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Combined immunotherapy with dendritic cells and cytokine-induced killer cells for solid tumors: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Immunotherapy utilizing dendritic cells (DCs) and cytokine-induced killer (CIK) cells is a promising treatment approach for solid tumors. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of DC-CIK immunotherapy by assessing overall survival, progression-free survival, overall response rate, disease control rate, and adverse events in relevant randomized controlled trials. The results of this analysis will contribute to optimizing treatment strategies and improving cancer immunotherapy outcomes.

Method This systematic review and meta-analysis adhered to PRISMA guidelines. A comprehensive search was conducted on multiple databases for RCTs studying the combination of DC-CIK immunotherapy for solid tumors. Inclusion criteria were RCTs comparing DC-CIK immunotherapy with control therapy and reporting OS, PFS, ORR, or DCR. Two authors independently performed study selection and data extraction, with disagreements resolved through consensus or consultation with a third reviewer. Extracted data included study characteristics, participant information, interventions, outcomes, and quality assessment. Statistical analysis was performed using Review Manager and Stata software. Heterogeneity was assessed using chi-square and I-squared statistics. Sensitivity analysis and assessment of publication bias were planned.

Results A total of 1013 records were initially retrieved, and after a thorough screening process, 13 randomized controlled trials (RCTs) were included in the meta-analysis. These studies involved a total of 1443 patients, with 730 receiving DC-CIK immunotherapy and 713 in the control groups. The included studies covered various cancer types, with the majority conducted in mainland China. The meta-analysis showed that DC-CIK immunotherapy

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was associated with improved overall survival (OS) and progression-free survival (PFS) compared to control therapy. Furthermore, DC-CIK immunotherapy demonstrated higher overall response rate (ORR) and disease control rate (DCR) compared to non-DC-CIK therapy. Adverse events were reported in both groups, with fever being more common in the DC-CIK immunotherapy group and bone marrow suppression and gastrointestinal reactions more common in the control group. Sensitivity analyses confirmed the stability of the results, while publication bias was observed for PFS and fever.

Conclusions DC-CIK immunotherapy shows promising efficacy and safety for solid tumors, improving survival rates and response rates. Further research is needed to optimize treatment regimens and identify predictive factors.

Keywords Dendritic cells, Cytokine-induced killer cells, Solid tumors, Combined immunotherapy

Introduction

Malignant solid tumor has been one of the most fatal factors of human death and the second leading cause of death worldwide [1]. Survival rates have significantly risen during the decades thanks to the advancement in tumor therapeutic options such as surgical techniques, chemotherapy, radiotherapy, targeting regimen as well as immune checkpoint blockade. Nevertheless, the current standard treatment for malignant tumors has also been problematic in terms of susceptibility to drug resistance, limited efficacy, low response rates, high recurrence rates and severe side effects, which remains an acquirement for novel anti-tumor strategy [2].

Adoptive cell therapy(ACT) stimulates the immune system to permanently eradicate residual or disseminated tumour cells and restore immune function weakened by radiotherapy and chemotherapy [3]. ACT has already made great strides in haematological oncology, with six Chimeric antigen receptor T-cell (CAR-T) immunotherapies now FDA-approved for the treatment of B-cell-related leukaemia, lymphoma and myeloma [4]. Sipuleucel-T approved by FDA for advanced prostate cancer. The current FDA approval of Lifileuel, the first TIL cell therapy for the treatment of patients with unresectable or metastatic melanoma, paves the way for the exploration of over-the-counter immunotherapy in solid tumors. Adoptive immunotherapy utilizing dendritic cells (DCs) and cytokine-induced killer (CIK) cells has emerged as a promising treatment approach for solid tumors. DCs, as key immune regulators, play a crucial role in initiating and coordinating immune responses [5] . DCs are a key target for inducing specific T-cell-mediated cancer immunity. They possess the capability to present tumor antigens to T cells and activate specific anti-tumor immune responses. CIK cells, on the other hand, as CD8 ± specific effector T cells and as NK-like cells, combine the cytotoxicity of natural killer (NK) cells with the antigen specificity of T cells, exhibiting non-specific and non-MHC-restricted cytotoxicity [6, 7]. Interactions between DC and CIK cells alter the expression of surface molecules in both cells, leading to increased IL-12 secretion and enhanced cytotoxic activity [8]. This combination aims to enhance the anti-tumor immune response by priming and expanding tumor-specific T cells with the assistance of DCs, which makes them attractive for adoptive cell therapy.

To date, the DC/CIK therapy has been utilized in a plethora of solid tumors, such as colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, esophageal carcinoma, breast cancer, renal cancer, cervical cancer, etc. [9–21]. Meanwhile, aiming to achieve a better clinical efficacy, most trials combined the DC/CIK therapy with the traditional chemotherapy, radiotherapy or immune checkpoint blockade like PD-1 inhibitor [18, 21, 22] . There have been many retrospective or prospective reports on the utilization of combined DC/CIK therapy focused on a specific tumor, with only a few articles examining solid tumors as a whole [22–31] . Furthermore, some new trials have been published following these articles, demanding an up-to-date and more comprehensive investigation in clinical outcomes and potential benefits of combined DC-CIK immunotherapy, requiring updated systematic evaluations.

Hence, we conducted a systematic review and meta-analysis of relevant randomized controlled trials (RCTs) [9–21] . Our analysis aimed to assess the impact of DC-CIK immunotherapy on overall survival (OS), progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and adverse events in patients with solid tumors.

By synthesizing the results of the included RCTs, we aim to provide an evidence-based analysis that elucidates the efficacy and safety of DC-CIK immunotherapy. This analysis will contribute to the optimization of treatment strategies and the improvement of patient outcomes in the field of cancer immunotherapy.

Methods

Search strategy and study selection

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA)

guidelines and has been registered in PROSPERO (CRD42024559948) [32].

We searched PubMed, Embase, Web of Science, ScienceDirect, Cochrane, Clinical Trails on May 11, 2024, for randomized controlled trials (RCTs) of combined immunotherapy with dendritic cells and cytokine-induced killer cells for solid tumors.

We conducted exhaustive searches using the following key terms: "tumor" OR "cancer" OR "carcinoma" OR "neoplasms" AND "DC" OR "CIK" OR "dendritic cells" OR "cytokine induced killer cells" AND "clinical trial" AND "randomized" to identify all publications eligible for inclusion in the review.

Studies were included if they met all of the following criteria: (1) randomized controlled trials on solid tumors comparing DC-CIK immunotherapy with control therapy. (2) reporting at least one of OS, PFS, ORR, or DCR during treatment. (3) publication in English.

