

FOLFOX regimen plus dendritic cells–cytokine-induced killer cells immunotherapy for the treatment of colorectal cancer: a meta-analysis

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Purpose: To systematically investigate the efficacy and safety of the combination of FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) regimen and cocultured dendritic cells and cytokine-induced killer cells (DC-CIK) immunotherapy for the treatment of colorectal cancer (CRC).

Methods: Publications reporting the clinical trials' responses or safety of FOLFOX regimen combined with DC-CIK immunotherapy in treating CRC patients were searched in PubMed, Embase, Cochrane Library, China National Knowledge Internet, and Wanfang databases. Trials meeting the selection criteria were analyzed. The overall survival (OS), overall response rate (ORR), disease control rate (DCR), tumor markers, immune function, and adverse events were evaluated.

Results: Ten trials including 881 CRC patients were analyzed in this meta-analysis. The combined therapy showed advantages over FOLFOX treatment-alone in 2-year OS (odds ratio [OR] = 2.77, confidence interval [CI] = 1.58–4.86, $P=0.0004$), ORR (OR = 1.85, CI = 1.34–2.56, $P=0.0002$), and DCR (OR = 2.54, CI = 1.76–3.67, $P<0.00001$), with statistical significance. After immunotherapy, lymphocyte subset percentages of CD3⁺ ($P=0.0006$) and CD4⁺ ($P=0.01$), CD4⁺/CD8⁺ ratio ($P=0.0003$), and levels of cytokines IFN- γ ($P=0.003$) and IL-2 ($P=0.01$) were significantly increased, whereas analysis of CD8⁺, CD3⁺CD56⁺, CD3⁺CD56⁺, CD4⁺CD25⁺, IL-6, and TNF- α did not show any significant difference ($P>0.05$). Moreover, the level of carcino-embryonic antigen was also decreased significantly upon immunotherapy ($P<0.00001$).

Conclusion: The combination of FOLFOX regimen and DC-CIK immunotherapy was safe and effective for CRC patients.

Keywords: FOLFOX, dendritic cells, cytokine-induced killer cells, colorectal cancer, meta-analysis

Introduction

Colorectal cancer (CRC) is the second most frequent cause of death in Europe and North America with about 600,000 deaths per year.^{1,2} In recent years, the incidence of CRC has risen significantly with ~1.2 million new cases being diagnosed every year worldwide, while the 5-year survival rate of patients with stage IV CRC is <10%.¹⁻⁴ Chemotherapy is the main treatment for CRC, and appropriate chemotherapy regimens effectively prolong patients' lives and improve their quality of life.^{2,4} FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) is one of the most common chemotherapy regimens and is a standard first-line therapy for CRC.^{1,5} However, many researchers have reported that chemotherapy alone was not able to completely eradicate small lesions and metastatic cells, which may raise the probability of cancer recurrence.⁶ Comprehensive treatments are therefore taken as the future for CRC therapy, and the

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combination of chemotherapy and adoptive cell therapy is one of the options.

Adoptive cellular immunotherapy is achieved upon in vitro expansion of autologous immune effector cells, such as cytokine-induced killer cells (CIK),^{7,8} natural killer cells⁹ and other immune cells,^{10–12} and transfusion back to the patients. Since conventional therapies are not able to eradicate the tumor cells thoroughly, the killing effect of adoptive cellular immunotherapy on tumor cells will make it an important supplement.⁸ CIK is a heterogeneous subset which consists primarily of CD3⁺CD56⁺ and can be easily induced from peripheral blood mononuclear cells.^{7,8} Compared with other immune cells, CIK show a broader antitumor spectrum and a stronger antitumor ability.¹³ Dendritic cells (DC) are the most potent antigen-presenting cells.¹⁴ Studies have shown that coculture with DC enhances the cytotoxicity of CIK, indicated by an increased proportion of CD3⁺CD56⁺ cells and improved levels of cytokines such as IL-2, IFN- γ , IL-12, and TNF- α .^{15–18} It has also been found that the combination of DC and CIK is more effective than CIK treatment.⁸

Chemotherapy combined with adoptive immunotherapy has shown satisfactory therapeutic effects in treating patients with advanced CRC.^{19–21} In a meta-analysis of treating advanced CRC with CIK or DC-CIK combined with chemotherapy or chemotherapy alone, the former showed significantly improved overall survival (OS) and overall response rate (ORR), while safety, tumor markers, and levels of cytokines were not involved in this analysis.²² Moreover, the therapeutic regimens among studies were different, which may have influenced the analysis of clinical therapy. In the present study, a more stringent inclusion criterion (only CRC patients treated by FOLFOX regimen with DC-CIK immunotherapy were included) was developed to exclude the impact of different treatments on the clinical efficacy. Meanwhile, a systematic review and meta-analysis were carried out to investigate the efficacy and safety of FOLFOX chemotherapy combined with DC-CIK immunotherapy in comparison with FOLFOX alone, in order to provide scientific evidence for future clinical trials.

