLH and ICAS were the second most commonly diagnosed grade 3 or higher adverse events, affecting roughly 1 in 10 patients. However, patients were less likely to suffer serious or fatal outcomes associated with these adverse events. However, the overall incidence of CRS and ICANS was found to be significantly higher in hematologic malignancies and with CD28 co-stimulation CAR-T therapies, further suggesting that the management of hematologic malignancies and the use of different co-stimulation of CAR-T should be carefully considered and guided. Other common treatment-related adverse events were also observed in this patient population, including various hematological toxicities, coagulatory dysfunction, cardiovascular disease, infections, liver/kidney dysfunction, gastrointestinal function disorder, and electrolyte imbalances. Some of these adverse events were notably associated with specific CAR-T targets. For instance, electrogram abnormalities and hepatic toxicity were more common in patients undergoing anti-CD19 CAR-T treatment, while infection and coagulatory dysfunction were more closely associated with anti-BCMA CAR-T therapies. Hepatic toxicities were more common among patients undergoing anti-CD20, anti-CLDN6, anti-CLND18.2, and anti-CAIX CAR-T treatment, whereas cardiovascular toxicity was most commonly associated with anti-CD7 CAR-T therapy, and gastrotoxicity was a more common complication of anti-CEA, anti-HER2, anti-CD22, and anti-CD30 CAR-T therapies. Anti-EGFR CAR-T treatment was more commonly linked to systemic edema and oral diseases, while infection was more common in patients being treated with anti-CD70 and anti-GCP3 CAR-T regimens. Neurotoxicity was most commonly associated with anti-GD2 and anti-NKG2D CAR-T treatment, while nail changes were most closely associated with anti-GPRC5D CAR-T treatment, and dermal toxicity was reported most often for anti-GD2, anti-PSCA, and anti-CD30 CAR-T therapies. Chills and hypoxia were adverse events most frequently reported for patients undergoing anti-TAG-72 CAR-T treatment, while anti-Mesothelin and anti-CLL-1 CAR-T therapies were the types most commonly associated with electrolyte imbalances. Based on these results, on-target toxicity may account for some of the adverse clinical outcomes associated with these treatments. To fully elucidate CAR-T-associated adverse events profiles, it is thus essential that target information be incorporated into safety databases, in addition to being considered in the context of CAR-T therapy selection and associated patient management.

Serious and fatal adverse events were also observed among patients included in this meta-analysis, with 48.70% (690/1418) and 3.20% (146/4574) respectively having experienced serious adverse events and treatment-related deaths. Infections were the most commonly reported serious adverse event and factor associated with treatment-related death, while the most commonly reported non-immune-related adverse event in these respective categories was sepsis. It was also found that infection was more likely to occur in hematologic malignancies and CAR-T with 4-1BB co-stimulation. This study also looked at the incidence of secondary primary malignancy, 7.6% (127/1677), of which myelodysplastic syndrome (1.79%)/acute myeloid leukemia (0.72%) and basal cell carcinoma (0.90%) were probably the most common types. Improving the current understanding of CAR-T-related toxicity is vital to guide the formulation of routine screening programs aimed at detecting signs of treatment-related toxicity and recognizing associated symptoms early point among patients undergoing CAR-T treatment.

To explore factors that influence CAR-T-related adverse events, subgroup analyses were conducted. The overall mean incidence of all-grade and grade 3 or higher adverse events was differ significantly between