Studies were excluded if they met any of the following criteria: (a) irrelevant to tumors (b) not RCTs including case studies, reviews, or non-human studies. (c) interventions other than DC-CIK immunotherapy. (d) Missing patient baseline characteristics and clinical outcomes. (e) Non-English publications. (f) Duplication of patient populations, with only the complete study included.

Data extraction and quality assessment

Two authors (J.W.D. and W.Z.D.) independently conducted the literature search, study selection, and data extraction, while any discrepancies were resolved through consensus among the authors. In cases where consensus could not be reached, a third reviewer (F.G.B.) was consulted.

The data extracted from the eligible studies included the following information: (1) Study characteristics: first author, year of publication, study name, and study design. (2) Participant information: sample size (N), age, gender, and history of previous surgery. (3) Interventions: details regarding the intervention, cell dose, and duration. (4) Outcomes: overall survival (OS), progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and adverse events. (5) Quality assessment: assessment of random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, attrition, selective reporting, and other biases.

A p-value threshold of 0.10 was employed to determine statistical significance for χ^2 test, and I^2 of 30% or less was considered to be a low degree of heterogeneity, 30% to 60% to be a moderate degree, and 60% or more to be a high degree.

In order to uphold the high standards of our research, we strictly adhere to a policy of faithfully summarizing data as explicitly reported in the original texts. We refrain from the use of graphical adjustments, estimation methods, or assumptions.

Data synthesis and analysis

Analyses were conducted using Review Manager Version 5.3 provided by the Cochrane Collaboration and Stata version 15.0 provided by Stata Corporation.

The pooled estimates for PFS and OS were presented with HRs, 95% CIs, and P values, calculated using the inverse-variance-weighted method. Measures for dichotomous data (OS rates, PFS rates, ORR, DCR, and frequency of adverse events) were pooled using risk ratios (RRs), 95% CIs, and P values calculated using the Mantel–Haenszel method. All data were either extracted from each study or calculated using available statistics.

Given the expected high heterogeneity due to clinical diversity, a random-effects model was used for all quantitative analyses performed in this review.

Heterogeneity across studies was assessed visually and statistically using the chi-square (χ^2) test and I-squared (I^2) statistics for each analysis.

A sensitivity analysis was carried out by excluding each study at a time individually.

We planned a priori to assess and quantify publication bias using Begg's funnel plots and Egger's test if more than 5 studies reported on the primary outcome.

Results

Search results

We retrieved a total of 1013 records using our search strategies (Fig. 1) [32]. Among these, 147 duplicates were excluded, leaving us with 866 unique records. We conducted a thorough screening of the titles and abstracts and eliminated records that were irrelevant to tumors (837 records), focused on other interventions (285 records), or were not randomized controlled trials (91 records). Unfortunately, we were unable to retrieve 4 reports. Upon further evaluation of the full-text articles, we discarded non-English publications (4 articles), cohort studies that were not randomized (4 articles), as well as records that involved other interventions (4 articles). Ultimately, we included 13 randomized controlled trials for our meta-analysis.

Study and patient characteristics

Study and patient characteristics are summarized in Table 1. All included studies were randomized controlled trials (RCTs), with one study conducted in Japan and the remaining 12 studies conducted in mainland China.

A total of 1443 patients were included in the analysis, with 730 patients receiving DC-CIK immunotherapy in

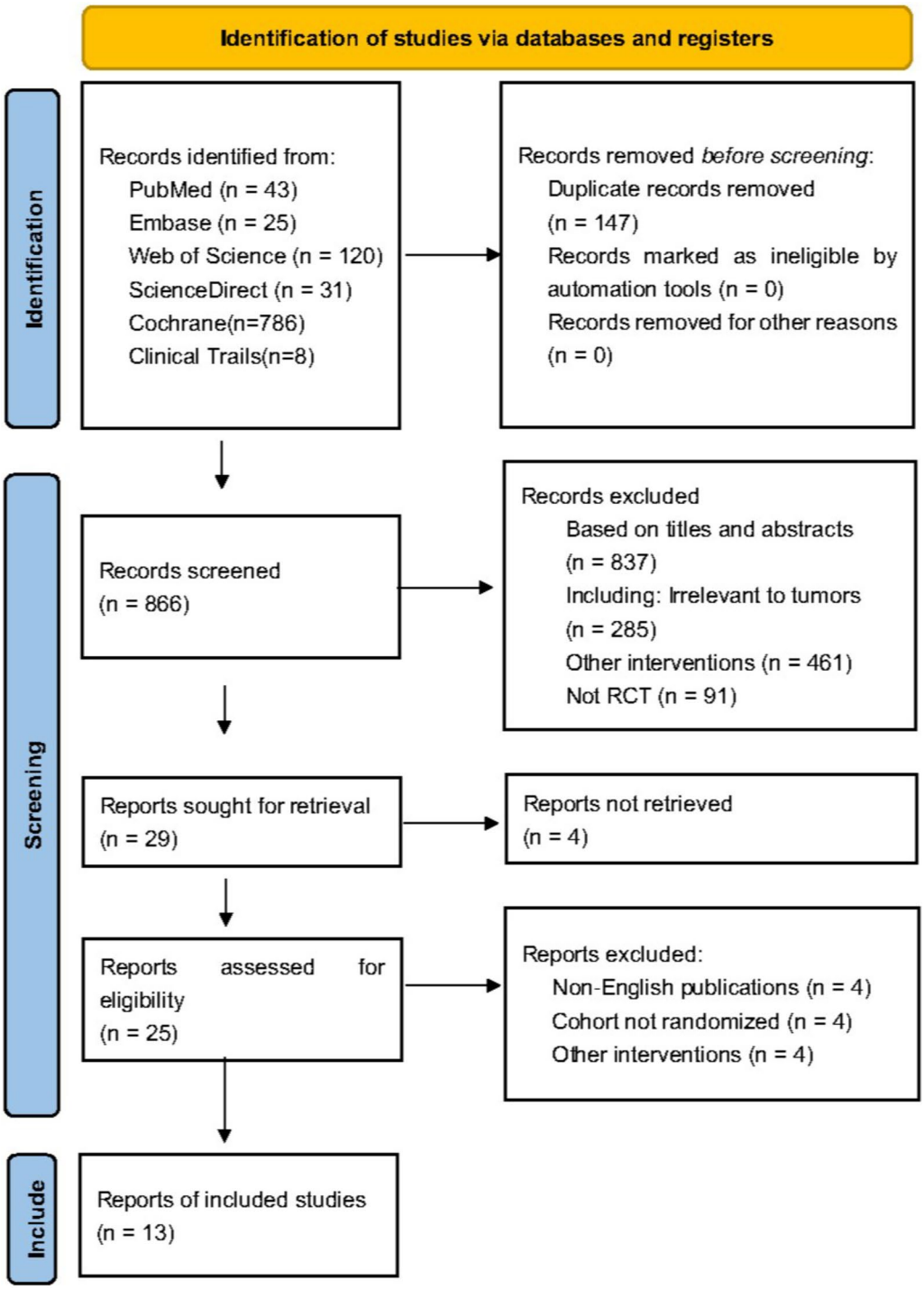


Fig. 1 Flowchart of study selection process. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. https://doi.org/10.1136/bmj.n71

the experimental groups and 713 patients in the control groups.