Materials and methods

Search strategy and selection criteria

Literature was searched in PubMed, Embase, Cochrane Library, China National Knowledge Internet, and Wanfang databases with key terms “dendritic cells” and “cytokine-induced killer cells” combined with “colorectal cancer.” No language limits were applied. The initial search was performed in January 2016 and updated in July 2016.

The study inclusion criteria were as follows: 1) randomized controlled trials in CRC patients and 2) patients in the experimental group received FOLFOX regimen combined with DC-CIK immunotherapy, and patients in the control group were treated by FOLFOX alone.

Data collection and quality assessment

Data were extracted by two researchers independently (Yan Liu and Zhong Zheng), and discrepancy was resolved upon discussing with a third researcher (Qixin Zhang). Extracted information included first author's names, years of publication, study locations, tumor stages, numbers of subjects, patient ages, in vitro cell culture conditions, and dosages of utilized immune cells. The quality of the included papers was evaluated based on Cochrane Handbook.²³

Definition of measurements

Treatment efficacy was assessed in terms of OS, complete response rate (CR), partial response rate (PR), stable disease rate (SD), progressive disease rate (PD), ORR (ORR = CR + PR), and disease control rate (DCR; DCR = CR + PR + SD). OS was defined as the duration from the initiation of treatment to death from any cause.²⁴ The immune function of CRC patients before and after treatment was determined by lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺, CD3⁺CD56⁺, CD3⁺CD56⁺, and CD4⁺CD25⁺) and cytokines secretion (IFN- γ , IL-2, IL-6, and TNF- α). Adverse events during therapy were also taken into an assessment.

Statistical analysis

The analysis was performed using Review Manager 5.2 (Cochrane Collaboration). $P < 0.05$ was considered statistically significant. Heterogeneity among studies was assessed to determine the most suitable analysis model.²⁵ Cochran's Q test was performed to evaluate the homogeneity of the results; $I^2 < 50\%$ or $P > 0.1$ indicated that the studies were homogenous. Odds ratio (OR) was the principal measurement for therapeutic effects and is presented with a 95% confidence interval (CI).

Results

Search results

A total of 3,055 articles were identified with the initial retrieve. After reviewing the titles and abstracts, 2,982 articles were excluded because they were not clinical trials ($n=2,593$) were a duplication or repetition ($n=257$) or were unrelated studies ($n=132$), and 73 studies were selected as potentially relevant. After full-text assessment, 27 studies

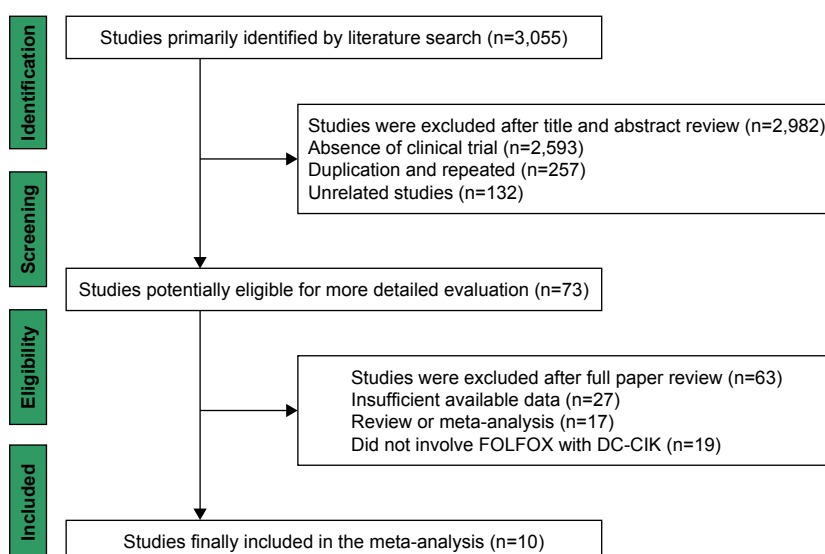


Figure 1 Flow diagram showing record identification, screening, and study inclusion process.

