

Systematic Review

The Use of CAR-T Immunotherapy in the Treatment of Acute Lymphoblastic Leukemia: A Systematic Literature Review with Meta-Analysis

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Abstract

Background: The objective of this study was to evaluate the efficacy and safety of CAR-T immunotherapy in inducing remission in patients with Acute Lymphoblastic Leukemia (ALL). **Methods:** The search strategy was conducted in the BVS, Embase, PubMed, and ScienceDirect databases, where 4138 studies were initially identified. **Results:** The final analysis resulted in the inclusion of 35 studies, all of which were incorporated into the meta-analysis, covering a cohort of 1313 patients. Statistical analysis was performed using R software (version 4.5.2), revealing a Complete Remission rate of 70.68% and a Minimal Residual Disease negativity rate of 76.68%. Tactical superiority was observed in the second-generation cells and in the dual CD19/CD22 target (82.20% CR). The risk of bias assessment using the ROBINS-I tool indicated high quality for most of the studies. The certainty of evidence according to the GRADE system was classified as moderate. Adverse events such as cytokine release syndrome (46.81%) and neurotoxicity (23.52%) were frequent but reversible. **Conclusions:** We thus observe that CAR-T therapy is an effective strategic bridge to bone marrow transplantation, with advances in cell persistence being fundamental for sustained cure.

Keywords: CAR-T; acute lymphoblastic leukemia; complete remission; adoptive immunotherapy



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1. Introduction

Acute Lymphoblastic Leukemia (ALL) is an aggressive hematological malignancy resulting from uncontrolled proliferation of B or T lymphoblasts, which ultimately leads to the replacement of bone marrow elements and other lymphoid organs resulting in a typical disease pattern. The B-cell Acute Lymphoblastic Leukemia (B-ALL) precursor cells

typically express CD10, CD19, CD22 and CD34 on their surface, along with nuclear terminal deoxynucleotide transferase (TdT), while precursor T-cell ALL cells commonly express CD2, CD3, CD7, CD34, and TdT. Specifically, CD19 is a characteristic pan-B-cell marker found on nearly all B-lineage blasts. It acts as a primary diagnostic and therapeutic target. Moreover, though rare CD19-negative cases exist, and the antigen can be lost following targeted therapies. CD22 is a surface antigen present in 60–95% of B-ALL cases, making it a key therapeutic target for immunotherapies [1].

Acute Lymphoblastic Leukemia is characterized by a marked biological heterogeneity that dictates discrepant clinical outcomes across age groups: while the five-year survival rate exceeds 90% in pediatrics, the overall survival in adult patients rarely surpasses 40%, reflecting greater intrinsic resistance to therapies and lower tolerance to systemic toxicity [2–4]. Clinically, marrow infiltration results in severe cytopenias, anemia, and profound immunosuppression, drastically increasing early mortality rates due to infectious complications and hemorrhagic episodes [5].

Historically, the management of ALL has been based on intensive multi-drug chemotherapy protocols and Hematopoietic Stem Cell Transplantation (HSCT) [6]. However, these approaches face critical barriers, such as cumulative toxicity in vital organs, the risk of graft-versus-host disease (GVHD), and the development of multi-drug resistant cell clones. For patients with relapsed or refractory (R/R) ALL, the prognosis is somber, with extremely low remission rates and mortality affecting most individuals in the short term, justifying the urgent need for more precise intervention technologies [7].

The search for immunological alternatives led to the development of Chimeric Antigen Receptor (CAR-T) technology. CAR T-cell therapy involves arming a patient's own T cells with a specialized protein called a chimeric antigen receptor (CAR). This receptor helps the T cells find and kill the cancer cells. The Food and Drug Administration (FDA) approved the first CAR T-cell therapy in 2017 to treat children with acute lymphoblastic leukemia (ALL). Since then, others have been approved to treat adults with blood cancers like non-Hodgkin lymphoma and multiple myeloma. The concept evolved from the first generation of receptors in the 1980s—which possessed only the signaling ζ (zeta) chain of CD3—to the second generation, which incorporated costimulatory domains (such as 4-1BB or CD28). This modification was the milestone that enabled the cell expansion and persistence necessary for sustained antitumor efficacy [8], the FDA approval of tisagenlecleucel (anti-CD19) consolidated this technique, which utilizes genetic engineering to program T lymphocytes to recognize markers such as CD19 and CD22, bypassing tumor evasion mechanisms without dependence on the Major Histocompatibility Complex (MHC) [5]. In Brazil, ANVISA followed this trend, authorizing commercialization and clinical trials between 2020 and 2023 [9].

Despite initial success, the large-scale implementation of CAR-T therapy reveals complex challenges. Although initial Complete Remission (CR) rates are high, the durability of these responses is variable. Factors such as tumor burden, genetic vector design, and the occurrence of severe adverse events, such as Cytokine Release Syndrome (CRS) and neurotoxicity (ICANS), limit therapeutic potential and raise safety concerns [8]. Furthermore, preliminary data suggest a post-immunotherapy relapse rate of approximately 33.90%, requiring a critical analysis of long-term efficacy. Given the rapid expansion of this technology and the dispersion of data across different phases of clinical trials, a robust quantitative synthesis is essential to validate the safety and efficacy of this intervention [10].

The objective of this systematic review and meta-analysis is to evaluate the efficacy and safety profile of CAR-T immunotherapy in the treatment of ALL in pediatric and adult patients. Through the analysis of an aggregate cohort, this study seeks to: determine the aggregate rate of Complete Remission (CR) and Minimal Residual Disease (MRD)

negativity; quantify the incidence of severe toxicities, specifically CRS, neurotoxicity, and cytopenias; and analyze the relapse rate and median overall survival, providing evidence for the consolidation of CAR-T therapy in the current clinical landscape.

2. Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-2020) recommendations (www.prisma-statement.org) guidelines [11], and the checklist is provided as Supplementary Material S1. Following the protocol that was registered and approved in the International Prospective Register of Systematic Reviews (PROSPERO) [12], with registration number CRD42024589553.

2.1. Eligibility Criteria

The studies considered were published from 2019 to 3 March 2026, both nationally and internationally, in English, and evaluated the effect of CAR-T immunotherapy in patients with acute lymphoblastic leukemia (ALL).

To ensure a high level of scientific evidence, only clinical trials that included complete remission rates and minimal residual disease rates among the evaluated outcomes were considered, as the primary intent of this study is to evaluate these two outcomes 30 days after treatment.

Studies involving patient populations without ALL, intervention lines that did not include CAR-T immunotherapy, and those that did not provide substantial data on therapy-induced remission were excluded.

2.2. Search and Selection Strategy

The study screening process was performed independently by two reviewers (M.G.S. and J.M.d.S.). For study retrieval, four databases were utilized: Virtual Health Library (BVS), Public Medline (PubMed), ScienceDirect, and Embase.

To define the search, terms from the MeSH (Medical Subject Headings) and Emtree vocabularies were established, aided by the search tool for health sciences descriptors from the BVS.

The search strategy was planned according to the PICO methodology (P—patients, I—Intervention, C—Comparator, O—Outcome). A pilot search was conducted across the databases to determine which terms would yield the best results. Five descriptors were established, all in English, consistent with the PICO strategy, in which it was decided not to include a comparator (C). They are: “Acute Lymphoblastic Leukemia” (P: population), “Adoptive Cell Therapy” or “Chimeric Antigen Receptors (CAR)” (I: intervention), and “Tumor Regression” or “Complete Remission” (O: outcome).

The descriptors were applied using the advanced search mode across all four databases. Additional filters were included to narrow the search, specifically “Clinical trial,” “Randomized controlled trial,” “Full text,” and a publication period restricted to the “Last seven years,” as demonstrated in Supplementary Materials S2 and S3.

Search results from each database were saved in “ris” format for continued selection on the RAYYAN platform for systematic review assistance [13].

The selection process was conducted in three phases: removal of duplicates identified by the platform, exclusion of works based on title and abstract that did not meet selection criteria, and exclusion after full-text reading.

Studies that featured the chosen descriptors, either fully or partially, in their titles or abstracts were considered qualified for full reading. After importing the studies into the platform, both reviewers conducted analysis and exclusion independently.

Divergences were resolved through discussion between the reviewers and consensus on the studies to be analyzed in full. After full-text reading, studies that still did not meet the inclusion criteria did not proceed to the data extraction stage, as shown in Supplementary Materials S2 and S3.

2.3. Data Collection Process

Data were extracted into an Excel spreadsheet exclusively for this review. The data structure includes: DOI and the link where the article can be found, authors, country and year of publication, number of patients, study type, therapy characteristics, patient demographic characteristics, refractory status, the timeframe in which the outcome was evaluated, primary outcome (complete remission), presence of minimal residual disease, and the main findings of each article—including those not directly linked to complete remission—to provide a better overview of the immunotherapy landscape.

Based on this table, the studies were analyzed and their corresponding data extracted. During the collection process, other data such as overall survival and event-free survival were captured but were not included in the final review due to a lack of homogeneity and consistency in the presentation of these data across studies.

The spreadsheet was filled such that each analyzed study represented a row, and the columns corresponded to the described variables. All studies include data on the number of patients who entered the study and how many achieved complete remission due to the therapy.

2.4. Risk of Bias Assessment

To evaluate the risk of bias in non-randomized clinical trials, the ROBINS-I (Risk Of Bias In Non-randomized Studies—of Interventions) tool was used, as recommended by the Cochrane Collaboration [14].

The analysis covered six fundamental domains: (1) bias due to confounding, (2) bias in the classification of interventions, (3) bias in the selection of participants for the study (or into the analysis), (4) bias due to missing data, (5) bias in the measurement of outcomes, and (6) bias in the selection of the reported result. Each domain was evaluated individually and classified as low, moderate, serious, or critical risk of bias. The global judgment followed the “worst domain” principle, where the overall risk of the study corresponds to the highest level of bias identified in any of the evaluated axes.

Additionally, publication bias was assessed through the construction and visual inspection of a funnel plot to check for potential asymmetries in the distribution of studies. To provide greater statistical rigor, Egger’s regression test (1997) was applied, with a p -value < 0.005 considered statistically significant for publication bias.