The cancer types represented in the studies included 4 articles on non-small cell lung cancer, 2 articles on renal cell carcinoma, 2 articles on colorectal cancer, and 1 article each on breast cancer, cervical cancer, esophageal carcinoma, gastric cancer, and colon cancer.

Table 1 Characteristics of included studies

Study	Country	Cancer types	Receiving surgery previously	Patients (n)			Stages (n)			Gender (M/F)		Age, years		
				Total	Exp	Con	Kinds	Exp	Con	Exp	Con	Kinds	Exp	Con
Zhan, [9]	China	Renal cell carcinoma	Yes	91	46	45	I/II/III	8/13/15	7/13/15	29/17	28/17	Mean ± SD	53.55 ± 2.56	53.58 ± 2.40
Ren, [20]	China	Metastatic breast cancer	No	166	87	79	IV	87	79	0/87	0/79	Median (range)	50(28–66)	52(32–71)
Zhao, [14]	China	Non-small cell lung cancers	Yes	157	79	78	III	79	78	49/30	46/32	Mean ± SD	58.2 ± 11.2	59.6 ± 10.7
Shi, [18]	China	Non-small cell lung cancers	No	54	26	28	III/IV	9/17	8/20	9/17	8/20	Median (range)	59.5(49–76)	62.5(45–77)
Kimura, [19]	Japan	Non-small cell lung cancers	Yes	101	50	51	I/II/III/IV	7/8/30/5	6/7/35/3	37/13	38/13	Mean ± SD	63.2 ± 8.1	64.5 ± 6.9
Chen, [13]	China	Cervical cancer	No	79	40	39	II/III/IV	27/12/1	27/11/1	0/40	0/39	Mean ± SD	52.4 ± 17.1	51.9 ± 16.8
Yan, [17]	China	Esophageal carcinoma	No	68	34	34	I/II/III/IV	2/6/15/11	1/7/14/12	22/12	23/11	Mean ± SD	70.46 ± 2.91	71.55 ± 2.23
Zhao, [12]	China	Renal cell carcinoma	Yes	60	30	30	I/II	25/5	24/6	19/11	19/11	20–39/40–59/60–79	6/15/9	3/18/9
Lin, [10]	China	Advanced colorectal cancer	Yes	255	134	121	III or IV	134	121	76/58	64/57	≤ 60/ > 60	55/79	53/68
Mu, [15]	China	Advanced gastric cancer	No	28	13	15	III/IV	9/4	8/7	10/3	10/5	≤ 60/ > 60	8/5	8/7
Zhang, [59]	China	Colon cancer	No	122	61	61	III/IV	40/21	39/22	30/31	29/32	Mean ± SD	52.62 ± 1.98	52.17 ± 2.21
Wang, [48]	China	Non-small cell lung cancers	No	60	30	30	III/IV	9/30	7/23	18/12	19/11	Mean ± SD	59.1 ± 3.6	58.7 ± 3.2
Pan, [21]	China	Metastatic colorectal cancer	No	202	100	102	III or IV	100	102	45/55	59/43	≤ 60/ > 60	41/59	50/52

Mean ± SD: mean ± sample standard deviation

Exp: experimental groups; Con: control groups

Among the included studies, 7 studies included patients who had previously undergone surgery, while the other 8 studies did not.

Additional details, such as stages, gender, and age of the patients, are also provided in Table 1.

Interventions

Interventions were compared in the included studies as follows: DC-CIK immunotherapy was compared with placebo in 2 studies, and 1 study compared Intensity-modulated radiation therapy (IMRT) plus DC-CIK immunotherapy versus IMRT alone. The remaining 10 studies compared DC-CIK immunotherapy plus chemotherapies with chemotherapies alone. It is interesting that one of these studies utilized bevacizumab in two arms as an additional immunotherapy. Further details, such as cell dose and treatment duration, are provided in Supplementary Table S1.

Risk of bias assessment

Among the included studies, only seven studies reported detailed methods of allocation sequence generation, such as using a random number table or computer-generated randomization. The remaining six studies only mentioned being "randomly allocated" without specifying the allocation procedures. Regarding allocation concealment, two studies used envelopes.

Two studies employed single-blinding, while double-blinding was utilized in two other studies.

The experimental and control groups in the study both had clear inclusion criteria, and the demographic and clinical characteristics of the patients were generally balanced. The follow-up data was clear, with no significant losses observed. The study collected the data as expected. Although no published protocols were found for any of the articles, they were still considered to have low risks in terms of blinding in result evaluation, data integrity, and selective publication.

As for other risks, all studies underwent ethical review, and all participants signed written informed consent forms, indicating that other risks were also considered low.

The quality assessment of the included studies, evaluated using the Cochrane Collaboration tool, ranked the risk for bias as medium. For specific details, please refer to Fig. 2 and Supplementary Table S2.

Overall survival and progression-free survival.

Original data extracted from included studies performed in Supplementary Table S3.

There were 5 studies involving 878 patients which contributed data to the meta-analysis on OS (Fig. 3A). The pooled HR was 0.64 (95%CI 0.47 to 0.86) indicating the OS benefit of DC-CIK immunotherapy over the control arm. Heterogeneity among the studies was high ($I^2 = 86\%$, $p < 0.00001$).

For PFS, 7 studies involving 1003 patients contributed the data to the meta-analysis (Fig. 3B). The pooled HR was 0.67 (95%CI: 0.53 to 0.85), again favoring CIK/DC-CIK immunotherapy. Heterogeneity among the studies was high ($I^2 = 75\%$, $p = 0.0005$).

Overall survival rates

In total, 4 (355 patients), 5 (456 patients), and 4 (493 patients) studies contributed data for 1, 2, and 3 year OS rate meta-analyses, respectively (Fig. 4). The pooled RR for all the analyses favored DC-CIK immunotherapy. The 1 year OS rate was 96.1% in the intervention arm and 78.5% in the control arm with a pooled RR of 0.19 (95%CI: 0.09 to 0.40). Heterogeneity among the studies was low ($I^2 = 0\%$, $p = 0.87$). The 2 year OS rate was 84.2% in the intervention arm and 72.4% in the control arm with a pooled RR of 0.51 (95%CI 0.27 to 0.98). There was a moderate level of heterogeneity among the studies ($I^2 = 59\%$, $p = 0.05$). The 3 year OS rate was 51.6% in the intervention arm and 43.6% in the control arm with an RR of 0.82 (95%CI 0.60 to 1.13). Heterogeneity among the studies was high ($I^2 = 63\%$, $p = 0.05$).