Abbreviations: FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; DC-CIK, dendritic cells and cytokine-induced killer cells.

with insufficient data, 17 reviews or meta-analyses and 19 studies which did not involve FOLFOX regimen and DC-CIK immunotherapy were excluded. Finally, 10 trials including a total of 881 patients were found to be eligible for inclusion in this meta-analysis (Figure 1).^{26–35}

Patient characteristics

All the involved trials were conducted in mainland China. In total, 444 patients were treated by FOLFOX regimen in combination with DC-CIK immunotherapy, and 437 patients were treated by FOLFOX alone. DC and CIK used in the 10 trials were all obtained from autologous peripheral blood. All DC and CIK were examined and confirmed free of bacterial and fungal contamination, and negative for mycoplasma. Cells were cultured for amplification in vitro. The DC and

CIK were suspended in saline containing 2% albumin (100 or 200 mL) and intravenously transfused into patients, except one trial in which DC were subcutaneously transfused.³³ DC-CIK were transfused for two or more treatment cycles. However, the accurate cell numbers were not provided in most studies. Detailed clinical information on the trials is presented in Tables 1 and 2.

Quality assessment

The assessment of bias risk is shown in Figure 2. The overall qualities of the involved studies ranged from moderate to high. Eight studies were determined as of low risk, and the remaining two studies did not show a clear description of the randomization process. The risks of allocation, performance, and detection were low; one research was regarded as of

Table 1 Clinical information from the eligible trials in the meta-analysis

Included studies	Nation	Tumor stage	Patients Con/Exp	Age (year)		Parameter types
				Con	Exp	
Bian ²⁶	China	ND	42/42	62.2±4.9 (mean ± SD)	62.7±4.9 (mean ± SD)	ORR, DCR, LYM subsets, AE
Hou ²⁷	China	II–III	40/40	57.4±3.0 (mean ± SD)	56.0±2.5 (mean ± SD)	OS, ORR, DCR
Li et al ²⁸	China	II–III	20/20	57.5 (mean ± SD)	54.5 (mean ± SD)	OS, LYM subsets, cytokines, AE
Li et al ²⁹	China	Ps ≤2	38/39	51.6±13.0 (mean ± SD)	53.4±13.6 (mean ± SD)	ORR, DCR, LYM subsets, cytokines, tumor markers, AE
Rui et al ³⁰	China	IV	45/45	58.6±12.6 (mean ± SD)	63.3±10.1 (mean ± SD)	OS, LYM subsets
Wang et al ³¹	China	III–IV	42/42	54 (median)	56 (median)	LYM subsets, cytokines
Weng et al ³²	China	III–IV	111/124	55 (median)	59 (median)	ORR, DCR, LYM subsets, cytokines, AE
Weng et al ³³	China	IV	48/41	53 (mean ± SD)	52 (mean ± SD)	OS, ORR, DCR, LYM subsets
Yuan et al ³⁴	China	Kps ≥60	21/21	58 (median)	60 (median)	ORR, DCR, LYM subsets
Zhou ³⁵	China	III–IV	30/30	65.1±4.5 (mean ± SD)	64.1±4.6 (mean ± SD)	ORR, DCR, AE

Notes: Control group: FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin)-alone group; Experimental group: FOLFOX regimen plus dendritic cells and cytokine-induced killer cells immunotherapy.

Abbreviations: Con, control group; Exp, experimental group; ND, not determined; Ps, performance status score; Kps, Karnofsky Performance score; ORR, overall response rate; DCR, disease control rate; LYM, lymphocyte; AE, adverse events; OS, overall survival.

Table 2 Information of DC-CIK immunotherapy

Included studies	Culture conditions	Cell dose (cycles)
Bian ²⁶	IFN- γ , IL-2, CD28 (CIK); GM-CSF, IL-4, TNF- α , PGE-2, IL-1 β (DC)	ND (2 cycles)
Hou ²⁷	ND	ND (2 cycles)
Li et al ²⁸	IFN- γ , IL-2, CD3 (CIK); GM-CSF, IL-4, IFN- γ (DC)	ND (2 cycles)
Li et al ²⁹	ND	ND (ND)
Rui et al ³⁰	IFN- γ , IL-1 α , IL-2, CD3 (CIK); GM-CSF, IL-4 (DC)	ND (≥ 3 cycles)
Wang et al ³¹	ND	ND (2–3 cycles)
Weng et al ³²	ND	ND (3 cycles)
Weng et al ³³	IFN- γ , IL-1 α , IL-2, CD3 (CIK); IFN- γ , LPS (DC)	3×10^7 /cycle (DC, 2 cycles); 5×10^9 /cycle (CIK, 2 cycles)
Yuan et al ³⁴	IFN- γ , IL-2, IL-1 α , CD3 (CIK); GM-CSF, IL-4, IFN- γ , TNF- α (DC)	$>1 \times 10^6$ (DC, 4 cycles); $>1 \times 10^{10}$ (CIK, 4 cycles)
Zhou ³⁵	ND	ND (2 cycles)