To ensure the robustness of our meta-analysis, a systematic approach was adopted to identify and manage potential outliers and influential studies. Initially, discrepancies were detected using studentized residuals from the random-effects model [15]. Absolute values with a z -score greater than 2.0 were considered indicative of potential outliers. Subsequently, to assess the influence of these studies on the overall model and the detection of publication bias, statistical tests were applied, including Cook’s Distance (Cook’s D) [16] and the Difference in Fits (DFFITS) [16]. High values in these metrics were considered indicative of high influence. Studies identified as outliers and highly influential, whose exclusion was justified by statistical and methodological criteria, were removed from the primary analysis to prevent distortion of the results, with due justification and description provided in the text.

2.5. Certainty of Evidence

The reliability of the evidence was assessed based on the risk of bias and categorized according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (www.gradeworkinggroup.org, accessed on 7 July 2026). The classification of certainty of evidence can be high if the results present low risk of bias, consistent, direct, and precise data. Therefore, the effect estimate is unlikely to change with other studies; moderate when new studies may impact and alter the effect estimate; low when new studies will have a significant impact; and very low when the effect estimate causes uncertainty [17,18].

2.6. Data Synthesis and Effect Measures

Continuous variables, at the time of analysis, were grouped into percentages (%), accompanied by 95% confidence intervals (95% CI). In the meta-analyses, results were also expressed as percentages. Statistical analysis was performed using R software (version 4.5.2; R Core Team) [19]. In the presence of low heterogeneity ($I^2 < 10\%$ and $p > 0.05$), a fixed-effects model using the Mantel–Haenszel method was applied. When high heterogeneity was observed ($I^2 > 75\%$ and $p < 0.05$), a random-effects model was used according to the DerSimonian–Laird method [20]. Due to the nature of the included studies, the metrics for the proportion of minimal residual disease and complete relapse were chosen, which are suitable for estimating prevalence in observational meta-analyses, as recommended by Nyaga [20] in a review of methods for proportions.

Heterogeneity was managed using the DerSimonian–Laird random-effects model, with sub-analyses by genotype, gestational trimester, and diagnostic method. I^2 values near 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively [20]. Sensitivity analysis was conducted using the “leave-one-out” method and by excluding studies with a high risk of bias (JBI $< 50\%$ “yes”) to verify if the pooled estimates remained stable.

Sensitivity and subgroup analyses were conducted to evaluate the robustness of the aggregate estimates in relation to several relevant study characteristics: (1) CAR-T cell subtype (CD19 or CD22); (2) CAR-T cell generation; (3) participant age group; (4) CAR-T cell vector; (5) toxicity (Cytokine Release Syndrome); (6) toxicity (Neurotoxicity); (7) toxicity (Cytopenias); (8) absolute relapse in days; and (9) overall survival in weeks.

Funnel plots provided a visual representation of the distribution of proportions among studies, along with their pooled estimates and observed heterogeneity, which was derived from the bivariate random-effects model [21].

2.7. Ethical Aspects

This review exclusively utilized secondary data available in scientific publications, and no additional data were requested from the research participants by any author. Thus, there was no direct involvement of human subjects, animals, or biological material; consequently, submission to an Ethical Review Board was not required.

3. Results

A total of 4138 studies were identified, of which 41 were retrieved from the Virtual Health Library (BVS), 26 from Embase, 182 from PubMed, and 3889 from ScienceDirect.

After duplicate removal, 99 articles were excluded, leaving 3489 studies for title and abstract screening. Of these, 3437 were excluded following the title and abstract analysis, and 52 proceeded to full-text review. The evaluation of the remaining 52 papers resulted in 17 exclusions: 9 due to different study populations (animal models/rats) and 8 because they were not clinical trials (incorrect study types) (Figure 1). The selection process concluded

with 35 CAR-T clinical trials for analysis, all of which were included in the meta-analysis. The table of excluded articles is available in Supplementary Material S4.

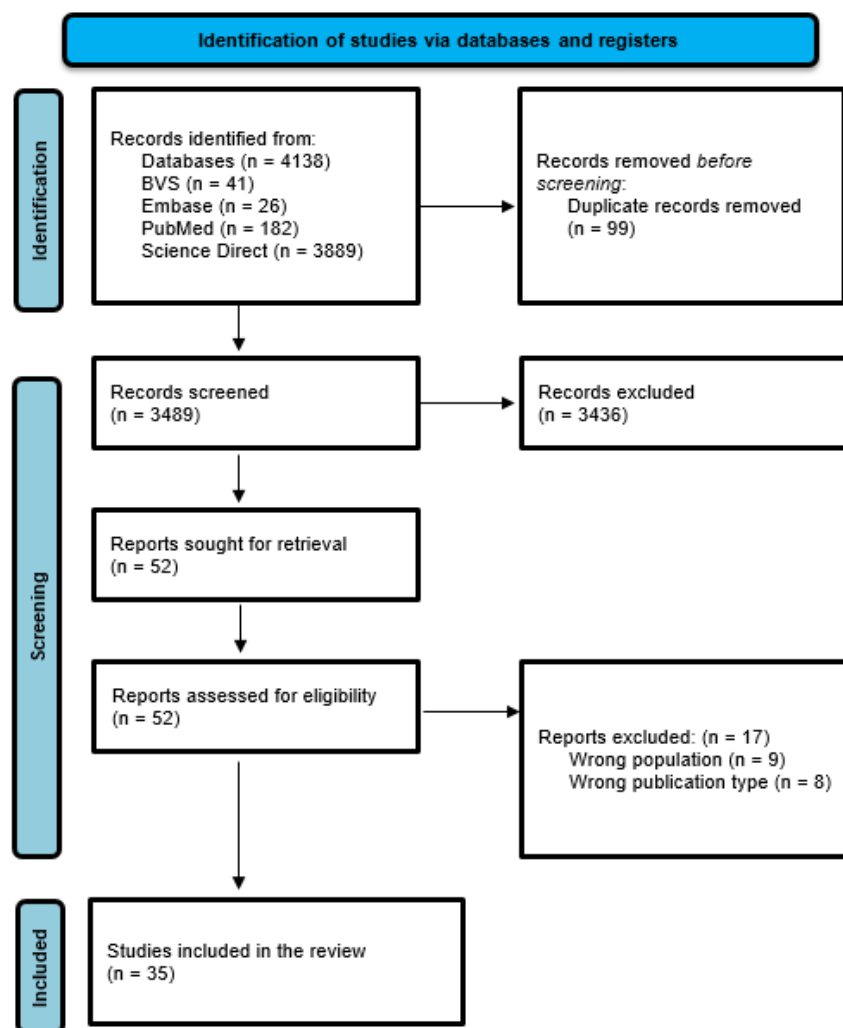


Figure 1. PRISMA flowchart for study selection.

The 35 studies encompassed 1313 patients, of whom 928 (70.67%) achieved complete remission and 858 (77.00%) reached minimal residual disease negativity, measured on the 30th day post-treatment. The results are summarized in Table 1.

3.1. Data Synthesis

The Summary Table synthesizes data from 35 studies and 1313 patients, detailing technical specifications (targets and generations) and outcomes for Complete Remission (CR) and Minimal Residual Disease (MRD) negativity at 30 days (Table 1).

We also observed that 71% (68–73%) of patients undergoing CAR-T therapy achieved complete remission 30 days after the start of treatment (Figure 2); when simultaneous dual-targeting (CD19 and CD22 cells) was used, the rate was 82% (76–87%) (Supplementary Material S5).

Table 1. Summary table.

	Author		Country	Type of Study	Age Range	Target/ Generation	CR	MDR	Total	Descriptive Summary
1	Benjamim et al., 2020	[22]	UK	NRCT	Mixed	CD19, 2nd Gen.	14	1	21	Reported 90% CRS and 38% ICANS. Median OS of 4.1 m and 47% relapse rate. Viable as a bridge to transplant.
2	Burleigh et al., 2025	[23]	USA	Cohort	Mixed	CD19, 2nd Gen.	69	69	86	Low toxicity (11% CRS, 21% ICANS) and 30% relapse rate. Confirmed efficacy in real-world settings.
3	Curran et al., 2019	[24]	USA	NRCT	Mixed	CD19, 2nd Gen.	18	16	25	High toxicity (80% CRS, 72% ICANS). OS of 7.7 m and 72% relapse rate. Effective in inducing molecular remission.
4	Del Bufalo et al., 2025	[25]	China	NRCT	Mixed	CD19, 2nd Gen.	19	19	19	Reported 68% CRS and 10% ICANS. OS of 36 m and 31% relapse rate. Potent and sustained clinical response.
5	Erdogan et al., 2022	[26]	Türkiye	NRCT	Adult	CD19, 2nd Gen.	2		7	Toxicity of 28% for both CRS and ICANS, with a 28% relapse rate. Limited activity in high-complexity adult cases.
6	Frey et al., 2020	[27]	USA	NRCT	Adult	CD19, 2nd Gen.	24	19	35	Reported 94% CRS and 40% ICANS. OS of 19.1 m and 31% relapse. Durable remissions observed in adult patients.
7	Fu et al., 2026	[28]	Vietnam	Cohort	Mixed	CD19, 2nd Gen.	37	36	55	Profile of 74% CRS and 5% ICANS. OS of 13.3 m and 32% relapse rate. Viable in SE Asia with low neurotoxicity.
8	Ghorashian et al., 2019	[29]	UK	NRCT	Mixed	CD19, 2nd Gen.	12	10	14	Reported 92% CRS and 50% ICANS. OS of 6 m and 42% relapse. Low-affinity CAR optimizes persistence and safety.
9	González-Martínez et al., 2025	[30]	China	NRCT	Pediatric	CD19/22, 2nd Gen.	8	7	10	Reported 80% CRS and 30% ICANS with OS of 18 m and 30% relapse. Dual target effective against antigen escape.
10	Heng et al., 2020	[31]	USA	NRCT	Mixed	CD19, 2nd Gen.	10	10	10	Reported 100% CRS and 0% ICANS. OS of 18 m and 20% relapse. Maximum efficacy in highly selected cohorts.
11	Hiramats et al., 2020	[32]	Japan	NRCT	Mixed	CD19, 2nd Gen.	4	4	6	Profile with 83% CRS and 0% ICANS. OS of 12 m and 50% relapse. Consistent safety and efficacy in the Japanese population.