Progression-free survival rates

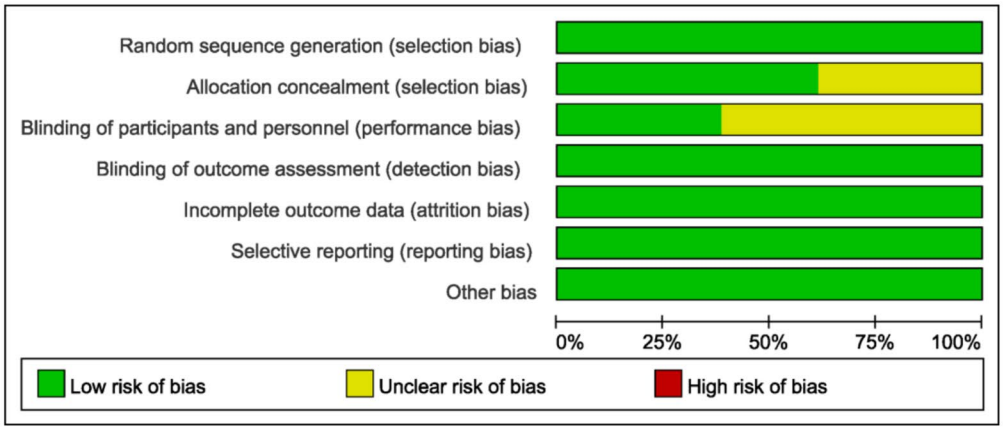
We identified 4 (386 patients), 5 (487 patients), and 4 (418 patients) studies that contributed data for meta-analysis on 1, 2, and 3 year PFS rates, respectively (Fig. 5). All the analyses indicated the superiority of DC-CIK immunotherapy over non-DC-CIK therapy. The observed 1 year PFS rate was 93.3% in the intervention arm and 79.3% in the control with the pooled RR of 0.35 (95% CI 0.20 to 0.62). Heterogeneity among the studies was low ($I^2 = 0\%$, $p = 0.79$). The 2 year PFS rate was 77.8% in the intervention arm and 57.4% in the control arm. The pooled RR was 0.55 (95% CI 0.43 to 0.71) and heterogeneity among the studies was low ($I^2 = 0\%$, $p = 0.67$). At 3 years, the PFS rate was 76.2% in the intervention arm and 49.5% in the control arm. The pooled RR was 0.39 (95% CI 0.20 to 0.76) and heterogeneity among the studies was high ($I^2 = 65\%$, $p = 0.04$).

Overall response rate and disease control rate

The ORR was 42.5% in the intervention (DC-CIK) and 32.4% in the control (non- DC-CIK) arm for 700 patients from 7 studies (Fig. 6). The pooled RR was 0.86 (95% CI: 0.76 to 0.97), and heterogeneity among the studies was low ($I^2 = 17\%$, $p = 0.30$).

The DCR was 86.0% in the intervention (DC-CIK) and 77.1% in the control (non- DC-CIK) arm for 700 patients from 7 studies. The pooled RR was 0.60 (95% CI: 0.41

A



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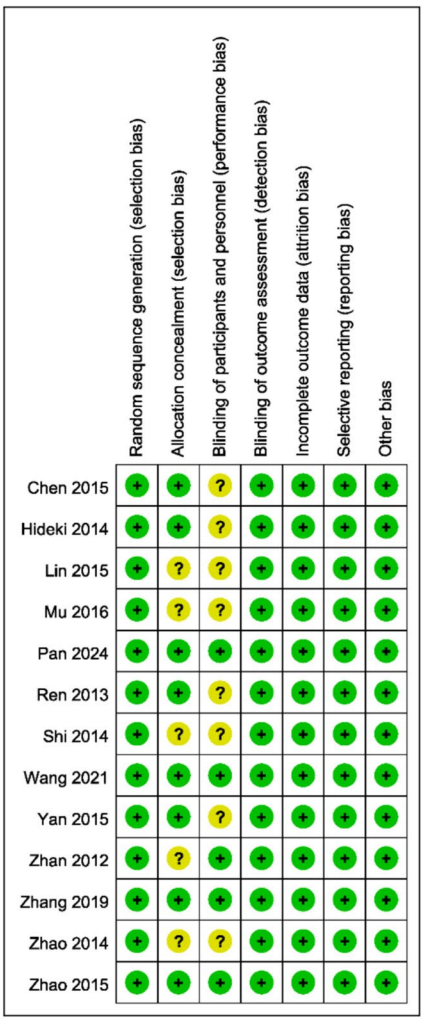

Fig. 2 **A** Risk of bias graph: a review of authors' judgments for each risk of bias item presented as percentages across all included studies. **B** Risk of bias summary: a review of authors' judgments for each risk of bias item for included studies

