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EFFICACY AND SAFETY OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELL (CAR-T) THERAPY IN LYMPHOMA: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

I Gede Krisna Arim Sadeva [1], I Gede Wikania Wira Wiguna [1], Ni Wayan Armerinayanti [2*], Putu Mirah Wahyu Subagia Putri [1], Christo Timothy Mamangdean [1], Putu Ari Shanti Dewi [1], Kadek Meryndha Kumala Tunga [1], I Komang Raditya Putra Pratama [1], Agung Brahmanthya Nadine Kepakisan [1], Komang Indra Parama Arta [1]

[1] Faculty of Medicine, Udayana University, Denpasar, 80232, Indonesia
[2] Faculty of Medicine Warmadewa University, Denpasar, 80235, Indonesia

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***Corresponding author**
Ni Wayan Armerinayanti,
e-mail:
armerinayantipranata
@gmail.com

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CAR-T cell therapy, efficacy, lymphoma, safety.

Abstract

Background: Lymphoma (Hodgkin and non-Hodgkin) is a malignancy of the lymphatic system, with global prevalence reaching 2.8% and mortality rates reaching 248,700 cases each year. Therefore, Chimeric Antigen Receptor-Modified T cell therapy (CAR-T) was developed as a new approach to improve survival rates in lymphoma patients.
Objective: This study aimed to evaluate the efficacy and safety of CAR-T cell therapy in lymphoma.
Methods: PRISMA 2020 was used in the literature search and systematic review with the keywords "CAR-T Cell Therapy" and "Lymphoma". All statistical analyses were performed with R statistical software version 3.3 and MedCalc software version 22. A p-value ≤ 0.05 was considered statistically significant.
Results: There were 16 studies involving 440 patients with lymphoma. The complete response rate was 62% (95% CI 55%-65%, I^2 = 40%). Meanwhile, cytokine release syndrome (CRS) occurred in 73% of cases (95% CI 49%-88%, I^2 = 80%). The overall Immune effector cell-associated neurotoxicity syndrome (ICANS) rate was 17% (95% CI 9%-30%, I^2 = 66%). There is no significant publication bias in all analyses (p-value>0.05). However, these results need to be interpreted with caution, considering the high heterogeneity in the pooled analysis results (I^2 > 50%).

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Conclusions: *This study found that CAR-T therapy showed promising efficacy with relatively good safety and borderline tolerability in lymphoma patients, yet these findings should be interpreted cautiously due to high heterogeneity.*

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INTRODUCTION

Lymphoma is a hematological malignancy with a prevalence of 2.8% worldwide in 2018, based on data from the Global Cancer Observatory (GLOBOCAN). Examining the scope of Indonesia, based on GLOBOCAN 2020 data, non-Hodgkin lymphoma cases ranked 7th, with 16,125 new cases covering 4.1% of all cancer cases. Meanwhile, in 2020, Hodgkin's lymphoma cases in Indonesia were reported to reach 83,087 cases (1). According to a study by Thandra et al., there are approximately 248,700 death cases from non-Hodgkin lymphoma worldwide, accounting for 2.6% of all cancer deaths (2). East Asia was identified as the region with the highest mortality rate from non-Hodgkin lymphoma in 2020, with a rate of 24.9% (3). Meanwhile, the mortality rate due to this disease in 2018 in Indonesia is known to reach 4.25% (4).

Given the high prevalence and mortality of lymphoma, it is necessary to develop superior management modalities in terms of efficacy or safety to improve the survival rate of lymphoma patients. Chimeric antigen receptor-modified T-cell (CAR-T) therapy is a curative immunotherapy targeting lymphocyte antigens, such as CD19, CD22, and B cell maturation antigen (BCMA), as a cancer treatment. Development of CAR-T cell-based therapy in lymphoma patients has developed rapidly, especially with the emergence of CAR-T cell therapy approved by the FDA, namely Yescarta (axicabtagene ciloleucel) for patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), Tecartus (Brexucabtagene autoleucel) for patients with refractory or relapsed mantle cell lymphoma (R/R MCL), Breyanzi (lisocabtagene maraleucel) for patients with non-Hodgkin lymphoma (NHL), and Kymriah (tisagenlecleucel) for patients with DLBCL (5).

However, each patient's response to CAR-T cell therapy did not show similar clinical outcomes. Various factors influence this; one contributing factor is resistance and relapse. After infusion, CAR-T cells can potentially fail to proliferate or survive, leading to a loss of therapeutic response. One mechanism that can lead to loss of function is CAR-T cell exhaustion (6). Loss or decreased expression of the target antigen can also affect the efficacy of CAR-T therapy. Cancer cells that lose or express reduced levels of antigens may develop resistance to CAR-T therapy (7). Additionally, CAR is also known to be a high-specification receptor. Nonetheless, the expression of the target antigen in normal cells may cause toxicity. Although previous systematic reviews and meta-analyses have evaluated CAR-T cell therapy in lymphoma, the rapidly evolving evidence from newly published clinical studies necessitates an updated synthesis. This updated meta-analysis incorporates the most recent available evidence to provide a more comprehensive assessment of the efficacy and safety of CAR-T cell therapy and to strengthen the current evidence base for clinical decision-making. Furthermore, due to the limitations of two-arm or network meta-analyses, this study focused on a narrative review based on pooled results to provide a comprehensive analysis of the costimulatory domain and the generation of CAR-T cell therapy administered to patients.Therefore, this study aimed to evaluate the efficacy and safety of CAR-T cell therapy in patients with lymphoma.