Table 1. Cont.

Author		Country	Type of Study	Age Range	Target/ Generation	CR	MDR	Total	Descriptive Summary
12	Hu et al., 2021	[33] China	NRCT	Mixed	CD19/22, 2nd Gen.	5	5	6	Reported 100% CRS and 0% ICANS. OS of 4.3 m and 16% relapse. Sequential strategy minimizes relapses from CD19 loss.
13	Hua et al., 2020	[34] China	NRCT	Adult	CD19, 2nd Gen.	8	7	11	Profile with 54% CRS and 0% ICANS. OS of 9 m and 27% relapse. Allogeneic CAR-T as a safe alternative for adults.
14	Jiang et al., 2019	[35] USA	NRCT	Mixed	CD19, 2nd Gen.	51	47	58	Low toxicity (38% CRS, 15% ICANS). OS of 36 m and 10% relapse. Excellent bridge to transplant.
15	Kato et al., 2025	[36] Japan	Cohort	Mixed	CD19, 2nd Gen.	39	35	42	Reported 78% CRS and 9% ICANS. OS of 12 m and 38% relapse. Confirmed clinical benefit in real-world data.
16	Liu et al., 2021	[37] China	NRCT	Mixed	CD19/22, 2nd Gen.	23	18	27	Profile with 92% CRS and 18% ICANS. OS of 8 m and 66% relapse. CD19 escape control via target combination.
17	Liu et al., 2024	[38] China	Cohort	Mixed	CD19/22, 2nd Gen.	26		30	OS of 12 m and 40% relapse rate. Sustained dual benefit in Asian centers.
18	Lussana et al., 2025	[39] Italy	NRCT	Mixed	CD19, 2nd Gen.	30	26	36	Reported 77% CRS and 19% ICANS. OS of 15 m and 2% relapse. Safe non-viral Sleeping Beauty technology.
19	Ma et al., 2019	[40] China	Cohort	Pediatric	CD19, 2nd Gen.	8	8	10	Frequent CRS profile (180%) and 0% ICANS. OS of 6 m and 90% relapse rate. High initial persistence in children.
20	Magnani et al., 2020	[41] Italy	NRCT	Mixed	CD19, 3rd Gen.	7	6	13	Low toxicity (7% CRS, 23% ICANS). OS of 7.5 m and 84% relapse rate. Validated concept for 3rd gen via transposon.
21	Myers et al., 2025	[42] USA	NRCT	Mixed	CD22, 2nd Gen.	14	12	19	Reported 89% CRS and 5% ICANS. OS of 6 m and 47% relapse rate. CD22 is effective after CD19 failure.
22	Nguyen et al., 2026	[43] Vietnam	NRCT	Mixed	CD19, 2nd Gen.	8	6	8	OS of 12 m and 37% relapse rate. Technical success in local cell therapy production.

Table 1. Cont.

	Author		Country	Type of Study	Age Range	Target/ Generation	CR	MDR	Total	Descriptive Summary
23	Ottavian et al., 2022	[44]	UK	NRCT	Pediatric	CD19, 2nd Gen.	4	4	6	High neurotoxicity (33% ICANS) and 100% CRS. OS of 3 m and 66% relapse. CRISPR-edited universal CAR is promising.
24	Pan et al., 2019	[45]	China	NRCT	Mixed	CD22, 2nd Gen.	24	18	30	with 80% CRS and 0% ICANS. OS of 12 m and 60% relapse. Proven efficacy for therapeutic rescue.
25	Pan et al., 2021	[46]	China	Cohort	Mixed	CD19, 2nd Gen.	11		76	Biomarker analysis indicated that Tregs negatively impact expansion and efficacy.
26	Pan et al., 2023	[47]	USA	NRCT	Pediatric	CD19/22, 2nd Gen.	60		81	Reported 27% CRS and 0% ICANS. OS of 12 m and 18% relapse. Dual target consolidated as a multicenter standard.
27	Qian et al., 2025	[48]	China	Cohort	Adult	CD19/22, 2nd Gen.	35	33	37	Profile with 59% CRS and 0% ICANS. OS of 24 m and 18% relapse. Clinical superiority of sequential therapy.
28	Roddie et al., 2021	[49]	UK	NRCT	Adult	CD19, 2nd Gen.	17	17	20	Reported 55% CRS and 20% ICANS. OS of 6 m and 20% relapse. Fast-off kinetics reduced severe toxicity.
29	Shah et al., 2021	[50]	USA	RCT	Adult	CD19, 2nd Gen.	39	42	55	Reported 23% CRS and 25% ICANS. OS of 12 m and 21% relapse rate. Superior to standard care in phase 3 trial.
30	Wang et al., 2022	[51]	China	NRCT	Adult	CD19, 3rd Gen.	17	15	18	Profile with 55% CRS and 11% ICANS. Low relapse (5%). STAR signaling significantly enhances response.
31	Wang et al., 2025	[52]	China	NRCT	Adult	CD19, 2nd Gen.	41	32	48	Low toxicity (10% CRS, 8% ICANS). OS of 12 m. Combined therapies improved overall survival.
32	Wayne et al., 2022	[53]	USA	NRCT	Mixed	CD19, 2nd Gen.	16	16	24	Reported 16% CRS and 25% ICANS. OS of 24 m and 66% relapse rate. Durable molecular remissions in young patients.
33	Yang et al., 2021	[54]	China	NRCT	Mixed	CD19, 2nd Gen.	25	o23	25	Reported 24% CRS and 28% ICANS with 4% relapse rate. Low tumor burden predicted success.
34	Zhang et al., 2020 (Pediatric)	[55]	USA	NRCT	Pediatric	CD19, 2nd Gen.	102	96	111	Profile with 10% CRS and 23% ICANS. OS of 12 m and 44% relapse. Consolidated pediatric safety.

Table 1. Cont.

	Author		Country	Type of Study	Age Range	Target/ Generation	CR	MDR	Total	Descriptive Summary
35	Zhang et al. (2020) [Adult]	[55]	USA	NRCT	Adult	CD19, 2nd Gen.	36	39	39	Reported 15% CRS and 35% ICANS. OS of 12 m and 41% relapse. Validated molecular efficacy in adult cohort.
35	Zhao et al., 2025	[56]	China	NRCT	Mixed	CD7, 2nd Gen.	23	26	27	OS of 12 m. Concluded CD7 is an effective target for T-cell leukemias.
36	Zou et al., 2025	[57]	USA	Cohort	Mixed	CD19, 1st Gen.	42	136	168	OS of 13.5 m and 25% relapse rate. Checkpoint inhibitors assist in post-CAR-T rescue.
samTotal							928	858	1313	

Caption: NRCT: Non-Randomized Clinical Trial; Non-Randomized Clinical Trial: Randomized Clinical Trial; CR: Complete Remission; MDR: Minimal residual disease; UK: United Kingdom.

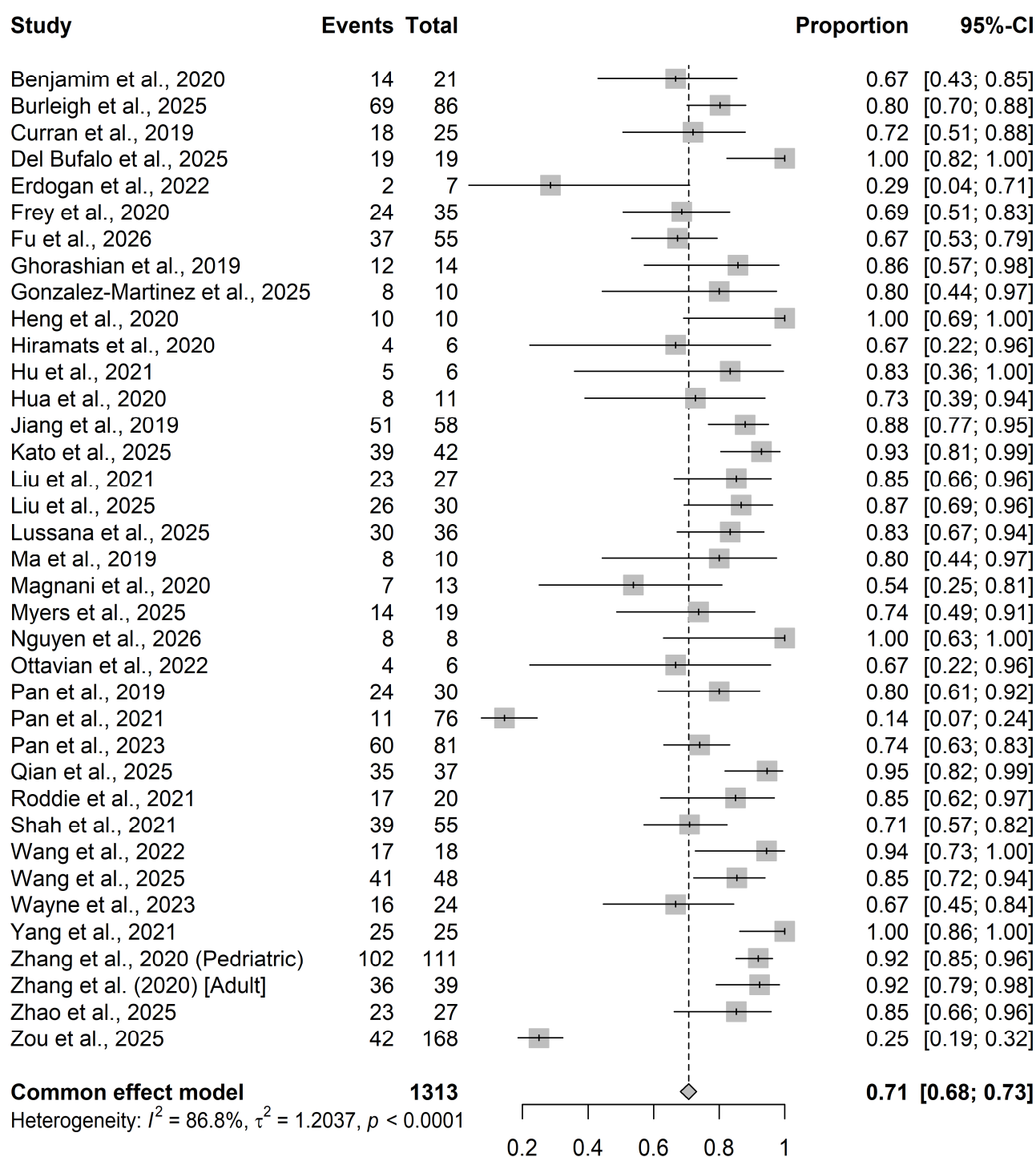


Figure 2. Forest plot of complete remission proportions in patients with Acute Lymphoblastic Leukemia undergoing CAR-T cell therapy. Citation: [23–58].