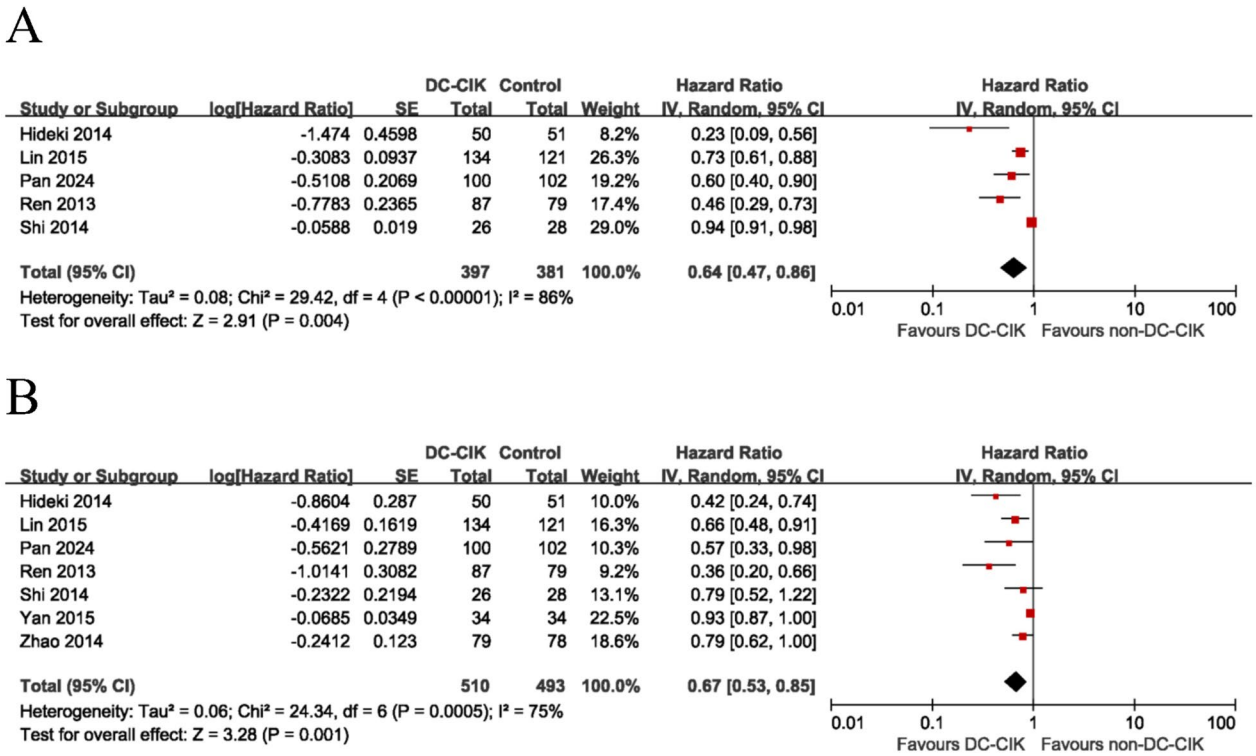

Fig. 3 Comparison of DC-CIK immunotherapy versus non- DC-CIK therapy for (**A**) overall survival (OS) and (**B**) progression free survival (PFS). five studies involving 878 patients and seven studies involving 1003 patients contributed data to OS and PFS analysis respectively. CIK, cytokine-induced killer cell; DC, dendritic cell

to 0.86), and heterogeneity among the studies was low ($I^2 = 17\%$, $p = 0.31$).

Adverse events

Adverse reactions observed during the course of treatment are listed in Supplementary Table 4. The most common adverse reaction was fever. Thrombocytopenia, anemia, nausea, vomiting, diarrhea had been reported from several studies. The adverse reactions reported in more than two studies were depicted using a forest plot, as shown in Supplementary Fig. S1. It can be observed that the proportion of fever was higher in the DC-CIK immunotherapy group, while bone marrow suppression and gastrointestinal reactions were higher in the control group. When considering all the reactions together, the proportion of adverse events in the immunotherapy group was 32.4%, compared to 31.7% in the control group. The pooled RR was 1 (95% CI: 0.80 to 1.26), and heterogeneity among the studies was high ($I^2 = 86\%$, $p < 0.00001$).

Sensitivity analyses

We carried out sensitivity analyses to assess the stability of the results of the meta-analysis by sequentially omitting each study. The leave-one-out sensitivity analyses indicated that no individual study changed the pooled data (HRs for OS and PFS, RRs for 1, 2, and 3 year OS rate, 1, 2, and 3 year PFS rates, ORR and DCR) qualitatively, suggesting that our results were stable and reliable.

Publication bias

We assessed publication bias using Begg's funnel plots and Egger's test if more than 5 studies reported on the primary outcomes (PFS, ORR, DCR, and fever) (Supplementary Fig. 2).

For PFS, 7 articles were analyzed, showing significant bias (Begg's test: $z = -2.25$, $p = 0.035$; Egger's test: $p = 0.002$). No additional articles were included in the trim and fill analysis, but a reversal in pooled relative risk (RR) indicated publication bias.

For ORR, 7 articles were analyzed, showing no significant bias (Begg's test: $z = -0.45$, $p = 0.764$; Egger's test: $p = 0.96$). For DCR, 6 articles were analyzed, showing no significant bias (Begg's test: $z = -0.56$, $p = 0.707$; Egger's test: $p = 0.829$). No trim and fill analysis was performed due to the absence of publication bias.

For the adverse reaction "Fever," 7 articles were analyzed, showing significant bias (Begg's test: $z = 2.25$, $p = 0.035$; Egger's test: $p = 0.016$). Trim and fill analysis