Abbreviations: DC-CIK, dendritic cells and cytokine-induced killer cells; CIK, cytokine-induced killer cells; DC, dendritic cells; ND, not determined.

unclear risk for lacking follow-up information; three trials were considered as of unclear risk for selective reporting, while the other four studies were considered as of high risk for missing primary outcome data.

Therapeutic efficacy assessments

As shown in Figures 3, 4, and S1 and Table 3, the pooled results indicated that patients in experimental group had significantly improved 2-year OS, CR, PR, ORR, and DCR (2-year OS: OR =2.77, CI =1.58–4.86, $P=0.0004$; CR: OR =2.30, CI =1.11–4.76, $P=0.03$; PR: OR =1.53, CI =1.07–2.18, $P=0.02$; ORR: OR =1.85, CI =1.34–2.56, $P=0.0002$; DCR: OR =2.54, CI =1.76–3.67, $P<0.00001$) and significantly decreased PD (PD: OR =0.39, CI =0.26–0.57, $P<0.00001$), whereas the 1-year OS and SD did not show significant difference from control group (1-year OS: OR =2.42, CI =0.86–6.79, $P=0.09$; SD: OR =1.24, CI =0.87–1.77, $P=0.24$). Fixed-effect models were used to analyze the OR rate because of low heterogeneity.

Tumor markers were also analyzed to evaluate the therapeutic effects of combination therapy (Figure 5).

Carcinoembryonic antigen (CEA) was significantly reduced after immunotherapy (OR =–22.80, CI =–25.98 to 19.62, $P<0.00001$), while no significant changes were found in carbohydrate antigen 199 (CA199) and carbohydrate antigen 242 (CA242) (CA199: OR =–2.60, CI =–7.61 to 2.41, $P=0.31$; CA242: OR =–1.00, CI =–6.07 to 4.07, $P=0.70$).

Immune function evaluation

The immune status of patients was examined before and after treatment. After DC-CIK treatment, percentages of CD3⁺ and CD4⁺ cells and CD4⁺/CD8⁺ ratio were significantly increased (CD3⁺: OR =5.04, CI =2.18–7.90, $P=0.0006$; CD4⁺: OR =3.38, CI =0.73–6.02, $P=0.01$; CD4⁺/CD8⁺: OR =0.39, CI =0.18–0.60, $P=0.0003$) (Figure 6), whereas no differences were found in the proportions of CD8⁺, CD3⁺CD56⁺, CD3⁺CD56⁺, and CD4⁺CD25⁺ cells (CD8⁺: OR =–0.30, CI =–3.46 to 2.86, $P=0.85$; CD3⁺CD56⁺: OR =4.04, CI =–0.36 to 8.45, $P=0.07$; CD3⁺CD56⁺: OR =1.11, CI =–1.64 to 3.85, $P=0.43$; CD4⁺CD25⁺: OR =–0.29, CI =–2.40 to 1.82, $P=0.79$). Moreover, the levels of IFN- γ and IL-2 were significantly increased after DC-CIK therapy (IFN- γ : OR =4.50,