MATERIALS AND METHODS

This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. This study has been registered on PROSPERO (CRD42024577010).

Identification of Relevant Literature

A systematic search was performed across four electronic databases, comprising PubMed, ScienceDirect, Cochrane Library, and ProQuest, to identify relevant studies. In PubMed, the search string applied was ("CAR-T"[Title/Abstract] OR "CAR-T cell"[Title/Abstract] OR "Chimeric Antigen Receptor T-Cell"[Title/Abstract] OR "Receptors, Chimeric Antigen"[MeSH Terms]) AND ("Lymphoma"[MeSH Terms] OR "Lymphoma"[Title/Abstract]) AND ("Efficacy"[Title/Abstract] OR "Safety"[Title/Abstract] OR "Treatment Outcome"[MeSH Terms]). In ScienceDirect, the search string applied was ("CAR-T" OR "CAR-T cell") AND ("Lymphoma") AND ("Efficacy" OR "Safety"), restricted to the title, abstract, and keyword fields, given the platform's limitation on boolean operator complexity in advanced search. In Cochrane Library, the search string applied was ("CAR-T" OR "CAR-T cell" OR "Chimeric Antigen Receptor T-Cell"): ti, ab,kw AND ("Lymphoma"): ti, ab,kw AND ("Efficacy" OR "Safety"): ti, ab,kw. In ProQuest, the search string applied was noft("CAR-T" OR "CAR-T cell" OR "Chimeric Antigen Receptor T-Cell") AND noft("Lymphoma") AND noft("Efficacy" OR "Safety"), with noft denoting a full-text search field. All authors participated in the screening process, followed by an independent evaluation of each study according to predetermined eligibility criteria. The final selection of included trials was determined through discussion among all authors, with unanimous agreement required for inclusion. Disagreements among reviewers were resolved by consensus.

Eligibility Criteria

Eligible studies had to meet the following inclusion criteria: 1) Assess the effectiveness of CAR-T cell therapy in treating lymphoma; 2) Evaluate the safety of the therapy in treating lymphoma; and 3) Provide sufficient details on the ratio of safety and effectiveness, including metrics such as complete response and adverse events. The exclusion criteria were 1) Review articles, 2) studies with overlapping data, and 3) case reports, correspondence, and conference abstracts. Figure 1 illustrates a flowchart of the study selection process.

Data Extraction

The selected studies extracted the following information: author name, year of publication, country, total sample size, type of lymphoma, proportion of complete responses, and adverse events.

Assessment of risk of bias

The Newcastle-Ottawa Scale (NOS), adapted for single-arm cohort studies, assesses methodological quality in studies lacking a comparator group. This instrument assesses bias in single-arm clinical research across three broad categories, comprising seven domains. These include selection of the treated cohort (representativeness of the population, ascertainment of the CAR-T exposure, and confirmation that the outcome was not present

at baseline), comparability (control for confounding variables between patient sub-groups), and outcome assessment (objectivity of outcome ascertainment, adequacy of follow-up duration, and completeness of follow-up). Two independent reviewers will assess the risk of bias and assign an overall rating of low, moderate, or high risk of bias based on the cumulative score across the seven domains.

Statistical analysis

Since no controls were used in the research, our study's primary and secondary outcomes were expressed as pooled proportions. Dichotomous outcomes (proportions) were pooled using the Freeman-Tukey double arcsine transformation under a random-effects model, given the substantial heterogeneity observed across included studies, yielding pooled percentages with corresponding 95% confidence intervals.

For this meta-analysis, all research parameters will be calculated using the following formula:

$$Proportion = \frac{Event}{Total\ Sample\ size}$$

I^2 was used to measure heterogeneity; heterogeneity of 50% or above is considered high, while heterogeneity below 50% is considered moderate. For low heterogeneity, fixed effects will be used; for significant heterogeneity, random effects will be applied. Because some studies have extremely small sample sizes, further analysis using funnel plots and Peters tests will be performed to identify small-study biases among the included studies. Sensitivity analysis was not performed because this study aimed to assess the general pooled results of each population, so only subgroup analysis was performed based on the co-stimulatory domain and CART cell generation. R Studio version 2023.03.0-daily+82.pro2 and R Statistical Software version 3.3 were used for all statistical studies.

RESULTS AND DISCUSSIONS

Literature searching

Based on the study selection flowchart, the initial search across four databases yielded 19,496 records: 297 from PubMed, 3,995 from ScienceDirect, 703 from the Cochrane Library, and 14,501 from ProQuest. Before the screening process, 4,625 records were excluded, including 1,277 duplicate records and 3,348 records marked ineligible by the automated tool. Thus, 14,871 records entered the title and abstract screening stage. At this stage, 14,812 records were excluded for not meeting the study criteria, leaving 59 reports for full-text search. Of these, 21 reports were not retrieved, leaving 38 reports for full eligibility assessment. During the eligibility assessment stage, 26 reports were excluded due to incomplete data (10) and irrelevant data (16). Finally, 12 studies met all inclusion criteria and were included in the systematic review (Figure 1).