We also observed that 77% (74–79%) of patients undergoing CAR-T therapy achieved minimal residual disease negativity 30 days after the start of treatment (Figure 3); when simultaneous dual-targeting (CD19 and CD22 cells) was used, the rate was 79% (68–86%) (Supplementary Material S6).

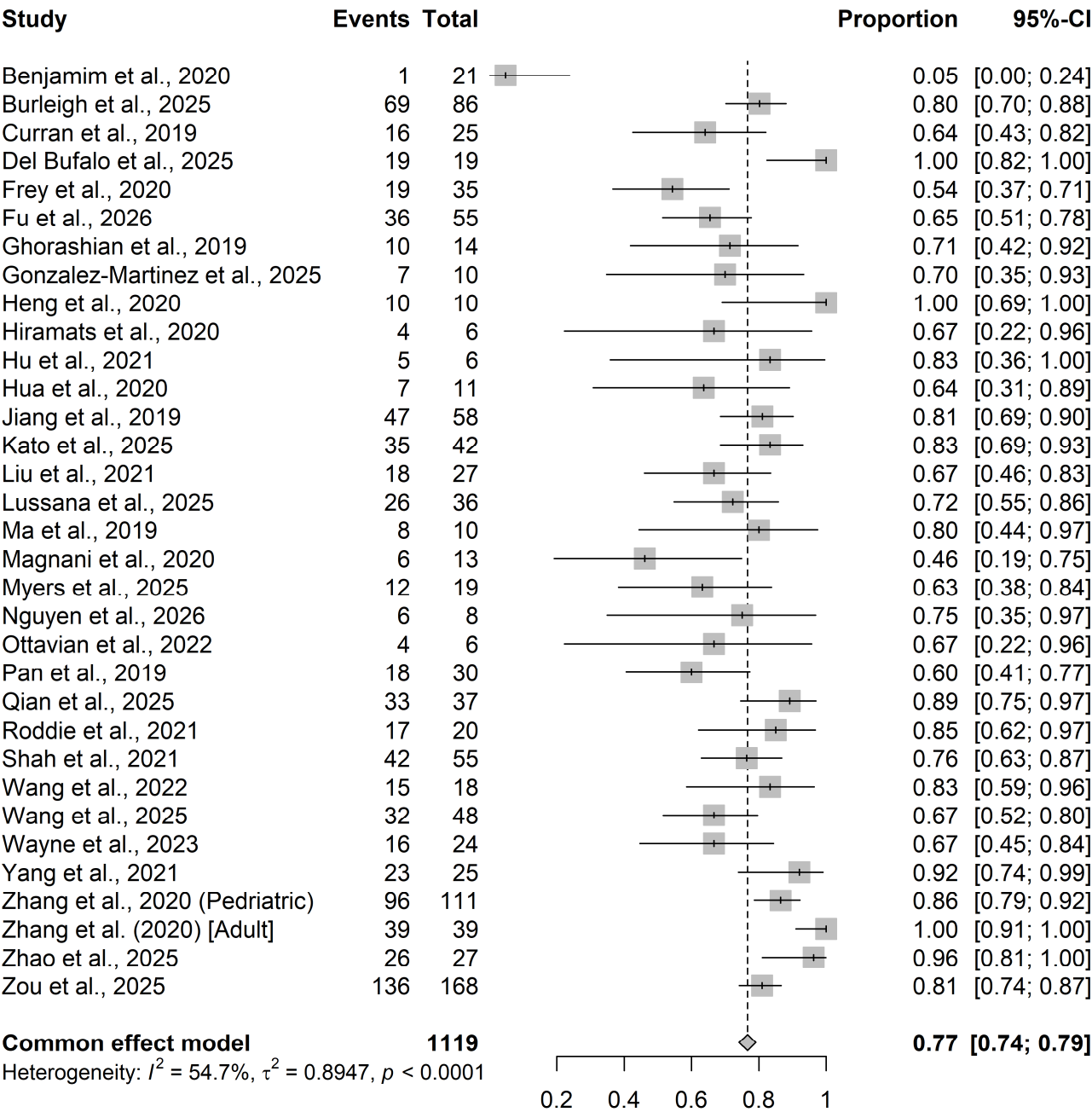


Figure 3. Forest plot of minimal residual disease proportions in patients with Acute Lymphoblastic Leukemia undergoing CAR-T cell therapy. Citation: [23–58].

The aggregate analysis of safety and efficacy, which included a total of 1313 patients, demonstrated that immunotherapy presents a robust response capacity, despite significant sustainability challenges. Regarding overall survival, a median survival of 12.0 weeks (95% CI: 11.5–12.5) was observed among the 1101 evaluated patients, with a range from 3.0 to 36.0 weeks. As for the safety profile, Cytokine Release Syndrome (CRS) was the most prevalent complication, affecting 46.81% of the sample (n = 1004), followed by cytopenia (45.16%) and neurotoxicity (23.52%). Concerning the durability of the therapeutic response, the relapse rate was 33.90% across 994 monitored patients, highlighting the complexity of maintaining long-term biological efficacy (Table 2).

Table 2. Safety profile and clinical outcomes of ALL patients undergoing CAR-T therapy.

Clinical Outcome	Events	n. Analyzed	Rate (%)	95% CI
Cytokine Release Syndrome (CRS)	470	1.004	46.81%	[43.74–49.91]
Neurotoxicity (ICANS)	187	795	23.52%	[20.71–26.59]
Cytopenia	196	434	45.16%	[40.54–49.87]
Relapse Rate	337	994	33.90%	[31.03–36.90]
Overall Survival (Median)	-	1.101	12 weeks	[11.5–12.5]

Regarding the sensitivity analysis, we observed that separate treatment (in children or adults), non-randomized clinical trials, allogeneic cell therapy, and second- and third-generation cells showed better results for the 30-day complete remission outcome (Table 3).

Table 3. Sensitivity analysis for the outcomes of complete remission and minimal residual disease in patients with acute lymphoblastic leukemia treated with CAR-T cells.

Variable	Number of Studies	Complete Remission			Minimal Residual Disease		
		N	% (CI)	<i>p</i>	N	%	<i>p</i>
Age *							
Adult		270	81 (76–85)	<0.0001	263	78 (72–82)	0.360
Pediatric		218	83 (78–88)		137	75 (72–78)	
Mixed		825	64 (61–67)		719	75 (72–78)	
Type of study **							
Non-Randomized Clinical Trial	28	754	82 (80–85)	<0.0001	666	75 (71–78)	0.20
Observational Cohort Study	6	505	53 (49–57)		398	80 (75–83)	
Randomized Clinical Trial	1	55	71 (49–57)		55	76 (74–79)	
Origin ***							
Allogeneic	12	282	81 (76–85)	<0.0001	252	68 (63–72)	0.0002
Autologous	23	1031	68 (65–71)		867	79 (76–82)	
Generation ****							
1st	2	168	25 (19–32)	<0.0001	168	81 (74–87)	0.20
2nd	32	1114	77 (75–80)		920	76 (73–79)	
3rd	1	31	77 (70–89)		31	68 (50–82)	
Vector *****							
Lentiviral	27	1034	69 (66–72)	0.09	921	77 (74–80)	0.144
Retroviral	6	230	76 (70–81)		149	77 (69–83)	
Transposon	2	49	76 (62–86)		0	-	
Financing							
Academic	26	493	64 (60–67)	<0.0001	717	73 (69–76)	<0.0001
Industry	9	420	86 (82–89)		402	84 (80–87)	

* S9 and S10, ** S11 and S12, *** S13 and S14, **** S15 and S16, ***** S17 and S18.

3.2. Quality Assessment of Information

3.2.1. Bias Analysis

Regarding the risk of bias, two articles [26,44] were found to have a high risk of bias, while 11 studies showed a moderate risk [23,28,36,38,40,42,43,47,53,55,56]. The remaining 22 [23,24,27,29–35,37,39,41,45,46,48–52,54,55] studies presented a low risk of bias, thereby reflecting the quality of the works included in this review (Figure 4).