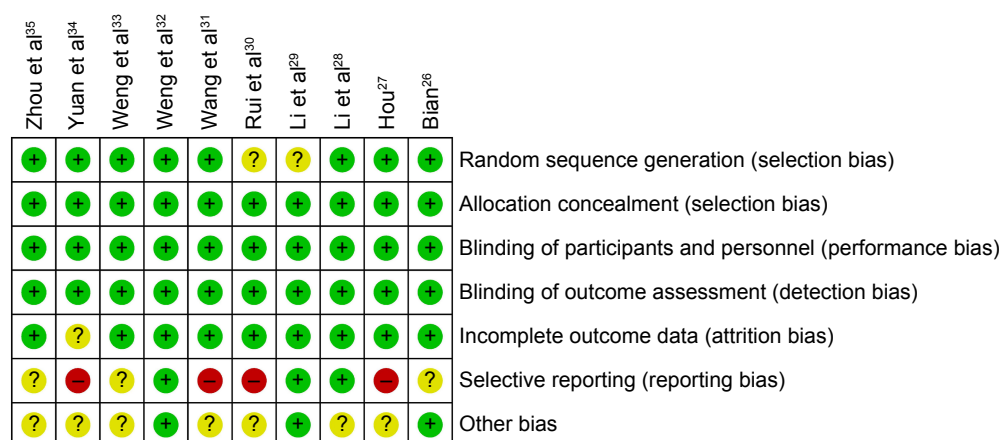


Figure 2 Risk-of-bias summary: review of authors' judgments about each risk-of-bias item for included studies.

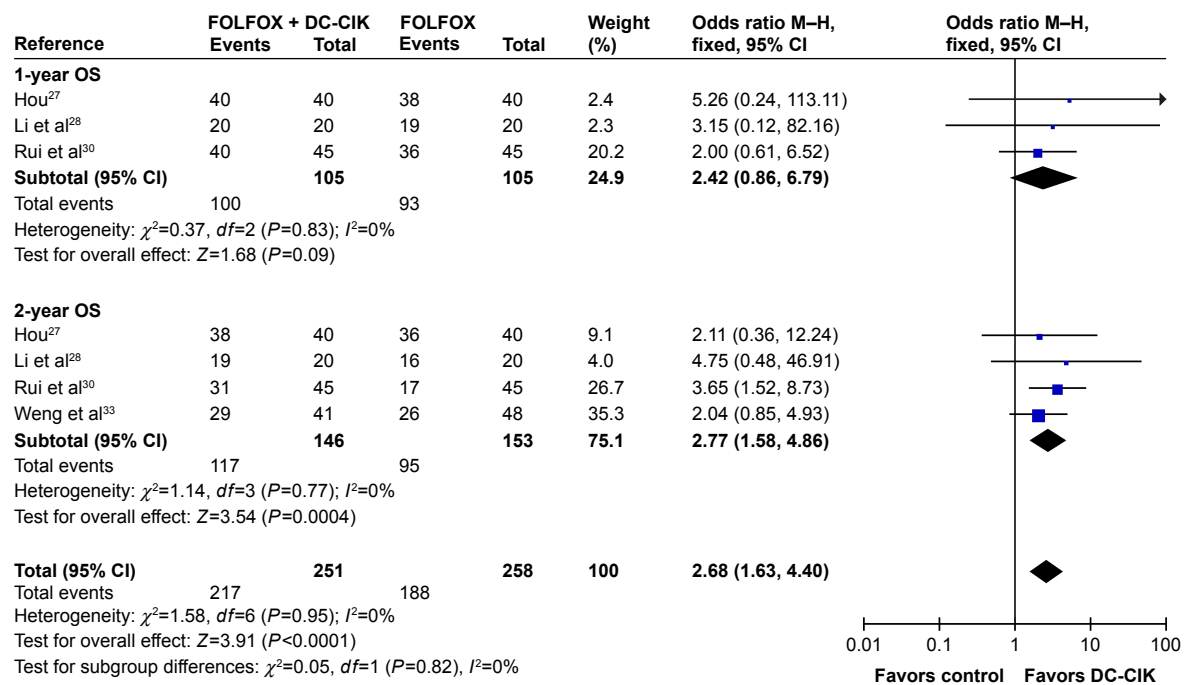


Figure 3 Forest plot of the comparison of OS between the patients who received FOLFOX + DC-CIK therapy and those who received FOLFOX alone. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

Abbreviations: OS, overall survival; FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; DC-CIK, dendritic cells and cytokine-induced killer cells; M–H, Mantel–Haenszel method; CI, confidence interval.