hematologic malignancies (98.40% and 84.21%) and solid tumors (94.66% and 68.88%), bulky tumor (98.48% and 81.71%) and non-bulky tumor (96.71% and 80.95%), and prior receiving (94.93% and 80.66%) and prior non-receiving autologous or allogeneic SCT (87.90% and 76.08%). Identifying patient populations that may have a potential impact on the occurrence of adverse events in a specific subgroup analysis may help to better guide the management of CAR-T patients, enabling clinicians to determine who is most likely to benefit from a stable benefit of CAR-T while more conducive to supporting an individualized treatment plan. In addition, the absence of head-to-head comparisons of different CAR-T regimens also underscores the need for indirect comparisons. Here, five approved CAR-T regimens were not associated with better treatment-related adverse events relative to standard chemotherapy, and comparisons of these five drugs were performed. The drugs that generally exhibited more favorable safety profiles included ciltacabtagene autoleucel (all-grade) and tisagenlecleucel (grade 3 or higher). Anti-CD19 CAR-T treatment and CAR-T cells with a 4-1BB co-stimulatory domain also tended to be safer in these analyses. As this study included published trials with large sample sizes when performing this network meta-analysis, the results offer value as a key reference for personalized treatment planning in clinical settings, while also better equipping clinicians to choose appropriate and safe drugs for cohorts of patients with the same form of cancer.

There are multiple limitations to this study. For one, the inclusion of studies with large sample sizes in the pooled analyses performed herein may have contributed to smaller effect sizes and wider CIs. Secondly, this study failed to incorporate risk or proportionality using an inverse probability weighting method based on population weights, which may affect the accuracy of the results, especially when there is selection bias between studies (such as English language limitations and potential confounders in clinical trials). However, we try to adjust for factors that may affect the incidence of adverse events (subgroup analysis). Third, the reliance of this study on the published literature inevitably means that these results will reflect any biases or errors attributable to the included studies, and the results of these pooled analyses will only apply to those patients who would be eligible for the included trials. Fourth, there remains a need to explore the potential effects of other variables on CAR-T-related adverse events, including patient age, manufacturing processes, and region, highlighting an avenue for further study. Sixth, the indirect comparisons herein were based on RCTs with the assumption that the included patients in these trials had comparable characteristics. Caution is thus warranted when interpreting these indirect comparisons, underscoring the need for validation through head-to-head studies in the future. Seventh, in the context of safety data meta-analysis, if some studies incompletely report AE results, the full-case analysis may lead to result bias. We use the Bayesian MAGEC model and consider the left-censored threshold to further reduce the bias. Lastly, the adverse events profiles for different cancer patients undergoing CAR-T therapies have not been characterized in detail, highlighting the importance of large-scale real-world trials addressing this issue.

In conclusion, to support the widespread uptake of innovative treatment strategies, data pertaining to both their safety and their efficacy are necessary. Given the limited safety data available for CAR-T regimens, in this study, the incidence of all common treatment-related adverse events, induced secondary primary malignancy types, and causes of death were summarized and characterized in detail. The key findings of these pooled analyses were that CRS and hematologic toxicities are commonly associated with CAR-T therapy. In subgroup analyses, differences in adverse events were noted among antigen targets, cancer types, tumor bulk, number of prior treatment lines, and previously treated with autologous or allogeneic SCT. In summary, large-scale global meta-analyses remain vital as a means of obtaining a clear overview of CAR-T toxicity profiles. The results from this study have the potential to offer a reference for the process of patient selection, guiding clinicians as they seek to design personalized treatment plans and supplement the current limitations in terms of the guidelines available for post-CAR-T treatment care.

Contributors

Hong Zhu: Conceptualization, Methodology, Software, Resources, Data Curation, Writing-Original Draft, Writing-Review & Editing, Supervision, Project administration, Funding acquisition. **Steven T Rosen and Wei Liu:** Conceptualization, Methodology, Data Curation, Writing-Original Draft, and Writing-Review & Editing. **Youwen Zhu:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing-Original Draft, Writing-Review & Editing, Visualization. **Kun Liu:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing-Original Draft, Writing-Review & Editing. All authors had full access to the data in the paper and verified the underlying data.

Data sharing statement

All authors had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis. The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of interests

All of the authors have indicated that they have no competing interests in the content of the article. This manuscript is original and has not been previously published, nor has it been simultaneously submitted to any other journal.