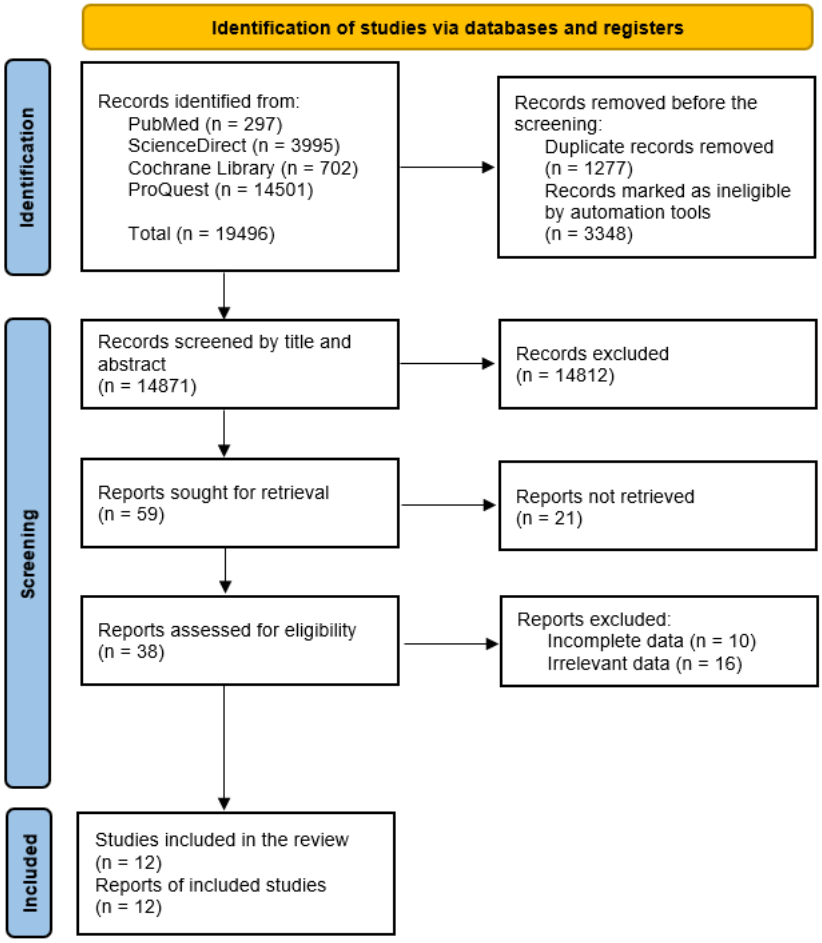

Figure 1. PRISMA Flowchart

Study characteristic

A total of 12 studies published between 2019 and 2022 were included, comprising 352 patients with lymphoma treated with CAR-T cell therapy, with sample sizes ranging from 4 to 111 and median or mean age ranging from 27.5 to 58.4 years. Most studies originated from China (n=8), followed by the United States (n=2) and Australia (n=1), and enrolled various lymphoma subtypes, including DLBCL, FL, LBCL, BCL, NHL, HL, and BL, several of which specifically involved relapsed/refractory populations. Lentiviral vectors were used in most studies (n=8), CD19 was the predominant antigen recognition moiety, either alone or combined with CD20 and/or CD22, and 4-1BB was the most common costimulatory domain (n=7), followed by CD28 (n=3), a dual CD28/4-1BB construct (n=1), and CD27 (n=1), with fludarabine plus cyclophosphamide serving as the standard lymphodepleting regimen before CAR-T cell infusion across nearly all studies. The number of studies and participants differed across pooled analyses (complete response, CRS, ICANS, and mortality) because not all included studies reported every outcome or disclosed the specific costimulatory domain, precluding their inclusion in certain analyses or subgroup analyses (**Table 1**).

Table 1. Study Characteristics

Author (Year)	Country	Sample size	Age	Lymphoma subtype	Vector	Ag Recognition Moieties	Costimulatory Domain	Lymphodepleting Therapy
Qu (2020)(10)	China	4	48[a]	DLBCL	Lentiviral	CD19, CD20, CD22	4-1BB	Fluradabine + cyclophosphamide
Hirayama (2019)(20)	United States	21	56[a]	*FL	-	CD19	4-1BB	Fluradabine + cyclophosphamide
Sang (2020)(12)	China	21	55[a]	DLBCL	Lentiviral	CD19, CD20	4-1BB	Fluradabine + cyclophosphamide
Ying (2021)(25)	China	59	56[a]	LBCL	Lentiviral	CD19	4-1BB	Fluradabine + cyclophosphamide
Schuster (2021)(26)	Australia	111	56[a]	*BCL	-	Tisagenlecleucel	4-1BB	Fluradabine + cyclophosphamide
Qu (2022)(27)	China	33	55[a]	NHL	Lentiviral	CD19, CD22	4-1BB	Fluradabine + cyclophosphamide, decitabine
Fan (2022)(15)	China	10	50.3[b]	BCL	Lentiviral	CD19	4-1BB	Fluradabine + cyclophosphamide
Bao (2019)(11)	China	5	58.4[b]	DLBCL	Lentiviral	CD19	CD28	Fluradabine + cyclophosphamide
Ramos (2020)(19)	Carolina, Texas	42	35[a]	HL	Retroviral gamma	CD30	CD28	Bendamustine + fluradabine, cyclophosphamide + fluradabine
Liu (2021)(14)	China	17	55[a]	*BCL	Lentiviral	CD19	CD28	Fluradabine + cyclophosphamide

Zhou (2020)(16)	China	21	50[b]	*NHL	Lentiviral	CD19	CD27	Fluradabine + cyclophosphamide
Zhou (2021)(13)	China	6	27.5[b]	BL	Lentiviral	CD19	CD28 & 4-1 BB	Fluradabine + cyclophosphamide