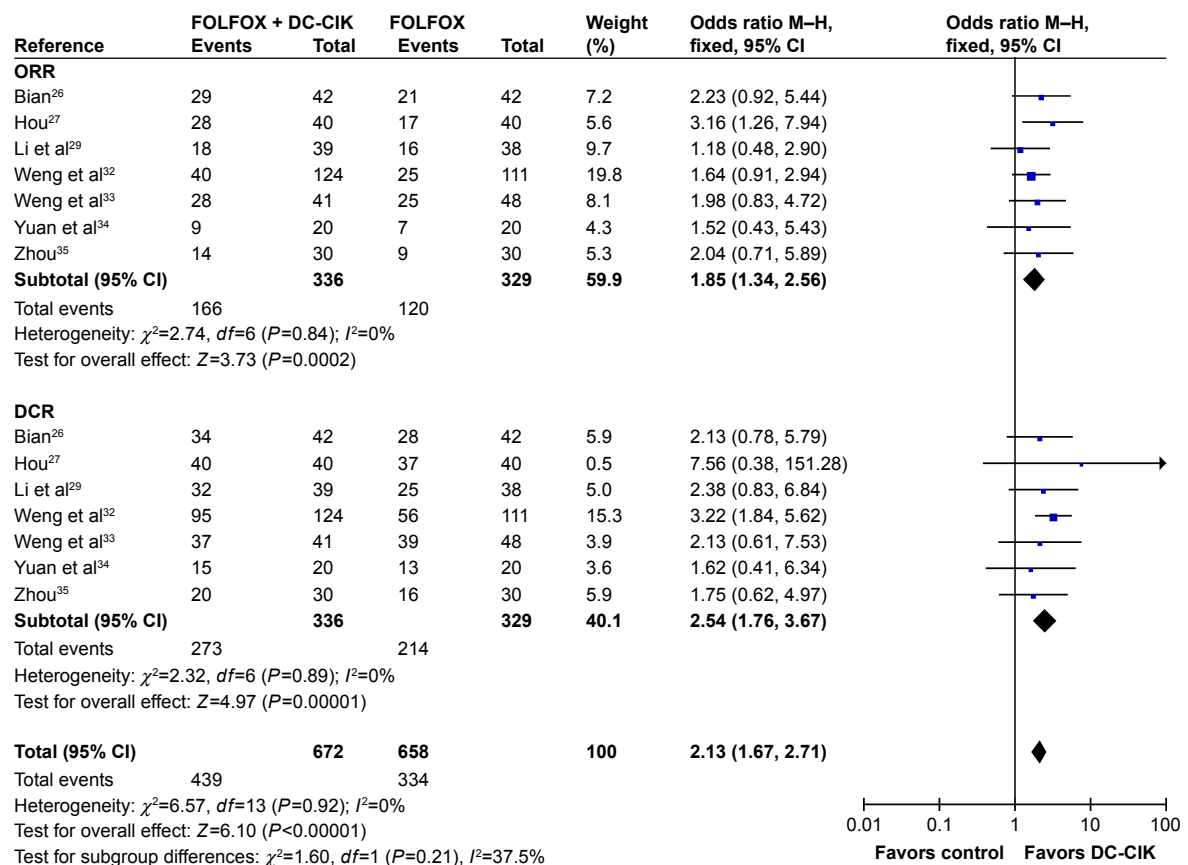


Figure 4 Forest plot of the comparison of ORR and DCR between the patients who received FOLFOX + DC-CIK therapy and those who received FOLFOX alone. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

Abbreviations: ORR, overall response rate; DCR, disease control rate; FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; DC-CIK, dendritic cells and cytokine-induced killer cells; M–H, Mantel–Haenszel method; CI, confidence interval.

Table 3 Comparison of CR, PR, SD, PD, ORR, and DCR between the FOLFOX + DC-CIK and FOLFOX-alone groups

Parameter	FOLFOX + DC-CIK	FOLFOX	Analysis method	Heterogeneity		Odds ratio	95% CI	P-value
	no of patients (n)	no of patients (n)		I ² (%)	P-value			
CR	295	281	Fixed	0	0.49	2.30	1.11–4.76	0.03
PR	295	281	Fixed	0	0.93	1.53	1.07–2.18	0.02
SD	295	281	Fixed	52	0.06	1.24	0.87–1.77	0.24
PD	295	281	Fixed	0	0.81	0.39	0.26–0.57	<0.00001
ORR	336	329	Fixed	0	0.84	1.85	1.34–2.56	0.0002
DCR	336	329	Fixed	0	0.89	2.54	1.76–3.67	<0.00001

Abbreviations: CR, complete response rate; PR, partial response rate; SD, stable disease rate; PD, progressive disease rate; ORR, overall response rate; DCR, disease control rate; FOLFOX + DC-CIK, oxaliplatin, 5-fluorouracil, and leucovorin + dendritic cells and cytokine-induced killer cells; FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; CI, confidence interval.

CI = 1.57–7.44, $P=0.003$; IL-2: OR = 1.88, CI = -0.46–3.30, $P=0.01$ (Figure 7), while no obvious changes were identified in the expression of IL-6 and TNF- α (IL-6: OR = -0.81, CI = -2.47 to 0.86, $P=0.34$; TNF- α : OR = 2.64, CI = -1.97 to 7.24, $P=0.26$).