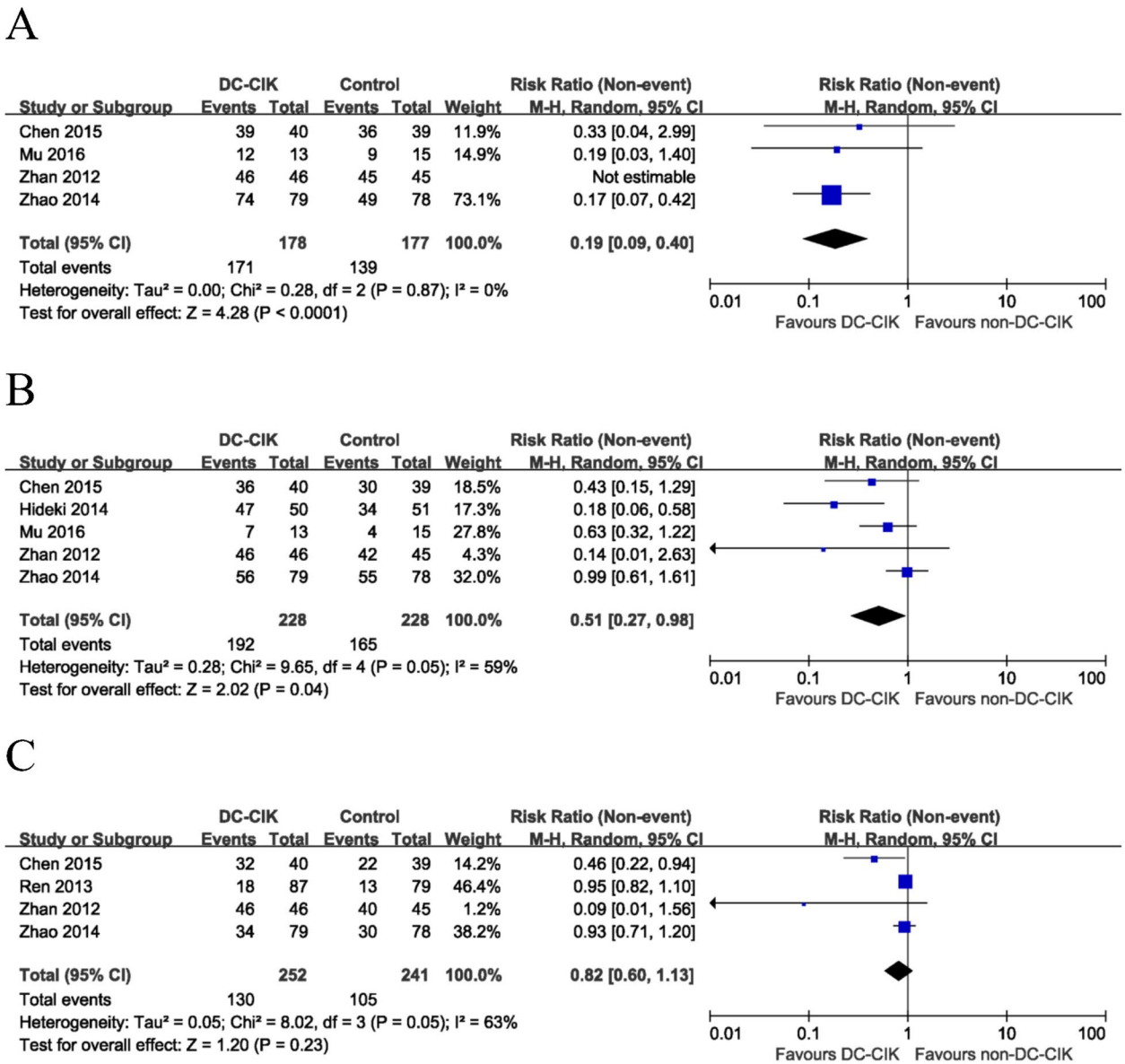

Fig. 4 Comparison of DC-CIK immunotherapy versus non- DC-CIK therapy for (**A**) 1 year, (**B**) 2 year and (**C**) 3 year overall survival (OS) rates. Four studies involving 355 patients, five studies involving 456 patients and four studies involving 493 patients contributed data to 1-,2-,3 year OS rates respectively. CIK, cytokine-induced killer cell; DC, dendritic cell

did not require additional articles, but pooled results revealed a reversal, indicating publication bias.

Discussion

For most patients with solid tumors, surgery, radiotherapy, and chemotherapy with/without combination of biologic therapy is the current standard of care. Immunotherapy, on the other hand, has become an important option for cancer treatment, improving the prognosis of many patients suffering from various haematological and solid malignancies [33]. There is evidence that DC-CIK enhances anti-tumour immunity in patients with non-small cell lung, colorectal, oesophageal, pancreatic, renal cell carcinoma and hepatocellular carcinomas, and more trials are currently investigating DC-CIK immunotherapy [12, 21, 34–37].

The findings of this meta-analysis provide strong evidence supporting the efficacy and safety of combined immunotherapy using DCs and CIK cells in the treatment of solid tumors. The pooled analysis demonstrated a significant improvement in overall survival (OS) and progression-free survival (PFS) in patients receiving DC-CIK

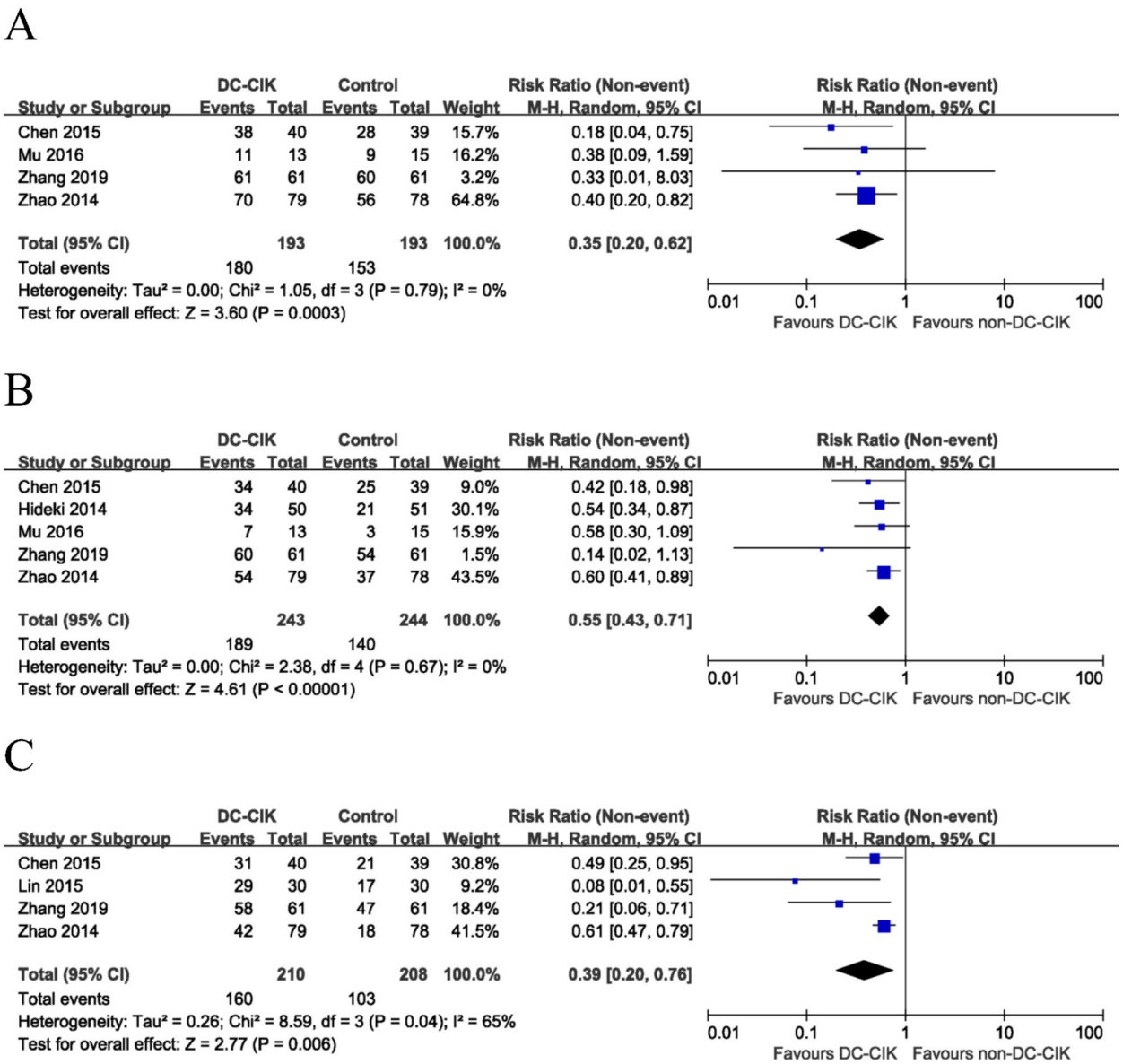

Fig. 5 Comparison of DC-CIK immunotherapy versus non- DC-CIK therapy for (**A**) 1 year, (**B**) 2 year and (**C**) 3 year progression free survival (PFS) rates. Four studies involving 386 patients, five studies involving 487 patients and four studies involving 418 patients contributed data to 1-,2-,3 year PFS rates respectively. CIK, cytokine-induced killer cell; DC, dendritic cell

immunotherapy compared to those in the control group. These results are consistent with previous studies indicating the potential of this combined approach in enhancing anti-tumor immune responses.