*R/R, Relapsed/Refractory; CRS, Cytokine Release Syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; MRS, Minimal Residual Disease; Ag, Antigen; [a] Median Age; [b] Mean Age

Table 2. Summary of Analysis Results

Events	Subgroup	Study	Summary effect size [95%CI]
Complete Response	-	12	0.62 [0.55 – 0.68]
Complete Response Based on Co-Stimulatory Domain	Overall	12	0.62 [0.55 – 0.68] p-value = 0.59
	4-1BB	7	0.61 [0.45 – 0.74]
	CD28	3	0.62 [0.47 – 0.75]
	CD27	1	-
	CD28 and 4-1BB	1	-
Complete Response Based on CAR-T Cell Generation	Overall	12	0.62 [0.55 – 0.68] p-value = 0.38
	2nd Generation	10	0.62 [0.55 – 0.69]
	3rd Generation	1	-
	4th Generation	1	-
Cytokine Release Syndrome	-	12	0.73 [0.49 – 0.88]
Cytokine Release Syndrome Based on Co-Stimulatory Domain	Overall	12	0.73 [0.49 – 0.88] p-value < 0.01*
	4-1BB	7	0.73 [0.50 – 0.88]
	CD28	3	0.79 [0.16 – 0.99]

	CD27	1	-
	CD28 and 4-1BB	1	-
Cytokine Release Syndrome Based on CAR-T Cell Generation	Overall	12	0.73 [0.49 – 0.88] p-value < 0.01*
	2nd Generation	10	0.75 [0.51 – 0.90]
	3rd Generation	1	-
	4th Generation	1	-
Immune Effector Cell-Associated Neurotoxicity Syndrome	-	12	0.17 [0.09 – 0.30]
Immune Effector Cell-Associated Neurotoxicity Syndrome Based on Co-Stimulatory Domain	Overall	12	0.17 [0.09 – 0.30] p-value = 0.11
	4-1BB	7	0.25 [0.14 – 0.40]
	CD28	3	0.06 [0.01 – 0.20]
	CD27	1	-
	CD28 and 4-1BB	1	-
Immune Effector Cell-Associated Neurotoxicity Syndrome Based on CAR-T Cell Generation	Overall	12	0.17 [0.09 – 0.30] p-value = 0.29
	2nd Generation	10	0.19 [0.10 – 0.34]
	3rd Generation	1	-
	4th Generation	1	-
Mortality	-	11	0.11 [0.04 – 0.26]
Mortality Based on Co-Stimulatory Domain	Overall	11	0.11 [0.04 – 0.26] p-value = 0.68
	4-1BB	6	0.11 [0.02 – 0.44]
	CD28	3	0.08 [0.03 – 0.19]

	CD27	1	-
	CD28 and 4-1BB	1	-
Mortality Based on CAR-T Cell Generation	Overall	11	0.11 [0.04 – 0.26] p-value = 0.46
	2nd Generation	9	0.11 [0.04 – 0.31]
	3rd Generation	1	-
	4th Generation	1	-

This meta-analysis analyzed 12 clinical trials published between 2019 and 2022 and conducted in Australia, Austria, Canada, France, Germany, Italy, Japan, China, the Netherlands, Norway, and the US. The cancer types in the clinical trials included non-Hodgkin lymphoma and Hodgkin lymphoma. The viruses used to produce CAR-T cells in clinical trials mostly use lentiviruses. For lymph-depleting therapy, fludarabine and cyclophosphamide are generally used in clinical trials. The use of random pooled or common pooled effect is determined by using 60% heterogeneity as the limit; studies with heterogeneity above 50% will use random pooled effect, while studies with heterogeneity of 50% or less will use common pooled effect.

Bias Test

To avoid bias in our data, we created a funnel plot to examine how each study's data spread and used Peter's test as an extension to assess asymmetry. The results of Peter's test and funnel plot of complete response (p-value = 0.5512), ICANS (p-value = 0.6958), CRS (p-value = 0.4474), and subgroups of CRS, CRS grade 0-2 (p-value = 0.4946) and grade 3-4 (p-value = 0.4946), showed no asymmetry in the funnel plot indicating that the results of the clinical trials showed no bias.

Risk of Bias Assessment Result

Risk of bias assessment using the Newcastle-Ottawa Scale adapted for single-arm cohort designs for the twelve included studies yielded a total score of 6–7 out of 7. Eleven studies (91.7%) were classified as having a moderate risk of bias, while one study was classified as having a low risk of bias because it was the only one to control for confounding through multivariate Cox regression and blinded central review. The main limitation of the remaining eleven studies stems from the confounding control domain, as the single-arm

design without a comparison group precludes statistical adjustment for confounding variables between patient groups (**Table 3**).

Table 3. Risk of Bias

Author, year	D1	D2	D3	D4	D5	D6	D7	Total score	Risk of Bias
Qu (2020)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Hirayama (2019)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Sang (2020)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Ying (2021)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Schuster (2021)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Qu (2022)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Fan (2022)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Bao (2019)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Ramos (2020)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Liu (2021)	✓	✓	✓	✓	✓	✓	✓	7/7	Low
Zhou (2020)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate
Zhou (2021)	✓	✓	✓	X	✓	✓	✓	6/7	Moderate

Outcome result

Based on our proportional meta-analysis results, CAR-T cell therapy has shown a favorable clinical response in lymphoma patients, with 62% (95% CI 55%-65%, I^2 = 40%) of all patients achieving a complete response (**Figure 2**). However, despite its high rate of complete response, patients who received this therapy also suffered from adverse events, which occurred in the majority of patients. Among these adverse events, CRS has the highest overall occurrence rate, with around 73% (95% CI 49% - 88%, I^2 = 80%) (**Figure 3)**. Another concerning adverse effect of CAR-T cell therapy is the development of ICANS; 17% (95% CI 9% - 30%, I^2 = 66%) of all patients have developed ICANS during therapy, which occurs at a significantly lower rate than CRS events (**Figure 4)**. Due to an alarming rate of adverse

events, mortality rates are also assessed to consider the possibility of lethal effects from CAR-T cell therapy. Here, overall mortality rates are low despite high rates of adverse events, affecting only 11% of patients receiving this treatment (95% CI 4%-26%, I^2 = 85%) (**Figure**). All parameters exhibit high heterogeneity (>40%) across study results.