Adverse events assessment

As shown in Figure 8, compared with patients treated by FOLFOX alone, those treated by FOLFOX and DC-CIK combined therapy suffered milder myelosuppression and gastrointestinal adverse reactions, but the combined therapy was not able to alleviate leucopenia, thrombocytopenia, nausea and vomiting, liver dysfunction, and peripheral neurotoxicity (myelosuppression: OR = 0.24, CI = 0.09–0.60, $P=0.002$; gastrointestinal adverse reaction: OR = 0.31, CI = 0.15–0.64, $P=0.001$; leucopenia: OR = 0.66, CI = 0.40–1.09, $P=0.11$;

thrombocytopenia: OR = 0.71, CI = 0.40–1.24, $P=0.23$; nausea and vomiting: OR = 0.77, CI = 0.44–1.34, $P=0.35$; liver dysfunction: OR = 0.83, CI = 0.41–1.67, $P=0.60$; peripheral neurotoxicity: OR = 0.27, CI = 0.06–1.15, $P=0.08$).

Discussion

To date, several clinical trials have been performed using chemotherapy plus DC-CIK immunotherapy for the treatment of CRC.^{20,21} However, the applied clinical protocols were unstandardized in these trials, which made therapeutic effects obscure for evaluation. In this study, a large number of comprehensive trials were investigated to achieve a higher statistical reliability. The meta-analysis revealed that the combination of FOLFOX regimen and DC-CIK immunotherapy improved OS, ORR, DCR, and immune function in CRC patients, without causing severe adverse events.

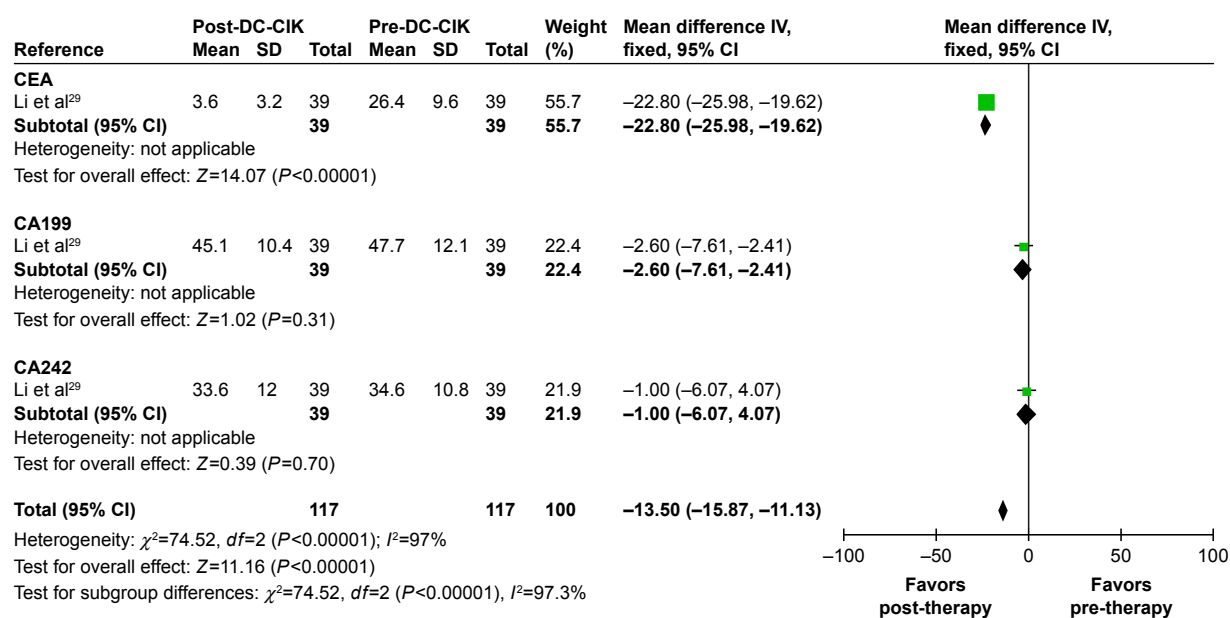


Figure 5 Forest plot of the comparison of tumor markers in pre- and post-DC-CIK immunotherapy. The patient data were obtained before (pre-DC-CIK) and after DC-CIK treatment (post-DC-CIK). The fixed-effects meta-analysis model (IV method) was used.