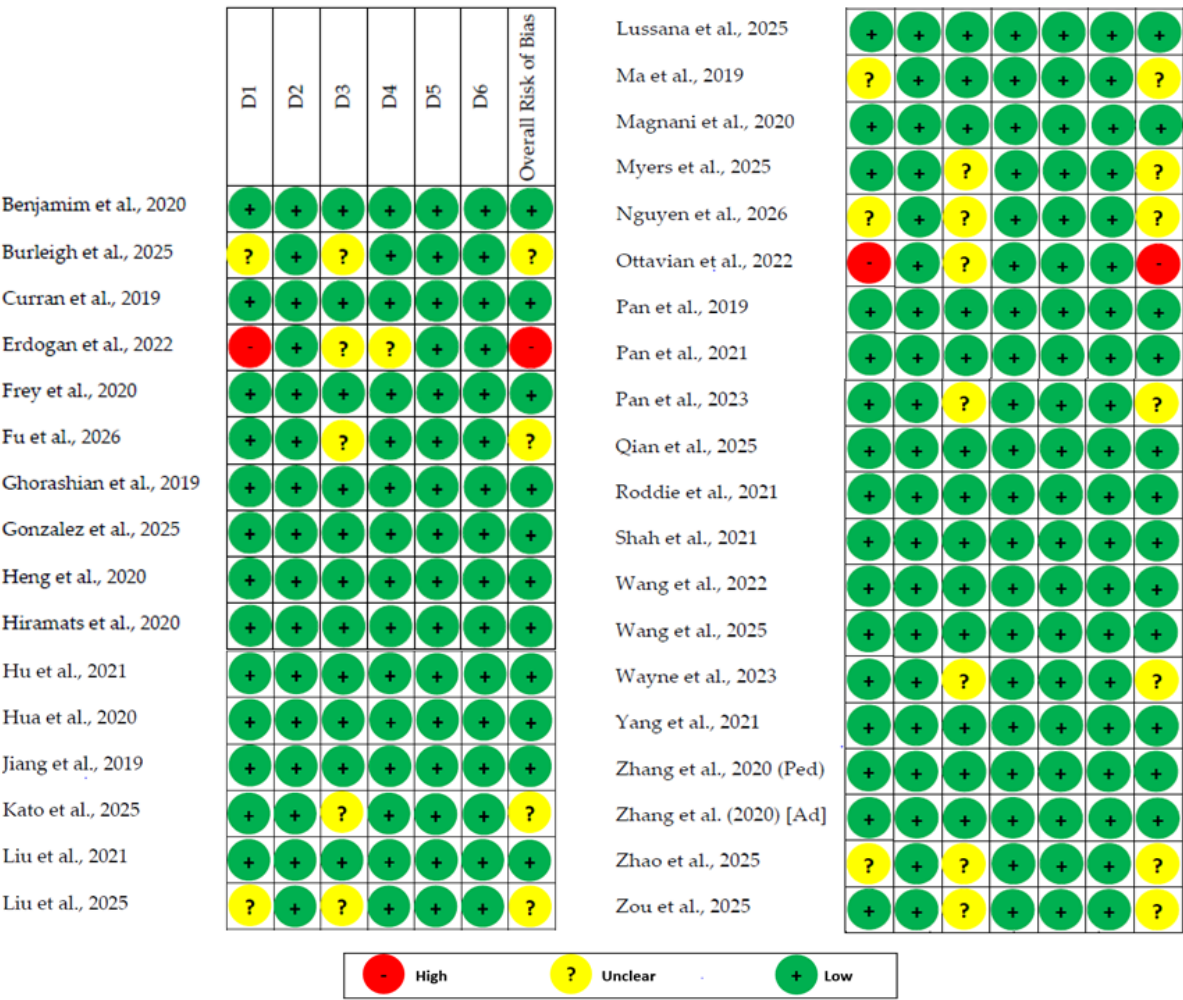


Figure 4. Risk of bias plot analyzed using the ROBINS-I tool in studies of patients with Acute Lymphoblastic Leukemia undergoing CAR-T cell therapy. Citation: [23–58].

- Domain 1: Risk of bias due to confounding.
- Domain 2: Risk of bias in classification of interventions.
- Domain 3: Risk of bias in selection of participants into the study (or into the analysis).
- Domain 4: Risk of bias due to missing data.
- Domain 5: Risk of bias arising from measurement of the outcome.
- Domain 6: Risk of bias in selection of the reported result.

The assessment of publication bias using Egger’s linear regression test demonstrated significant asymmetry in the funnel plot, with an estimated bias coefficient of 3.14 ($p = 0.0009$). This suggests the presence of small-study effects, possibly due to the preferential reporting of positive outcomes in smaller cohorts or the high methodological heterogeneity intrinsic to the analyzed cell therapies (Figure 5).

However, after an in-depth investigation using studentized residuals of the random-effects model [15] we identified the articles by Pan et al. (2021) [46] and Zou et al. (2025) [55], with z-scores of -2.8626 and -2.6904 , respectively. Upon applying diagnostic tests, including Cook’s Distance (Cook’s D) [15] and the Difference in Fits (DFFITS) [16], we detected the influential nature of these studies on the overall result and excluded them from the publication bias analysis. After exclusion, Egger’s test was reapplied, resulting in an estimated bias coefficient of 1.10 ($p = 0.0527$), which does not suggest asymmetry (Supplementary Material S7). We therefore conclude that the initially observed asymmetry

was driven by these two studies and that the remaining body of evidence does not present substantial publication bias; notably, both studies received academic funding.

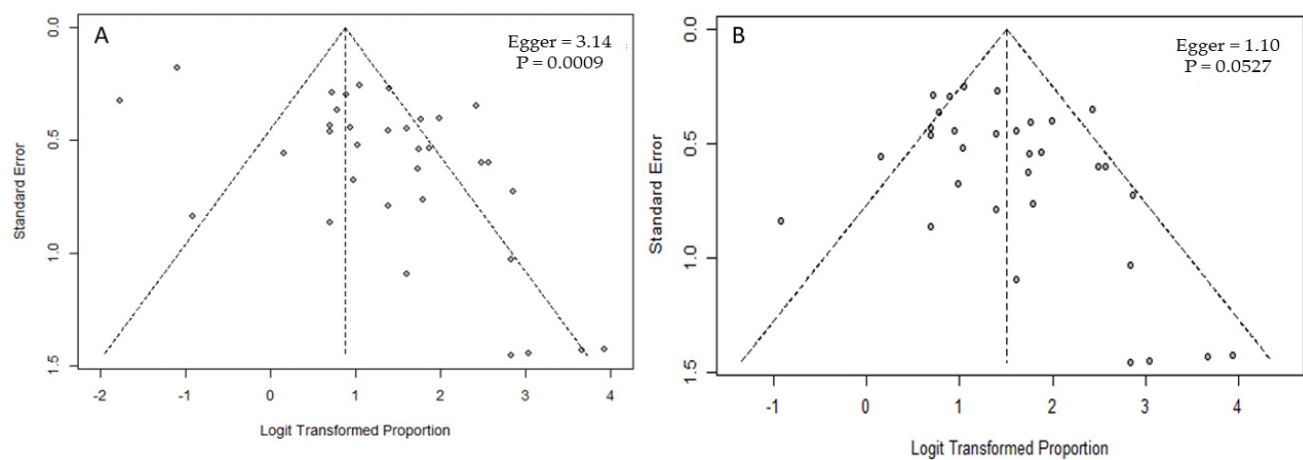


Figure 5. Funnel plot showing the risk of publication bias and the distribution of the included studies ((A): including influential articles; (B): after removing influential articles).

3.2.2. Analysis of Certainty of Evidence

Regarding the certainty of evidence, it was observed that for both complete remission and minimal residual disease outcomes, the evidence was moderate (Table 4).

Table 4. Summary of results and certainty of evidence analysis (GRADE) of the effect of CAR-T cell therapy in patients with Acute Lymphoblastic Leukemia.

Analysis Criteria						n° of Patients		Effect	Certainty of Evidence
n° of Studies	Design	Quality	Consistency	Directness	Imprecision	Other Modifying Factors		Absolute and Percentage (IC)	
						Publication Bias	A Significant Effect	Total	
Complete remission									
35	28: NRCT 6: Cohort 1: RCT	not serious	serious a	non-serious	non-serious	serious b	Large	1313 928 71% (68–73%)	⊕⊕⊕○ moderate
Minimal residual disease									
32	25: NRCT 6: Cohort 1: RCT	not serious	serious a	non-serious	non-serious	serious b	large	1189 858 77% (74–79%)	⊕⊕⊕○ moderate

Caption: NRCT: Non-Randomized Clinical Trial, RCT: Randomized Clinical Trial, ⊕⊕⊕○: moderate certainty of evidence; a—Serious risk of bias: Significant variability in MRD-rates between academic and multicenter studies. b—Serious risk of bias: Probability of preferential reporting of positive molecular outcomes (Downgraded (−1)).

4. Discussion

Although Acute Lymphoblastic Leukemia (ALL) is predominantly observed in children for whom survival rates are considerably favorable due to the body’s greater resilience, ALL also affects adults. In these patients, overall survival rarely exceeds 40% [2,3], highlighting the critical need for more effective interventions. The refractory or relapsed nature of the disease, combined with the inherent toxicity of conventional treatments such as chemotherapy and hematopoietic stem cell transplantation, necessitates a continuous search for more effective therapeutic technologies with enhanced safety profiles.

In this context, immunotherapy with T cells equipped with Chimeric Antigen Receptors (CAR-T) has emerged as a transformative advancement in the treatment of hematological malignancies. The results of this study consolidate CAR-T immunotherapy as

an intervention with high biological efficacy for relapsed or refractory (R/R) Acute Lymphoblastic Leukemia (ALL). An overall Complete Remission (CR) rate of 70.68% (928/1313) was observed, with a significant conversion to Minimal Residual Disease (MRD) negativity of 76.68% (858/1119). These outcomes, obtained at a median of 28 days post-infusion, surpass the historical milestones of conventional chemotherapy, where remission rates in multi-treated patients rarely exceed 40% [3,4].

The observed superiority over traditional cytotoxic regimens stems from the ability of CAR-T cells to bypass tumor evasion mechanisms through direct and sustained immunological activation, independent of antigen presentation via the Major Histocompatibility Complex (MHC) [5]. The high rate of MRD negativity (76.68%) is particularly notable, as it suggests a deep eradication of leukemic clones at a submicroscopic level, which is a critical predictor for extended event-free survival [40]. Unlike chemotherapy, which presents a dose-dependent response curve limited by toxicity in vital organs, CAR-T therapy acts as a ‘living drug,’ whose efficacy is enhanced by *in vivo* clonal expansion following recognition of the CD19 or CD22 target [38]. However, the variation in the remission rate across our global cohort—slightly lower than the 90% reported in smaller-scale pivotal clinical trials—reflects the heterogeneity of the ‘real world,’ where pre-infusion tumor burden, the functional exhaustion of lymphocytes in multi-treated patients, and biological disparities between adults and children impose limits on therapeutic performance [4].

Regarding age, although the literature points to greater resilience in children, our data show that both adults (81.11%) and pediatric patients (83.49%) achieve CR rates above 80%. The drop in the overall average to 70.68% is due to lower performance in mixed-cohort studies, possibly influenced by higher tumor burden and immunological exhaustion.