The observed higher overall response rate (ORR) and disease control rate (DCR) in the intervention arm further validate the therapeutic efficacy of DC-CIK immunotherapy. The combination of DCs and CIK cells appears to synergistically enhance the anti-tumor immune response, leading to higher tumor response rates and disease control rates. This suggests that the activation and expansion of tumor-specific T cells by DCs, along with the NK-like cytotoxicity of CIK cells, contribute to the effective elimination of cancer cells.

There are some limitations to this study, with six trials not providing detailed information on blinding.There is heterogeneity in the DC-CIK culture system, including the medium, the concentration of cytokines added, the time regimen of cytokine addition to the culture, and the timing of DC-CIK cell product infusion are not published in detail, and the differing cell subset content prior to cell product infusion may also result in an

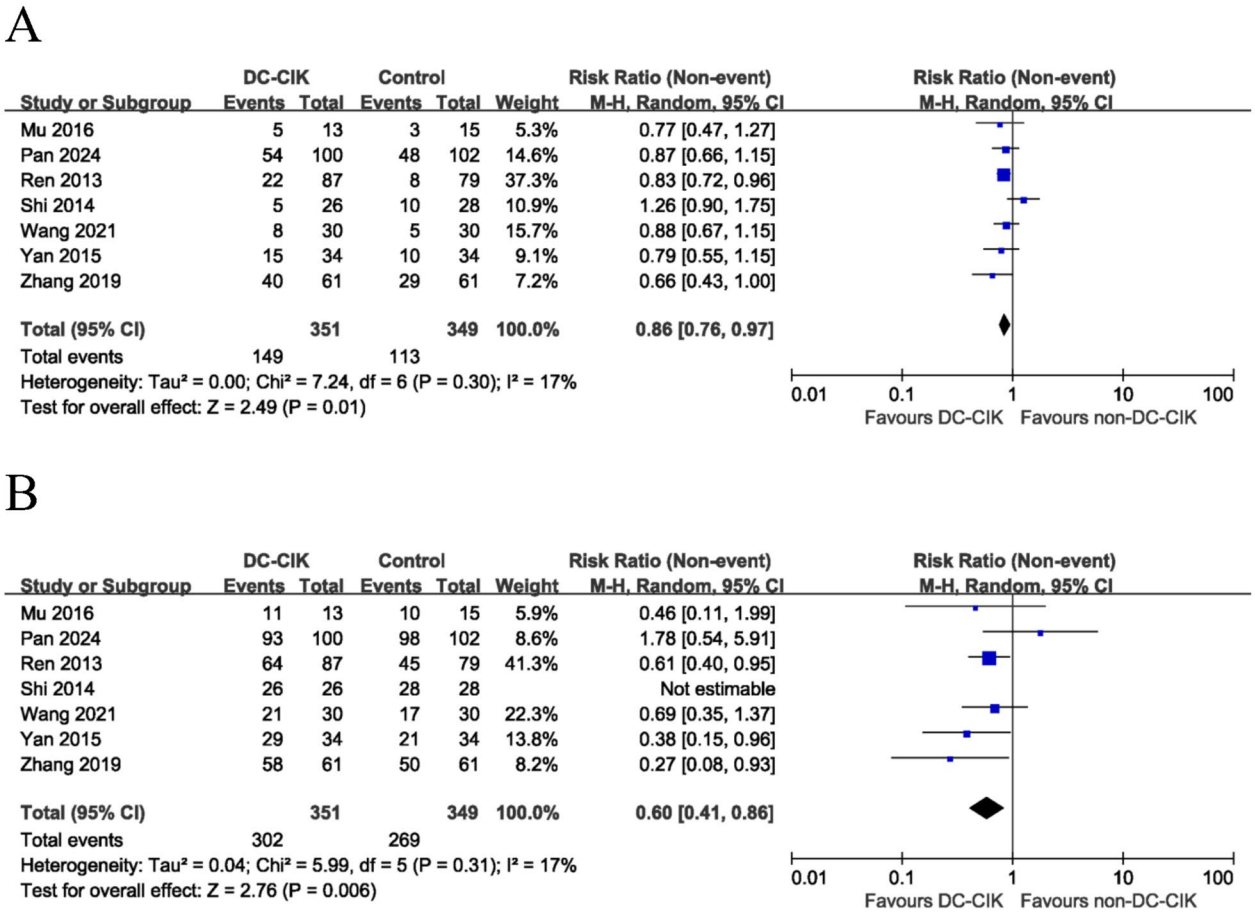

Fig. 6 Comparison of DC-CIK immunotherapy versus non- DC-CIK therapy for (**A**) Overall response rate ORR, (**B**) Disease control rate (DCR). Seven studies involving 700 patients contributed data to ORR and DCR respectively. CIK, cytokine-induced killer cell; DC, dendritic cell

inadequate assessment of anti-tumour immunity and tumour responses were inadequately assessed. In addition, most of the included articles in the analysis of this study focused on short-term outcomes, with limited data on long-term outcomes. Only two studies performed survival analyses beyond three years. China, on the other hand, is a leader in research on over-the-counter immunotherapy, including CIK therapy. Articles published in Chinese were not included in this study and it is necessary to include articles published in Chinese. Since most of the included studies were conducted in China and a few in Japan, clinical trials among non-Asians are needed to confirm their efficacy beyond Asian patients.

All factors potentially affecting the cytotoxicity of CIK cells will influence the actual clinical efficacy of DC/CIK treatment. The selection of antigens is undoubtedly the most critical factor. According to published reports, different studies have chosen various tumor antigens: some utilize tumor-associated antigen, and some directly lyse tumor cells to obtain more comprehensive and personalized tumor antigens [38–41]. Different antigen selections have shown certain clinical efficacy, but currently, there are no large-scale clinical studies to determine which method would bring out better results. Considering the challenging issue of tumor heterogeneity, new antigen peptides based on individual tumor genetic testing and lysates from individual tumor cells may provide a more diverse and targeted antigen repertoire, potentially offering greater clinical benefits [42].