Overall analysis of mortality showed 11% (95% CI 3.97-26.36), with I^2 = 85.3% indicating a total random effect (**Figure 5A**). Mortality rates were also lower in patients receiving CAR-T cells using CD-28, 4-1BB, and CD27 costimulatory domains. Besides that, the high mortality observed in patients receiving 4-1BB costimulatory domains rather than CD28, with a difference of 53% (95% CI 44.78-61.23), I^2 = 85% vs 8% (95% CI 3.49-18.56), I^2 = 0% (**Figure 5B**). Additionally, based on a sub-analysis of CAR-T cell generations, the 3rd and 4th generations had the lowest mortality rate compared to other generations, followed by the 2nd generation, with 11% (95% CI 3.59-30.64), I^2 = 87% (**Figure 5C**). Notably, the final pooled effect of the sub-analysis of all parameters differs slightly from that shown in Figures 3 and 4; this is due to some included studies not disclosing the chosen costimulatory domain. Hence, it is necessary to exclude them from the sub-analysis. Yet, these results must be interpreted with caution because some groups in the subgroup analysis only consist of 1 study.

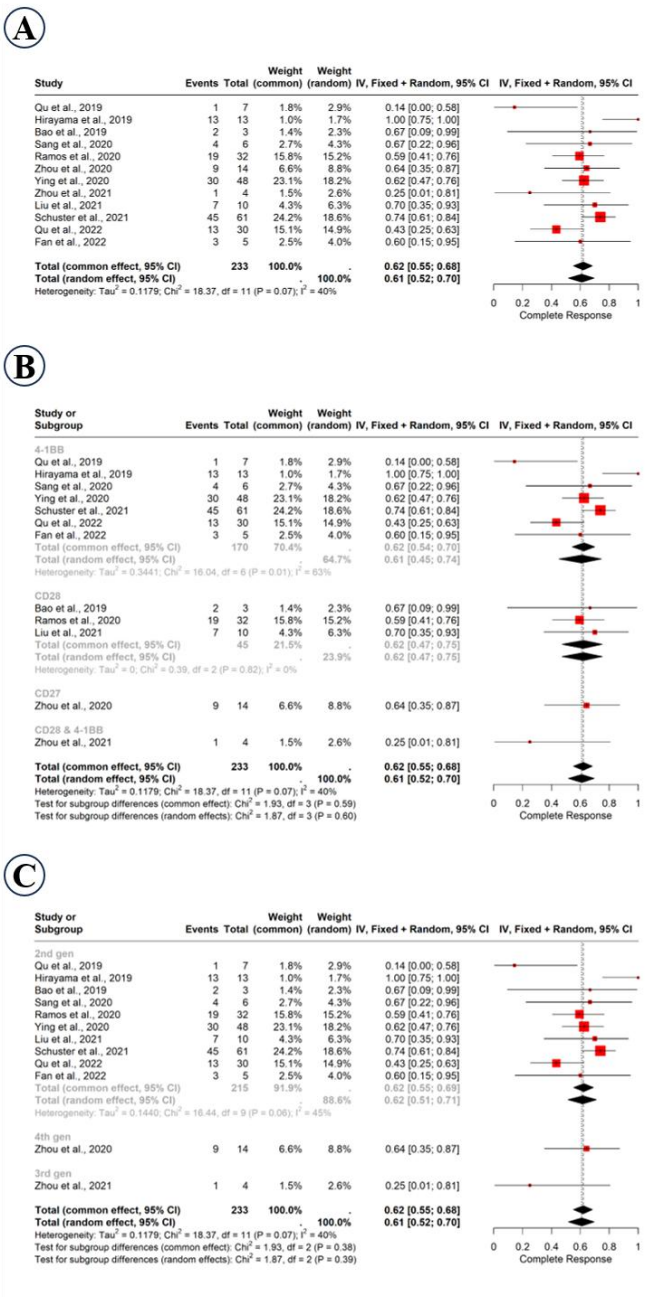

Figure 2. Forest plot of CR. (A) Overall analysis; (B) Sub-analysis based on Co-stimulatory domain; (C) Sub-analysis based on CAR-T cell generation.