This balance in CR rates between adults and children challenges the conventional notion that advanced age is an absolute limiting factor for cellular immunotherapy. This parity may be explained by the enhancement of costimulatory domains in second-generation cells, which partially compensate for the immunosenescence process observed in adult patients [7]. However, the reduction in the global average to 70.68% in mixed cohorts raises a critical discussion regarding T-cell ‘fitness.’ As suggested by Paul [4], patients with a history of multiple relapses and prolonged exposure to alkylating agents present lymphocytes with a terminal exhaustion phenotype, characterized by the expression of checkpoint markers that hinder robust CAR-T cell expansion. Additionally, the higher tumor burden frequently found in these mixed cohorts not only favors the occurrence of severe adverse events but also fosters an immunosuppressive microenvironment that may lead to the phenomenon of cellular ‘fratricide’ or early functional exhaustion [48], explaining the statistical decline observed when subgroups are not stratified by age group purity or treatment line.

As for cell type and generation, target dominance is centered on CD19 (67.88%), but the dual-target approach (CD19/CD22) demonstrated tactical superiority with an 82.20% CR, suggesting that combating antigenic escape is the key to maximum efficacy. In terms of generation, the second generation (4-1BB/CD28) is the gold standard for efficacy (77.38%), vastly outperforming the first generation (25%) [38].

Stratified analysis by molecular configuration reveals that genetic engineering refinement is the primary determinant of clinical efficacy. The shift in CR rate from 67.88% in the CD19-monotarget group to 82.20% in the dual-target approach (CD19/CD22) materializes the solution to the main obstacle of immunotherapy in ALL: antigenic escape. As discussed by [33,47], the selective pressure imposed by strictly anti-CD19 CAR-T cells often results in the emergence of leukemic clones with loss or downregulation of this antigen. The inclusion of the CD22 target creates a ‘synergistic barrier,’ where the probability of a tumor

cell simultaneously evading two synthetic receptors is drastically reduced, ensuring a more homogeneous and comprehensive cytotoxic pressure over the tumor mass [37,45].

Regarding the evolution of receptor generations, the statistical disparity between the first generation (25% CR) and second generation (77.38% CR) is grounded in the bioengineering of intracellular signaling. The first generation, limited solely to the ζ (zeta) signaling chain of the CD3 complex, lacked the capacity to sustain clonal proliferation *in vivo*, resulting in premature exhaustion of effector cells [56]. The advent of the second generation, characterized by the incorporation of costimulatory domains (4-1BB or CD28), allowed for the mimicry of complete physiological T-lymphocyte activation. As noted by Liu et al. (2024) [38], these domains not only increase the initial remission rate but also modulate the mitochondrial metabolism of CAR-T cells, favoring the formation of memory cells and increasing their persistence in the body. However, despite the success of the second generation, the 33.90% relapse rate observed in this review, often associated with low persistence and antigenic escape [40,52], suggests that the current 'gold standard' still faces functional exhaustion challenges. This scenario drives the use of cutting-edge tools, such as the CRISPR system, for the knockout of negative signaling regulators (such as the FAS gene), aiming to 'supercharge' the resistance of these cells to the immunosuppressive tumor microenvironment [28]. On the other hand, it is important to note that the process of activating the immune system is associated with the development of adverse reactions that can be fatal.

Regarding origin, surprisingly, cells of allogeneic origin presented a CR rate of 80.85%, compared to 67.90% for autologous ones. This may indicate that lymphocytes from healthy donors possess greater functional vigor (fitness) than those collected from patients exhausted by multiple lines of chemotherapy.

ALL patients undergoing multiple lines of intensive chemotherapy and rescue regimens suffer from 'iatrogenic exhaustion' of their T cells, resulting in an autologous product with shortened telomeres, increased expression of inhibitory receptors (such as PD-1 and LAG-3), and reduced proliferative capacity [5,56]. In contrast, the use of lymphocytes from healthy donors ensures access to naïve and central memory T cells with high functional vigor (fitness), capable of more robust and persistent clonal expansion after gene transfection [38]. As highlighted by [31], the use of 'off-the-shelf' allogeneic cells not only bypasses the critical manufacturing time essential for patients with rapidly progressing disease but also provides a 'younger' immune system that is more resilient to the immunosuppressive tumor microenvironment. However, it is imperative to note that the tactical superiority of allogeneic cells in inducing remission requires rigorous management of Graft-Versus-Host Disease (GVHD), often achieved through the knockout of the T-cell receptor (TCR) via CRISPR technology, which reinforces the trend that the future of maximum efficacy in ALL lies in the combination of healthy donors and precision genetic engineering [31].

Regarding gene transport, retroviral vectors (76.09%) proved to be slightly superior to lentiviral vectors (69.25%) in inducing immediate remission. This tactical superiority is due to the biological affinity of gammaretroviruses for actively dividing cells, resulting in more homogeneous genomic integration and a robust initial cytotoxic 'boost' [24,45,46]. In contrast, lentiviral vectors, although showing slightly lower acute rates, are preferred at the forefront of research because they offer greater genomic safety and stability for long-term immunological memory formation [45].

As for survival and relapse, response durability remains the Achilles' heel of the technology. With a median survival of 12 weeks and a relapse rate of 33.90%, it is evident that inducing remission does not guarantee a definitive cure, being frequently associated with the loss of CAR-T cell persistence [33,40].

Given the expressive acute efficacy contrasted by the limited durability of the response, the hypothesis emerges that CAR-T immunotherapy acts as a strategic ‘bridge to transplant’ for hematopoietic stem cell transplantation (HSCT). Obtaining an MRD-negative state in 76.68% of patients, even if transient, offers an unprecedented clinical window of opportunity for individuals previously considered ineligible for transplant due to persistent tumor burden or refractoriness to chemotherapy. By eradicating chemoresistant clones and restoring a favorable marrow environment, CAR-T therapy conditions the body to receive the graft under conditions of minimal tumor burden, which is one of the most robust predictors of success and reduction in post-transplant relapse [40]. Therefore, for the portion of the cohort at risk of losing the persistence of modified cells, CAR-T should not be seen merely as a terminal therapy, but as a critical facilitator that prepares the biological ground for definitive consolidation via HSCT, transforming a temporary remission into a concrete possibility of sustained cure [4,34].

In terms of toxicity, the safety profile is marked by a high incidence of CRS (46.81%) and neurotoxicity (23.52%). Although treatable, the high rate of cytopenias (45.16%) reinforces the need for intensive hematological support and careful management of systemic inflammatory events [57–59].

The main limitation of the included evidence lies in methodological heterogeneity. The variation between Phase I and II trials, combined with different lymphodepletion protocols, introduces variability in safety outcomes. Additionally, the lack of randomization in most studies increases the risk of selection bias.

Regarding the review process, outlier management was rigorous. Identifying two highly influential studies [45,55] using Cook’s Distance (D) [15] and the DFFITS metric [16] was fundamental. Their exclusion allowed for a more precise assessment of publication bias, ensuring that the funnel symmetry reflected the real body of evidence, free from distortion by atypical studies.

5. Conclusions

This work confirms that CAR-T immunotherapy represents an unprecedented advancement in the treatment of Acute Lymphoblastic Leukemia (ALL), presenting a robust capacity for inducing Complete Remission and deep disease eradication, as evidenced by the high rate of MRD negativity. The data demonstrate that the therapy’s efficacy transcends age barriers, with success rates exceeding 80% in both adults and children, establishing it as the most effective strategy for patients refractory to conventional protocols. Molecular analysis reinforces the tactical superiority of second-generation cells and dual-target approaches (CD19/CD22), which prove essential for mitigating antigenic escape.

However, response durability remains the central challenge, with a high relapse rate and low median survival, often limited by functional T-cell exhaustion or loss of cellular persistence. In this scenario, the results suggest that CAR-T therapy performs excellently as a strategic bridge to bone marrow transplantation, creating ideal clinical conditions through a deep, albeit transient, cytological remission. Although the safety profile is marked by significant incidences of CRS and neurotoxicity, the high reversibility of these conditions confirms a favorable risk–benefit balance.

Ultimately, the future of sustained cure in ALL lies in the evolution of genetic engineering. The integration of tools such as CRISPR for developing ‘supercharged’ cells and the use of healthy donors to ensure cellular functional vigor (fitness) are the paths identified to overcome immunological exhaustion. Taken together, the results presented here demonstrate that CAR-T therapy can be considered an important tool for the clinical management of patients diagnosed with ALL.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/futurepharmacol6030038/s1>, PRISMA Checklist S1; Concept Map S2; Search Strategy Conducted S3; List of excluded itens S4; Forest plot of complete remission proportions in patients with Acute Lymphoblastic Leukemia undergoing CAR-T cell therapy S5; Sensitivity plot for complete remission by cell subgroup S6; Forest plot of minimal residual disease proportions in patients with Acute Lymphoblastic Leukemia undergoing CAR-T cell therapy S7; Sensitivity plot of minimal residual disease by cell subgroup S8; Influence Analysis and Outlier Diagnosis S9; Software, R packages, versions, and direct URLs used in the analyses S10; Sensitivity plot of complete remission by age S11; Sensitivity plot of minimal residual disease by age S12; Sensitivity plot for complete remission by type of study S13; Sensitivity plot of minimal residual disease by type of study S14; Sensitivity plot for complete remission by origin S15; Sensitivity plot of minimal residual disease by origin S16; Sensitivity plot of complete remission by generation S17; Sensitivity plot of minimal residual disease by generation S18; Sensitivity plot of complete remission by vector S19; Sensitivity plot of minimal residual disease by vector S20.