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Appendix A. Supplementary data

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References

1 Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365(8):725–733.
2 June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science*. 2018;359(6382):1361–1365.
3 Boyiadzis MM, Dhodapkar MV, Brentjens RJ, et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: clinical perspective and significance. *J Immunother Cancer*. 2018;6(1):137.
4 Wang D, Wang J, Hu G, et al. A phase 1 study of a novel fully human BCMA-targeting CAR (CT103A) in patients with relapsed/refractory multiple myeloma. *Blood*. 2021;137(21):2890–2901.
5 Del Bufalo F, De Angelis B, Caruana I, et al. GD2-CART01 for relapsed or refractory high-risk neuroblastoma. *N Engl J Med*. 2023;388(14):1284–1295.
6 Mackensen A, Haanen J, Koenecke C, et al. CLDN6-specific CAR-T cells plus amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial. *Nat Med*. 2023;29(11):2844–2853.
7 Qi C, Liu C, Gong J, et al. Claudin 18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial final results. *Nat Med*. 2024;30(8):2224–2234.
8 Schett G, Müller F, Taubmann J, et al. Advancements and challenges in CAR T cell therapy in autoimmune diseases. *Nat Rev Rheumatol*. 2024;20(9):531–544.
9 Mao R, Hussein MS, He Y. Chimeric antigen receptor engineered T cells and their application in the immunotherapy of solid tumours. *Expert Rev Mol Med*. 2022;24:e7.
10 Sumransub N, El Jurdi N, Chiraphapphaiboon W, Maakaron JE. Putting function back in dysfunction: endothelial diseases and current therapies in hematopoietic stem cell transplantation and cellular therapies. *Blood Rev*. 2022;51:100883.
11 Flugel CL, Majzner RG, Krenciute G, et al. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours. *Nat Rev Clin Oncol*. 2023;20(1):49–62.
12 Lei W, Xie M, Jiang Q, et al. Treatment-related adverse events of chimeric antigen receptor T-cell (CAR T) in clinical trials: a systematic review and meta-analysis. *Cancers (Basel)*. 2021;13(15).
13 Luo W, Li C, Zhang Y, et al. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis. *BMC Cancer*. 2022;22(1):98.
14 Cao JX, Wang H, Gao WJ, You J, Wu LH, Wang ZX. The incidence of cytokine release syndrome and neurotoxicity of CD19 chimeric antigen receptor-T cell therapy in the patient with acute lymphoblastic leukemia and lymphoma. *Cytotherapy*. 2020;22(4):214–226.
15 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
16 Zhou X, Yao Z, Bai H, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitor-based combination therapies in clinical trials: a systematic review and meta-analysis. *Lancet Oncol*. 2021;22(9):1265–1274.
17 Huang HY, Andrews E, Jones J, Skovron ML, Tilson H. Pitfalls in meta-analyses on adverse events reported from clinical trials. *Pharmacoepidemiol Drug Saf*. 2011;20(10):1014–1020.
18 Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5(7):1008–1019.
19 Qi X, Zhou S, Peterson CB, et al. Meta-analysis of censored adverse events. *N Engl J Stat Data Sci*. 2024;2(3):380–392.
20 Zhu Y, Liu K, Zhu H. Immune checkpoint inhibitor combinations for patients with advanced endometrial cancer: a network meta-analysis and cost-utility analysis. *Int J Gynecol Cancer*. 2024;34(10):1570–1579.
21 Stang A, Poole C, Kuss O. The ongoing tyranny of statistical significance testing in biomedical research. *Eur J Epidemiol*. 2010;25(4):225–230.
22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
23 Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10(10):Ed000142.
24 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
25 Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol*. 2014;67(8):897–903.
26 Zhou Z, Tian Z, Peterson CB, Bao L, Zhou S. Shiny-MAGEC: a Bayesian R Shiny application for meta-analysis of censored adverse events 2025 March 01. *arXiv*; 2025. Available from: https://ui.adsabs.harvard.edu/abs/2025arXiv250305982Z.
27 Chen LR, Li YJ, Zhang Z, et al. Cardiovascular effects associated with chimeric antigen receptor T cell therapy in cancer patients: a meta-analysis. *Front Oncol*. 2022;12:924208.