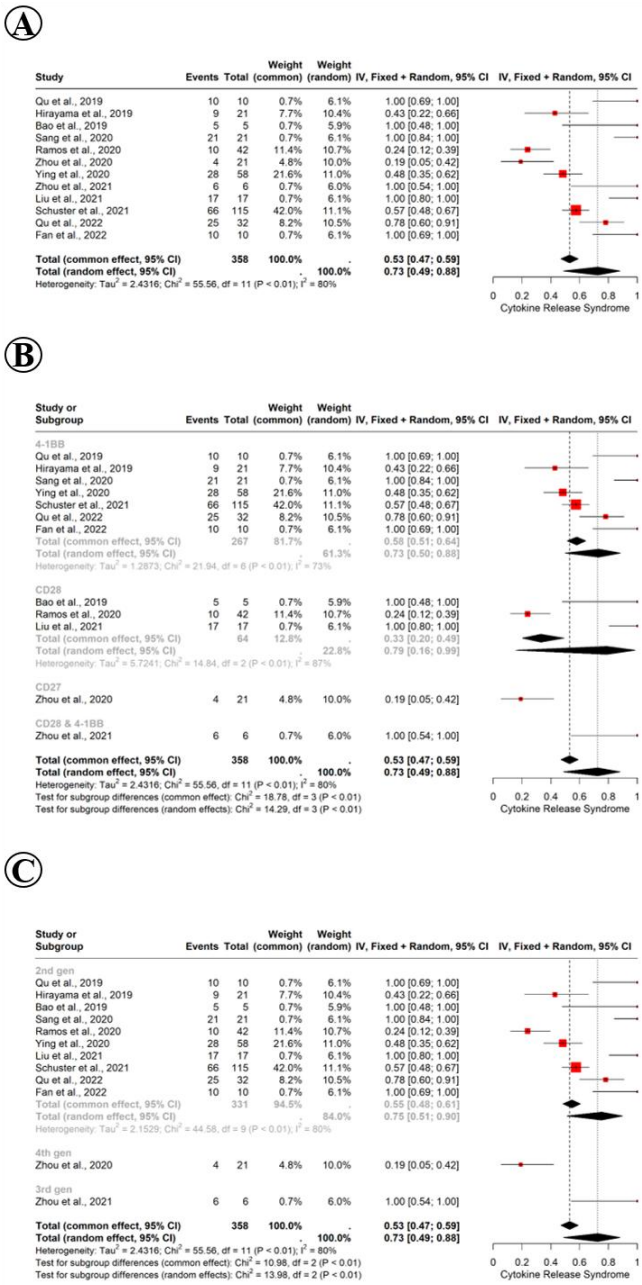

Figure 3. Forest plot of CRS. (A) Overall analysis; (B) Sub-analysis based on Co-stimulatory domain; (C) Sub-analysis based on CAR-T cell generation.

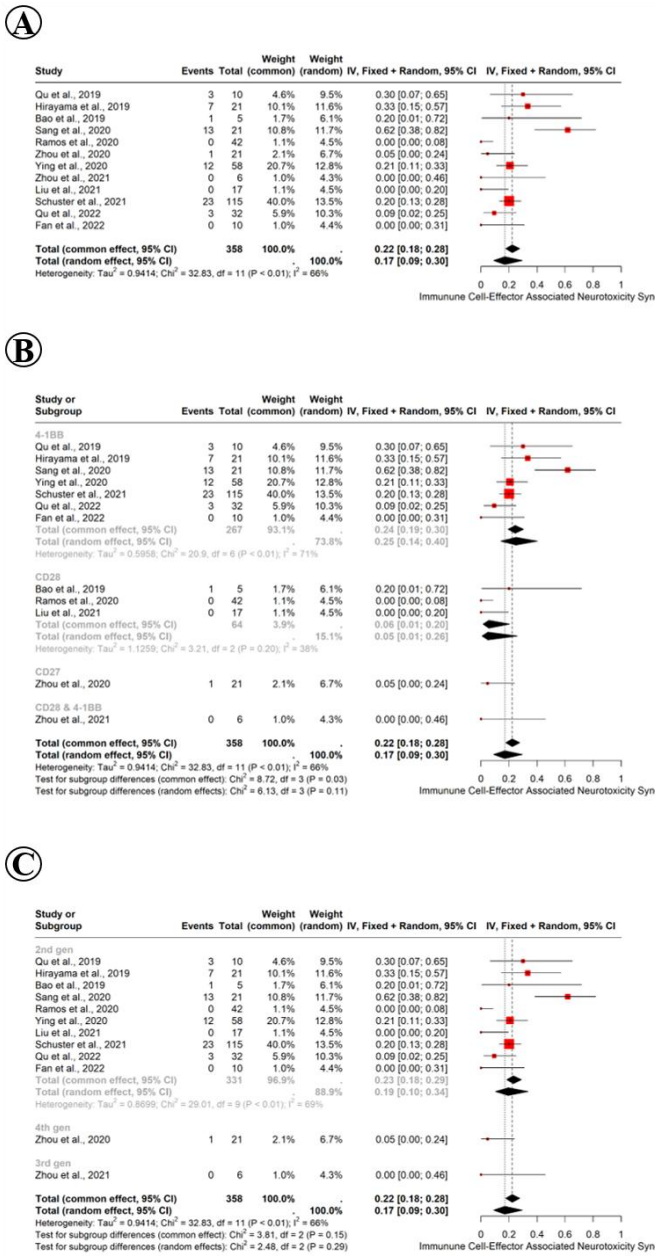

Figure 4. Forest plot of ICANS. (A) Overall analysis; (B) Sub-analysis based on Co-stimulatory domain; (C) Sub-analysis based on CAR-T cell generation.