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Abbreviations

Acronym	Full Term
ALL	Acute Lymphoblastic Leukemia
BVS	Virtual Health Library (Biblioteca Virtual em Saúde)
CAR-T	Chimeric Antigen Receptor T-cell
CI	Confidence Interval
CR	Complete Remission
CRS	Cytokine Release Syndrome
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HSCT	Hematopoietic Stem Cell Transplantation
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
LD	Laser Diode (ou conforme contexto do template)

MDR/MRD	Minimal Residual Disease
OS	Overall Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
TLA	Three Letter Acronym (ou conforme contexto do template)
UFT	Federal University of Tocantins

References

- O’Gorman, M.R.G. Measurement of Minimal Residual Disease in Acute Leukemia. *Cytom. Part B Clin. Cytom.* **2016**, *90*, 111–112. [CrossRef]
- Correa, B.T.; Silva, G.S.S.; Mendes, W.J.S.; Soares, L.L.; Lima, J.A.; Pereira, C.G.S.; Souza, J.V.T.; Santos, M.E.F.; Aleluia, A.C.M.; da Guarda, C.C.; et al. Acute Lymphoblastic Leukemia: An Update on Treatment and Brazilian Perspective. *Front. Oncol.* **2026**, *16*, 1637924. [CrossRef] [PubMed]
- Hall, A.G.; Schultz, L.M.; Baggott, C.; Prabhu, S.; Pacenta, A.M.; Phillips, C.L.; Rossoff, J.; Stefanski, H.E.; Talano, J.A.; Curran, K.J.; et al. Access to Chimeric Antigen Receptor T Cell Clinical Trials in Underrepresented Populations: A Multicenter Cohort Study of Pediatric and Young Adult Acute Lymphoblastic Leukemia Patients. *Transplant. Cell. Ther.* **2023**, *29*, 356.e1–356.e7. [CrossRef] [PubMed]
- Paul, S.; Kantarjian, H.; Jabbour, E.J. Adult Acute Lymphoblastic Leukemia. *Mayo Clin. Proc.* **2016**, *91*, 1645–1666. [CrossRef] [PubMed]
- Abbas, A.K.; Lichtman, A.H.; Pillai, S. *Imunologia Básica: Funções e Distúrbios do Sistema Imune*; Revinter: Rio de Janeiro, Brazil, 2003.
- Mohapatra, D.; Meena, J.P.; Gupta, A.K.; Seth, R. Evolution of Therapy in Pediatric Acute Lymphoblastic Leukemia: From Aminopterin to Chimeric Antigen Receptor T-Cell Therapy: Global Advancements, Adaptations in India, and Lessons for Low-and Middle-Income Countries. *JCO Glob. Oncol.* **2026**, *12*, e2500478. [CrossRef] [PubMed]
- Gökbuget, N.; Hoelzer, D. Treatment of Adult Acute Lymphoblastic Leukemia. *Semin. Hematol.* **2009**, *46*, 64–75. [CrossRef] [PubMed]
- Liu, S.; An, L.; Yin, Z.; Lin, Y.; Ling, Z.; Deng, B.; Yu, X.; Zheng, Q.; Zhao, D.; Wu, T.; et al. Five-Year Outcome of CD19 Followed by CD22 Chimeric Antigen Receptor T-Cell Therapy in B-Cell Acute Lymphoblastic Leukemia Patients Who Relapsed After Allo-Transplantation. *Haematologica* **2025**, *110*, 286534.
- Anvisa. Anvisa Autoriza Pesquisa Clínica com Células CAR-T no Brasil. Available online: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-autoriza-pesquisa-clinica-com-celulas-201ccar-2013-t201d-no-brasil> (accessed on 2 November 2024).
- Champlin, R.; Gale, R.P. Acute Lymphoblastic Leukemia: Recent Advances in Biology and Therapy. *Blood* **1989**, *73*, 2051–2066. [CrossRef] [PubMed]
- Galvão, T.F.; Pansani, T.S.A.; Harrad, D. A Declaração PRISMA 2020: Diretriz Atualizada para Relatar Revisões Sistemáticas. *Epidemiol. Serv. Saúde* **2022**, *31*, e2022101. [CrossRef]
- PROSPERO. International Prospective Register of Systematic Reviews. Available online: <https://www.crd.york.ac.uk/PROSPERO/> (accessed on 8 May 2026).
- Rayyan. Rayyan—Intelligent Systematic Review. Available online: <https://www.rayyan.ai/> (accessed on 20 August 2024).
- Sterne, J.A.; Hernán, M.A.; Reeves, B.C.; Savović, J.; Berkman, N.D.; Viswanathan, M.; Henry, D.; Altman, D.G.; Ansari, M.T.; Boutron, I.; et al. ROBINS-I: A Tool for Assessing Risk of Bias in Non-Randomised Studies of Interventions. *BMJ* **2016**, *355*, i4919. [CrossRef] [PubMed]
- Student. The Probable Error of a Mean. *Biometrika* **1908**, *6*, 1–25. [CrossRef]
- Cook, R.D. Detection of Influential Observation in Linear Regression. *Technometrics* **1977**, *19*, 15–18. [CrossRef]
- Cook, R.D.; Weisberg, S. *Residuals and Influence in Regression*; Chapman & Hall: New York, NY, USA, 1982.
- Atkins, D.; Best, D.; Briss, P.A.; Diguer, B.; Falck-Ytter, Y.; Flottorp, S.; Guyatt, G.H.; Harbour, R.T.; Haugh, M.C.; Henry, D.; et al. Grading Quality of Evidence and Strength of Recommendations. *BMJ* **2004**, *328*, 1490. [CrossRef] [PubMed]
- Higgins, J.P.T.; Green, S. *Cochrane Handbook for Systematic Reviews of Interventions*; John Wiley & Sons Ltd.: Chichester, UK, 2008.
- R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2024. Available online: <https://www.R-project.org/> (accessed on 6 May 2026).
- Nyaga, G.N.; Arbyn, M.; Aerts, M. Methods for Meta-Analysis of Proportions: A Review of Tests, Models, Transformations, and Software. *Res. Synth. Methods* **2014**, *5*, 333–348.
- Higgins, J.P.; Thompson, S.G. Quantifying Heterogeneity in a Meta-Analysis. *Stat. Med.* **2002**, *21*, 1539–1558. [CrossRef] [PubMed]

23. Benjamin, R.; Graham, C.; Yallop, D.; Jozwik, A.; Mirci-Danicar, O.C.; Lucchini, G.; Pinner, D.; Jain, N.; Kantarjian, H.; Boissel, N.; et al. Genome-Edited, Donor-Derived Allogeneic Anti-CD19 Chimeric Antigen Receptor T Cells in Paediatric and Adult B-Cell Acute Lymphoblastic Leukaemia: Results of Two Phase 1 Studies. *Lancet* **2020**, *396*, 1885–1894. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Burleigh, K.; Stratton, K.G.; Smith, J.L.; Jensen, M.C.; Turtle, C.J.; Keenan, C.; Annesley, C.; Summers, C.; Webb-Robertson, B.-J.; Hirayama, A.V.; et al. Low Peripheral Blood Counts and Elevated Proinflammatory Cytokines Signal a Poor CD19 CAR T-Cell Response in Acute Lymphoblastic Leukemia. *Transplant. Cell. Ther.* **2025**, *31*, 551–564. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Curran, K.J.; Margossian, S.P.; Kernan, N.A.; Silverman, L.B.; Williams, D.A.; Shukla, N.; Kobos, R.; Forlenza, C.J.; Steinherz, P.; Prockop, S.; et al. Toxicity and Response After CD19-Specific CAR T-Cell Therapy in Pediatric/Young Adult Relapsed/Refractory B-ALL. *Blood* **2019**, *134*, 2361–2368. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Del Bufalo, F.; De Angelis, B.; Caruana, I.; Del Baldo, G.; De Ioris, M.A.; Serra, A.; Mastronuzzi, A.; Bertaina, A.; Pagliara, D.; Qi, J.; et al. Point-of-Care Fresh CAR T Cells for Pediatric or Young Adult BCP-ALL That Is Relapsed/Refractory or in Very-High-Risk First Relapse. *Blood Adv.* **2025**, *9*, 5091–5102. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Erdoğan, E.; Yalçın, K.; Hemşinlioğlu, C.; Sezgin, A.; Seyis, U.; Kancağı, D.D.; Taştan, C.; Yurtsever, B.; Turan, R.D.; Çakırsoy, D.; et al. Preliminary Report of the Academic CAR-T (ISIKOK-19) Cell Clinical Trial in Turkey: Characterization of Product and Outcomes. *Turk. J. Haematol.* **2022**, *39*, 206–210. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Frey, N.V.; Shaw, P.A.; Hexner, E.O.; Pequignot, E.; Gill, S.; Luger, S.M.; Mangan, J.K.; Loren, A.W.; Perl, A.E.; Maude, S.L.; et al. Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults with Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2020**, *38*, 415–422. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Fu, S.; Yu, Y.; Zhang, M.; Feng, J.; Wang, W.; Tu, S.; Zhang, Q.; Zhao, M.; Huang, H.; Hu, Y.; et al. Long-Term Follow-Up of CD19 CAR T-Cell Therapy in ALL Patients Relapsed After Allogeneic Transplantation. *Cytotherapy* **2026**, *28*, 102074. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Ghorashian, S.; Kramer, A.M.; Onuoha, S.; Wright, G.; Bartram, J.; Richardson, R.; Albon, S.J.; Casanovas-Company, J.; Castro, F.; Popova, B.; et al. Enhanced CAR T-Cell Expansion and Prolonged Persistence in Pediatric Patients with ALL Treated with a Low-Affinity CD19 CAR. *Nat. Med.* **2019**, *25*, 1408–1414. [\[CrossRef\]](#) [\[PubMed\]](#)
31. González-Martínez, B.; Galán-Gómez, V.; Navarro-Zapata, A.; Mirones-Aguilar, I.; Cobo, M.; Pernas-Sánchez, A.; Vallejo, S.; Sánchez-Zapardiel, E.; León-Triana, O.; Echecopar, C.; et al. Tandem CD19/CD22 CAR T-Cells as Potential Therapy for Children and Young Adults with High-Risk r/r B-ALL. *eBioMedicine* **2025**, *118*, 105872. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Heng, G.; Jia, J.; Li, S.; Fu, G.; Wang, M.; Qin, D.; Li, Y.; Pei, L.; Tian, X.; Zhang, J.; et al. Sustained Therapeutic Efficacy of Humanized Anti-CD19 CAR-T Cells in Relapsed/Refractory Acute Lymphoblastic Leukemia. *Clin. Cancer Res.* **2020**, *26*, 1606–1615. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Hiramatsu, H.; Adachi, S.; Umeda, K.; Kato, I.; Eldjerou, L.; Agostinho, A.C.; Natsume, K.; Tokushige, K.; Watanabe, Y.; Grupp, S.A. Efficacy and Safety of Tisagenlecleucel in Japanese Pediatric and Young Adult Patients With Relapsed/Refractory B-ALL. *Int. J. Hematol.* **2020**, *111*, 303–310. [\[PubMed\]](#)
34. Hu, Y.; Zhou, Y.; Zhang, M.; Ge, W.; Li, Y.; Yang, L.; Wei, G.; Han, L.; Wang, H.; Yu, S.; et al. Universal CD19/CD22 Dual-Targeted CAR-T Cell Therapy via CRISPR/Cas9 for R/R B-ALL. *Clin. Cancer Res.* **2021**, *27*, 2764–2772. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Hua, J.; Zhang, J.; Wu, X.; Zhou, L.; Bao, X.; Han, Y.; Miao, M.; Li, C.; Fu, Z.; Wu, D.; et al. Allogeneic Donor-Derived CAR-T Cells as Therapy for R/R B-ALL After Stem-Cell Transplantation. *Clin. Lymphoma Myeloma Leuk.* **2020**, *20*, 610–616. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Jiang, H.; Li, C.; Yin, P.; Guo, T.; Liu, L.; Xia, L.; Wu, Y.; Zhou, F.; Ai, L.; Shi, J.; et al. Anti-CD19 CAR-T Therapy Bridging to HSCT for R/R B-ALL. *Am. J. Hematol.* **2019**, *94*, 1113–1122. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Kato, I.; Tomizawa, D.; Kato, M.; Hirabayashi, S.; Manabe, A.; Irie, M.; Sasahara, Y.; Arakawa, Y.; Koh, K.; Sakaguchi, H.; et al. Real-World Outcomes of Commercial Tisagenlecleucel for Children, Adolescents, and Young Adults with Acute Lymphoblastic Leukemia in Japan. *Transplant. Cell. Ther.* **2025**, *31*, 86–96. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Liu, S.; Deng, B.; Yin, Z.; Lin, Y.; An, L.; Liu, D.; Pan, J.; Yu, X.; Chen, B.; Wu, T.; et al. Combination of CD19 and CD22 CAR-T cell therapy in relapsed B-cell acute lymphoblastic leukemia after allogeneic transplantation. *Am. J. Hematol.* **2021**, *96*, 671–679. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Liu, Z.; Lei, W.; Wang, H.; Liu, X.; Fu, R. Challenges and Strategies Associated With CAR-T Cell Therapy in Blood Malignancies. *Exp. Hematol. Oncol.* **2024**, *13*, 152. [\[CrossRef\]](#)
40. Lussana, F.; Magnani, C.F.; Galimberti, S.; Gritti, G.; Gaipa, G.; Belotti, D.; Cabiati, B.; Napolitano, S.; Ferrari, S.; Moretti, A.; et al. Donor-derived CARCIK-CD19 cells engineered with Sleeping Beauty transposon in acute lymphoblastic leukemia relapsed after allogeneic transplantation. *Blood Cancer J.* **2025**, *15*, 54. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Ma, F.; Ho, J.-Y.; Du, H.; Xuan, F.; Wu, X.; Wang, Q.; Wang, L.; Liu, Y.; Ba, M.; Wang, Y.; et al. Evidence of long-lasting anti-CD19 activity of engrafted CD19 chimeric antigen receptor–modified T cells in a phase I study targeting pediatrics with acute lymphoblastic leukemia. *Hematol. Oncol.* **2019**, *37*, 601–608. [\[CrossRef\]](#) [\[PubMed\]](#)