Another crucial factor is the penetrance of immune cells. It is well known that solid tumors are rapidly growing cell masses interspersed with distorted blood vessels. Hence, all medicine treatments, including chemotherapy, targeted therapy, and immune checkpoint inhibitors, face a significant challenge: how to penetrate the interior of tumors. Adoptive cell therapy faces the same dilemma. Direct injection of immune cells into tumors is an option, though this requires accessible tumor locations, posing limitations of implementation and increasing risks of complications such as infection and bleeding [43, 44]

. Furthermore, using tumor-infiltrating lymphocytes (TILs) instead of peripheral blood mononuclear cells (PBMCs) collected from circulation is an appealing solution. TILs are considered to have stronger tumor infiltration capabilities and may be capable of overcoming the problem of antigenic heterogeneity, and experiments using TILs in adoptive cell therapy have shown promising results [45–48].

Additionally, the immune-suppressive microenvironment of tumors hinders the efficacy of immunotherapy. The DC-CIK therapy combines the antigen-presenting function of dendritic cells with the cytotoxicity of cytokine-induced killer cells, enhancing the antitumor activity. However, the immunosuppressive tumor microenvironment can inhibit the function of DCs and reduce the antitumor activity of CIK cells. Tumor cells in the tumor microenvironment, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T lymphocytes (T-regs) all inhibit the immune activity of cytotoxic cells [49–52] . Furthermore, among the ex vivo expanded CIK cell populations, the proportions of cellular subsets are not uniform. Studies have shown that alterations in the proportions of CD4 + T cells, regulatory T lymphocytes, and CD3 + CD56 + T cells within the CIK cell population significantly affect the antitumor activity of CIK cells. CD4 + T cells play an important role in CIK therapy, enhancing the tumoricidal function of CIK cells, promoting the migration and motility of CIK cells, and studies have also found that the addition of anti-PD-1 therapy can promote the CIK antitumor response [53]. The combination of DC-CIK with immune checkpoint inhibitors (ICIs) may be a feasible strategy to enhance antitumor activity, with clinical trials indicating that PD-1 blockade-activated DC-CIK cell therapy in combination with XELOX and bevacizumab significantly improves progression-free survival and overall survival in patients with metastatic colorectal cancer compared to XELOX and bevacizumab alone [21]. Additionally, optimizing the ex vivo induction and expansion protocols of CIK cells to reduce the proportion of Treg cells and alleviate the suppressive effects on CIK cells is another direction to improve the efficacy of DC-CIK therapy [54]. Currently, multiple studies have identified several therapeutic targets that can improve DC function, such as lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) [55–58]. The development of new combination therapies and treatment strategies is an urgent need to enhance the antitumor effects of DC-CIK.

Importantly, the occurrence of adverse events associated with DC-CIK immunotherapy was comparable to that in the control group. This is a critical finding, as it demonstrates the feasibility of this treatment approach without significantly increasing the risk of adverse events. However, it is worth noting that the reporting of adverse events in the included studies varied, and further studies with standardized reporting guidelines are needed to obtain a more comprehensive understanding of the safety profile of DC-CIK immunotherapy.

One interesting point of discussion is the potential optimization of treatment regimens. Although the overall efficacy and safety of DC-CIK immunotherapy have been demonstrated, the optimal dosing, scheduling, and combination strategies of these two types of immune cells are still under investigation. Future studies should explore the impact of different treatment regimens on clinical outcomes, including the dosage and frequency of DC administration, the timing and route of CIK cell infusion, as well as the combination with other immunotherapies.

Another interesting aspect to consider is the identification of predictive biomarkers for patient selection. While DC-CIK immunotherapy has shown benefits in overall survival and progression-free survival, not all patients may respond equally to this treatment approach. Therefore, it is crucial to identify biomarkers that can accurately predict the response to DC-CIK immunotherapy. These biomarkers could include immune cell subsets, cytokines, or tumor-related factors that can help identify patients who are more likely to benefit from this treatment, enabling a more personalized approach to cancer immunotherapy.

In conclusion, this meta-analysis provides robust evidence supporting the efficacy and safety of combined immunotherapy using DCs and CIK cells in the treatment of solid tumors. The improved overall survival, progression-free survival, overall response rate, and disease control rate observed in the intervention arm demonstrate the potential of this treatment approach. However, further research is needed to optimize treatment regimens, identify predictive biomarkers, and explore potential combinations with other immunotherapies. Long-term follow-up data and head-to-head comparisons with other treatment modalities will provide additional insights into the role of DC-CIK immunotherapy in personalized cancer treatment.

Conclusion

In conclusion, this systematic review and meta-analysis provide strong evidence for the efficacy and safety of DC-CIK immunotherapy in the treatment of solid tumors. The results demonstrate improved overall survival, progression-free survival, overall response rate, and disease control rate in patients receiving DC-CIK immunotherapy. DC-CIK treatment was well tolerated, with fever being its most common adverse event. Despite some

limitations, these findings support further research and clinical applications of DC-CIK immunotherapy. Continued investigation and optimization of treatment regimens are necessary to enhance the therapeutic outcomes and identify patient-specific factors that can predict treatment response.

Abbreviations

DCs	Dendritic cells
CIK	Cytokine-induced killer
RCTs	Randomized controlled trials
OS	Overall survival
PFS	Progression-free survival
ORR	Overall response rate
DCR	Disease control rate
ACT	Adoptive cell therapy
CAR-T	Chimeric antigen receptor T-cell
FDA	Food and Drug Administration
TILs	Tumor-infiltrating lymphocytes
NK	Natural killer
IL-12	Interleukin-12
PD-1	Programmed cell death protein 1
IMRT	Intensity-modulated radiation therapy
Exp	Experimental groups
Con	Control groups
FOLFOX	Fluorouracil plus leucovorin and oxaliplatin
XELOX	Capecitabine plus oxaliplatin
DCF	Docetaxel plus cisplatin and fluorouracil
1y-OS	1 Year overall survival rate
1y-PFS	1 Year progression-free-survival rate
RRs	Risk ratios
HRs	Hazard ratios
PBMCs	Peripheral blood mononuclear cells
MDSCs	Myeloid-derived suppressor cells
TAMs	Tumor-associated macrophages
ICIs	Immune checkpoint inhibitors
T-regs	Regulatory T lymphocytes
LAG-3	Lymphocyte activation gene-3
TIM3	T cell immunoglobulin and mucin-domain containing-3
TIGIT	T cell immunoreceptor with Ig and ITIM domains
Ig	Im-munoglobulin
ITIM	Immunoreceptor tyrosine-based inhibitory motif

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Author contributions
ZL, GF, XC and LJ designed the study and directed the study. WJ, ZW and QL collected most of the data and wrote the manuscript. ZD, JZ, XT, YX and YD intellectually contributed throughout the project. ZL, GF, XC, and LJ guided the project and revised the manuscript. All authors have consented to the manuscript.

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Availability of data and material
All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

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Competing interests
The authors declare that they have no competing interests.

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