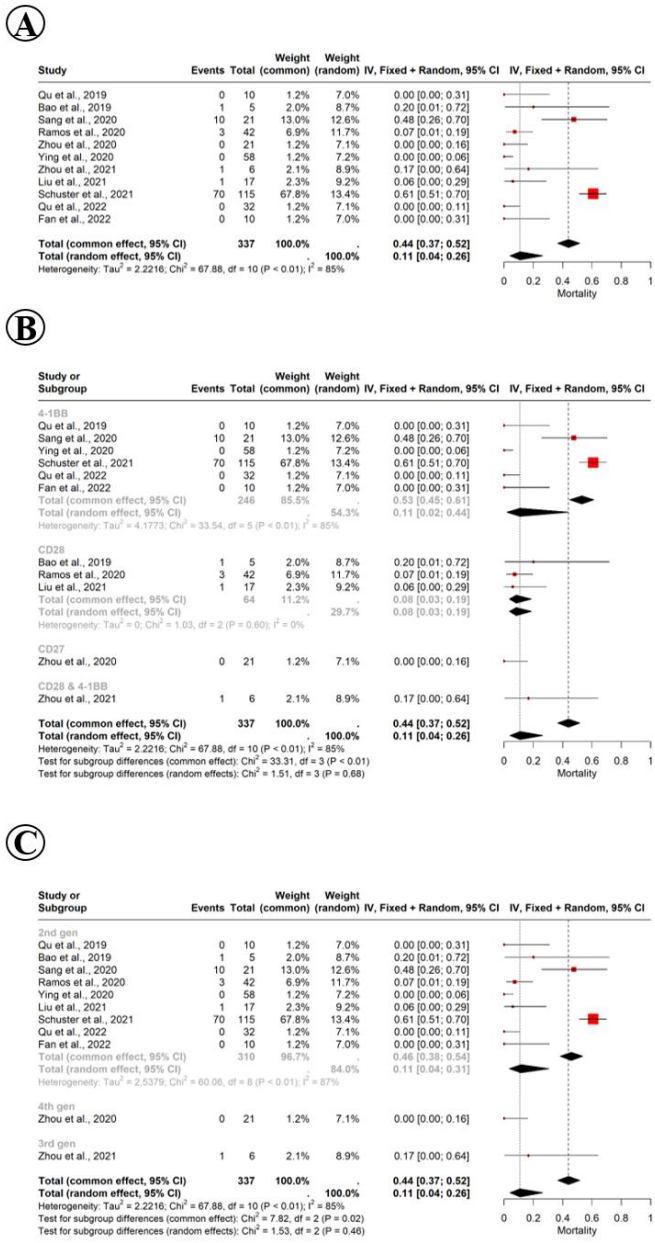

Figure 5. Forest plot of mortality. (A) Overall analysis; (B) Sub-analysis based on Co-stimulatory domain; (C) Sub-analysis based on CAR-T cell generation.

This study found that CAR-T cell immunotherapy has potential as a therapy for lymphoma. The moderate combined CR rate (62%) likely reflects biological and technical heterogeneity in CAR-T cell constructs across the included studies. Differences in costimulation domains between 4-1BB and CD28 directly influence the kinetics of CAR-T cell expansion and persistence. The 4-1BB domain generally results in better long-term persistence, while CD28 provides faster initial expansion but with a higher risk of T cell

exhaustion. Variations in the generations of CAR-T constructs used across studies also contribute to heterogeneity in response, as each generation has a different intracellular activation profile and duration of costimulation signaling.

Although the complete response is not satisfactory, the safety of CAR-T cell therapy is favorable, with only mild side effects. Yet, the interpretation of the CAR-T cell safety profile needs to be cautiously reflected to better balance the magnitude and clinical significance of adverse events, given that the incidence of CRS (73%), ICANS (17%), and mortality (11%) is relatively substantial and cannot be categorized as merely mild adverse events. While the majority of CRS cases are grades 1-2, a proportion of grades 3-5 CRS cases still require intensive monitoring due to the potential for life-threatening manifestations such as refractory hypotension, hypoxia, or multiple organ dysfunction. The 11% mortality rate showed that, despite the clinical outcomes, CAR-T cell therapy in lymphoma patients is still facing the possibility of fatal risks. The findings in this study are consistent with a previous meta-analysis conducted by Shargian et al., which found a significant OS improvement in patients receiving CAR-T cells compared to standard of care (8). Kim et al. conducted a meta-analysis on a population of DLBCL patients and reported a favorable pooled OS in patients treated with CAR-T therapy, which is aligned with this study (9). However, several features of our clinical trial data may have influenced our results, making them far from representative of the lymphoma cancer patient population.

Subgroup analysis based on the co-stimulatory domain, CD28 co-stimulated CAR-T cells showed a higher incidence of CRS than other single co-stimulatory designs. This might be associated with a delayed CRS onset observed in patients receiving 4-1BB CAR-T cells (17). Furthermore, studies suggest that a mild, persistent killing effect associated with 4-1BB co-stimulation was mediated by the THEMIS-SHP1 complex, correlating with its ability to antagonize CD3ζ domain phosphorylation and, consequently, decrease the expression of IFN-γ and other cytokines (18). This finding aligns with Bao et al. and Liu et al., who report 100% incidence (11,14). However, Ramos et al. reported a significantly lower CRS incidence (24%). These discrepancies might be attributed to variations in the sample population and CAR-T construction, with HL patients and the CD30 antigen-recognition group showing a lower CRS percentage in Ramos et al (19). Similar trends were observed by 4-1BB CAR-T cells, with 73% CRS incidence. This is in line with Qu et al., Sang et al., and Fan et al., with 100% ICANS incidence (10,12,15). A lower percentage was found in Hirayama et al., which still showed a high proportion (20). Furthermore, the incidence of ICANS with CAR-T CD27 had the lowest percentage result of 19% in Zhou et al (16). Interestingly, the combination of CD28 and 4-1BB co-stimulation in Zhou et al. resulted in a 100% incidence of ICANS (13).