42. Magnani, C.F.; Gaipa, G.; Lussana, F.; Belotti, D.; Gritti, G.; Napolitano, S.; Matera, G.; Cabiati, B.; Buracchi, C.; Borleri, G.; et al. Sleeping Beauty–engineered CAR T cells achieve antileukemic activity without severe toxicities. *J. Clin. Investig.* **2020**, *130*, 6021–6033. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Myers, R.M.; DiNofia, A.M.; Li, Y.; Diorio, C.; Liu, H.; Wertheim, G.; Fraietta, J.A.; Gonzalez, V.; Plesa, G.; Siegel, D.L.; et al. CD22-targeted chimeric antigen receptor-modified T cells for children and adults with relapse of B-cell acute lymphoblastic leukemia after CD19-directed immunotherapy. *J. Immunother. Cancer* **2025**, *13*, e011549. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Nguyen, L.T.; Nguyen, D.D.; Bach, Q.K.; Dao, L.T.M.; Phan, T.T.K.; Nguyen, H.-P.; Dao, H.-N.; Pham, T.H.; Pham, P.T.; Mai, H.T.; et al. Outcomes of point-of-care manufactured CAR T cell therapy for B cell acute lymphoblastic leukemia and non-Hodgkin lymphoma in Vietnam. *Mol. Ther. Oncol.* **2026**, *34*, 201156. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Ottaviano, G.; Georgiadis, C.; Gkazi, S.A.; Syed, F.; Zhan, H.; Etuk, A.; Preece, R.; Chu, J.; Kubat, A.; Adams, S.; et al. Phase 1 clinical trial of CRISPR-engineered CAR19 universal T cells for treatment of children with refractory B cell leukemia. *Sci. Transl. Med.* **2022**, *14*, eabq3010. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Pan, J.; Niu, Q.; Deng, B.; Liu, S.; Wu, T.; Gao, Z.; Liu, Z.; Zhang, Y.; Qu, X.; Zhang, Y.; et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. *Leukemia* **2019**, *33*, 2854–2866. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Pan, Y.; Wang, H.; An, F.; Wu, F.; Tao, Q.; Li, Y.; Ruan, Y.; Zhai, Z. CD4+CD25+CD127low regulatory T cells associated with the effect of CD19 CAR-T therapy for relapsed/refractory B-cell acute lymphoblastic leukemia. *Int. Immunopharmacol.* **2021**, *96*, 107742. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Pan, J.; Tang, K.; Luo, Y.; Seery, S.; Tan, Y.; Deng, B.; Liu, F.; Xu, X.; Ling, Z.; Song, W.; et al. Sequential CD19 and CD22 chimeric antigen receptor T-cell therapy for childhood refractory or relapsed B-cell acute lymphocytic leukaemia: A single-arm, phase 2 study. *Lancet Oncol.* **2023**, *24*, 1229–1241. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Qian, C.-S.; Wang, Z.-H.; Li, Z.; Yao, Z.; Gong, W.-J.; Wu, Y.-J.; Zhou, H.-X.; Xu, M.-Z.; Qiu, Y.; Xu, S.-Z.; et al. A phase 2 trial of a “sandwich” strategy: Sequential CD22/CD19 chimeric antigen receptor T-cells therapy combined with autologous hematopoietic stem cell transplantation in patients with Philadelphia chromosome–negative B-cell acute lymphoblastic leukemia. *Cancer* **2025**, *131*, e70168. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Roddie, C.; Dias, J.; O'Reilly, M.A.; Abbasian, M.; Cadinanos-Garai, A.; Vispute, K.; Bosshard-Carter, L.; Mitsikakou, M.; Mehra, V.; Roddy, H.; et al. Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. *J. Clin. Oncol.* **2021**, *39*, 3352–3363. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Shah, B.D.; Ghobadi, A.; Oluwole, O.O.; Logan, A.C.; Boissel, N.; Cassaday, R.D.; Leguay, T.; Bishop, M.R.; Topp, M.S.; Tzachanis, D.; et al. KTE-X19 for relapsed/refractory adult B-cell acute lymphoblastic leukemia: Phase 2 results from the single-arm, multicenter ZUMA-3 study. *Lancet* **2021**, *398*, 491–502. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Wang, J.; Zhang, X.; Zhou, Z.; Liu, Y.; Yu, L.; Jia, L.; Yang, J.; Li, J.; Yu, H.; Li, W.; et al. A novel adoptive synthetic TCR and antigen receptor (STAR) T-Cell therapy for B-Cell acute lymphoblastic leukemia. *Am. J. Hematol.* **2022**, *97*, 992–1004. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Wang, Y.; Lv, L.; Song, Y.; Wei, X.; Zhou, H.; Liu, Q.; Xu, K.; Yan, D.; Zhang, C.; Liu, S.; et al. Inaticabtagene autoleucel in adult relapsed or refractory B-cell acute lymphoblastic leukemia. *Blood Adv.* **2025**, *9*, 836–843. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Wayne, A.S.; Huynh, V.; Hijjiya, N.; Rouce, R.H.; Brown, P.A.; Krueger, J.; Kitko, C.L.; Dela Ziga, E.; Hermiston, M.L.; Richards, M.K.; et al. Three-year results from phase I of ZUMA-4: KTE-X19 in pediatric relapsed/refractory acute lymphoblastic leukemia. *Haematologica* **2023**, *108*, 747–760. [\[PubMed\]](#)
55. Yang, J.; He, J.; Zhang, X.; Li, J.; Wang, Z.; Zhang, Y.; Qiu, L.; Wu, Q.; Sun, Z.; Ye, X.; et al. Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia: First-in-human clinical study. *Blood Cancer J.* **2022**, *12*, 104. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Zhang, X.; Lu, X.-A.; Yang, J.; Zhang, G.; Li, J.; Song, L.; Su, Y.; Shi, Y.; Zhang, M.; He, J.; et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. *Blood Adv.* **2020**, *4*, 603–613. [\[CrossRef\]](#)
57. Zhao, X.; Yang, J.; Zhang, X.; Li, J.; Li, W.; Song, D.; Lu, P. Autologous CD7 CAR-T cells generated without T cell preselection in pediatric r/r T-ALL: A phase I study. *Mol. Ther.* **2025**, *33*, 1525–1534. [\[CrossRef\]](#)
58. Zou, M.; Wan, B.; Hu, J. Efficacy and safety of PD-1/PD-L1 inhibitors in combination with chemotherapy or CAR-T cells for relapsed/refractory acute lymphoblastic leukemia: A multicenter phase II trial. *Leuk. Res.* **2026**, *160*, 108148. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Brudno, J.N.; Kochenderfer, J.N. Toxicities of CAR-T Cells: Recognition and Management. *Blood* **2024**, *143*, 1120–1133.

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