CAR-T cells with the 4-1BB co-stimulatory domain showed a slightly higher likelihood of causing ICANS compared with those bearing other co-stimulatory domains, in contrast to the pattern observed for CRS incidence. This finding contradicts previous studies suggesting a worse ICANS profile associated with CD28 co-stimulation (22). Furthermore, studies suggest elevated cytokine levels (IL6, IFNγ, TNFα) in cerebrospinal fluid (CSF) may be linked to ICANS development, potentially hindering it through systemic inflammation (23). Meanwhile, studies in B-ALL-carrying mice showed that 4-1BB-based CAR-T detected higher levels of IL-6, IL-10, TNF, and IFN-γ than CD28. Although it had a different design and research sample, this study succeeded in showing the effect of 4-1BB-based CAR-T cells (24). However, the incidence of patients experiencing ICANS reached

25%. This aligns with Fan et al., who reported no ICANS events (15), while a higher proportion was reported by Sang et al (12). The sub-analysis with the CD28 co-stimulatory domain showed a lower ICANS incidence of 5%. Ramos et al. and Liu et al. reported a consistent proportion of 0 patients with ICANS (14,19). Bao et al. reported a higher incidence (20%), corresponding to one case in five patients. The sample population in Bao et al. was considerably smaller, causing the incidence percentage to appear inflated. The DLBCL population showed a higher incidence of cases, with slightly older patients (11), which may be related to the worse clinical condition of patients at older ages. CD27 co-stimulator subanalysis demonstrated a similar trend (incidence of 5%), with one case reported in 21 patients (16). The sub-analysis with combined CD28 and 4-1BB co-stimulatory domains showed no ICANS incidence (13). The small participant size in this sub-analysis limited the generalizability of this finding beyond the present study. The analysis of CD27 and CD28 combined with 4-1BB was based on single studies. This limitation prevented definitive conclusions due to the lack of comparative data.

Sub-analysis of ICANS incidence based on CAR-T cell generation was also performed, which included the second, third, and fourth generations. Analysis of the second generation showed 19% of patients experienced ICANS. This aligns with Ramos et al. and Fan et al., with 0% cases of ICANS (15,19). In contrast, Sang et al. reported 13 ICANS events from 21 patients with an analysis proportion of 62% (12). This variability may be due to differences in patient demographics and the antigen recognition moieties construction as described previously in Sang et al (12). The third-generation analysis was conducted by Zhou et al. (13), and the fourth-generation analysis was conducted by Zhou et al. (16), each based on a single study and reporting no ICANS events.

CLINICAL IMPLICATION

The clinical implications of these findings suggest that CAR-T cell therapy has relatively promising efficacy in lymphoma patients. Although the analysis was conducted in a single-arm design, this study provides a preliminary overview of the proportion of patients achieving a complete response and the adverse event profile, both overall and based on subgroup analyses based on differences in costimulatory domains in CAR-T cell designs. Theoretically, differences in costimulatory domains can influence CAR-T cell activity, persistence, and toxicity. These findings indicate that variations in CAR-T cell design could potentially contribute to patient clinical outcomes. This information can provide an initial basis for developing patient selection strategies and selecting more appropriate therapy designs. However, the interpretation of these findings remains hypothetical due to design limitations and data collection, requiring further validation through comparative studies with larger sample sizes.

LIMITATIONS

This study has limitations in that it lacks in-depth analysis and a critical review of each type of lymphoma. Therefore, the findings cannot be interpreted in this patient population, given the highly heterogeneous population. The high heterogeneity in the analysis results of this study means that the interpretation of the results cannot directly reflect the actual conditions in the field. This study design was single-arm from the outset. Interpretation of the results was limited to pooled CAR-T therapy outcomes stratified by co-

stimulatory domain and CAR-T generation. The lack of a comparator therapy and the lack of a specific population evaluated contributed to this high heterogeneity. The results of this study provide a snapshot of CAR-T cell therapy outcomes in lymphoma patients only. The predominance of included studies originating from China limits the potential for generalizability of the findings. The pooled results in this study largely reflect outcomes in patients in China or East Asia.

CONCLUSIONS

This study found that CAR-T therapy has shown promising efficacy and tolerability in patients with lymphoma with a relatively low incidence of ICANS and CRS. However, these findings should be interpreted with caution, as several pooled analyses demonstrated moderate to high heterogeneity and the included studies involved heterogeneous patient populations and lymphoma subtypes. More information and additional randomized controlled trials are needed regarding the long-term effectiveness of CAR-T cell therapy. Differences in subject characteristics may affect the efficacy and safety of CAR-T cells, necessitating further investigation and reassessment.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest regarding this study.

AUTOR CONTRIBUTIONS

I.G.K.A.S. and I.G.W.W.W. conceived and designed the study. N.W.A. and I.G.W.W.W. supervised the overall research process and provided critical intellectual input throughout the study. C.T.M. conducted the data and statistical analysis. P.M.W.S.P., P.A.S.D., K.M.K.T., I.K.R.P.P., A.B.N.K., and K.I.P.A. contributed to data collection, data curation, literature review, and manuscript preparation. All authors participated in manuscript revision, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

The authors used Grammarly to assist in improving the language and grammar of the manuscript. The authors reviewed and verified the content to ensure accuracy and integrity

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