Abbreviations: DC-CIK, dendritic cells and cytokine-induced killer cells; SD, standard deviation; IV, inverse variance; CI, confidence interval; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242.

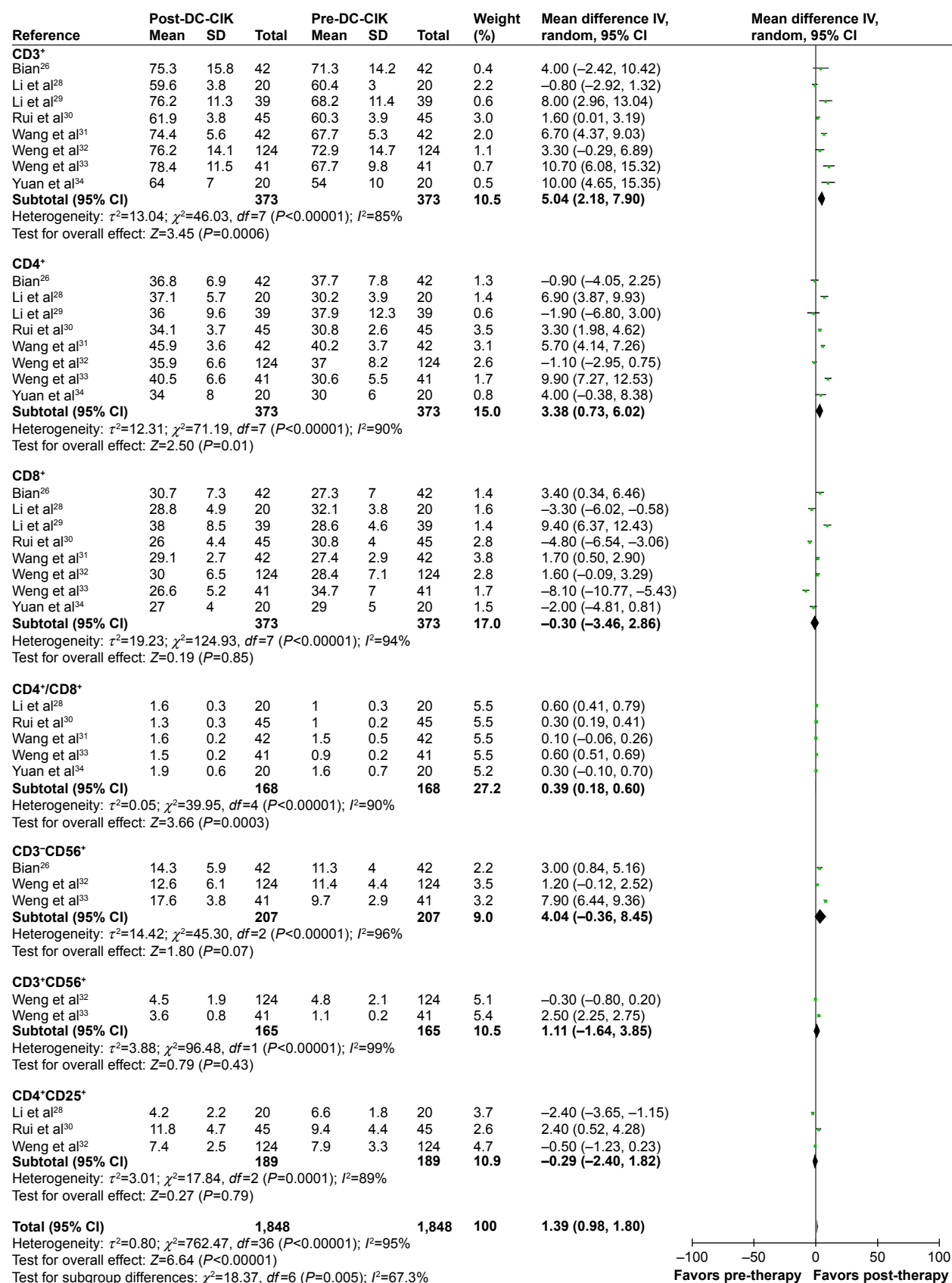


Figure 6 Forest plot of the comparison of immunophenotype in pre- and post-DC-CIK immunotherapy. The patient data were obtained before (pre-DC-CIK) and after DC-CIK treatment (post-DC-CIK). The random-effects meta-analysis model (IV method) was used.

Abbreviations: DC-CIK, dendritic cells and cytokine-induced killer cells; SD, standard deviation; IV, inverse variance; CI, confidence interval.

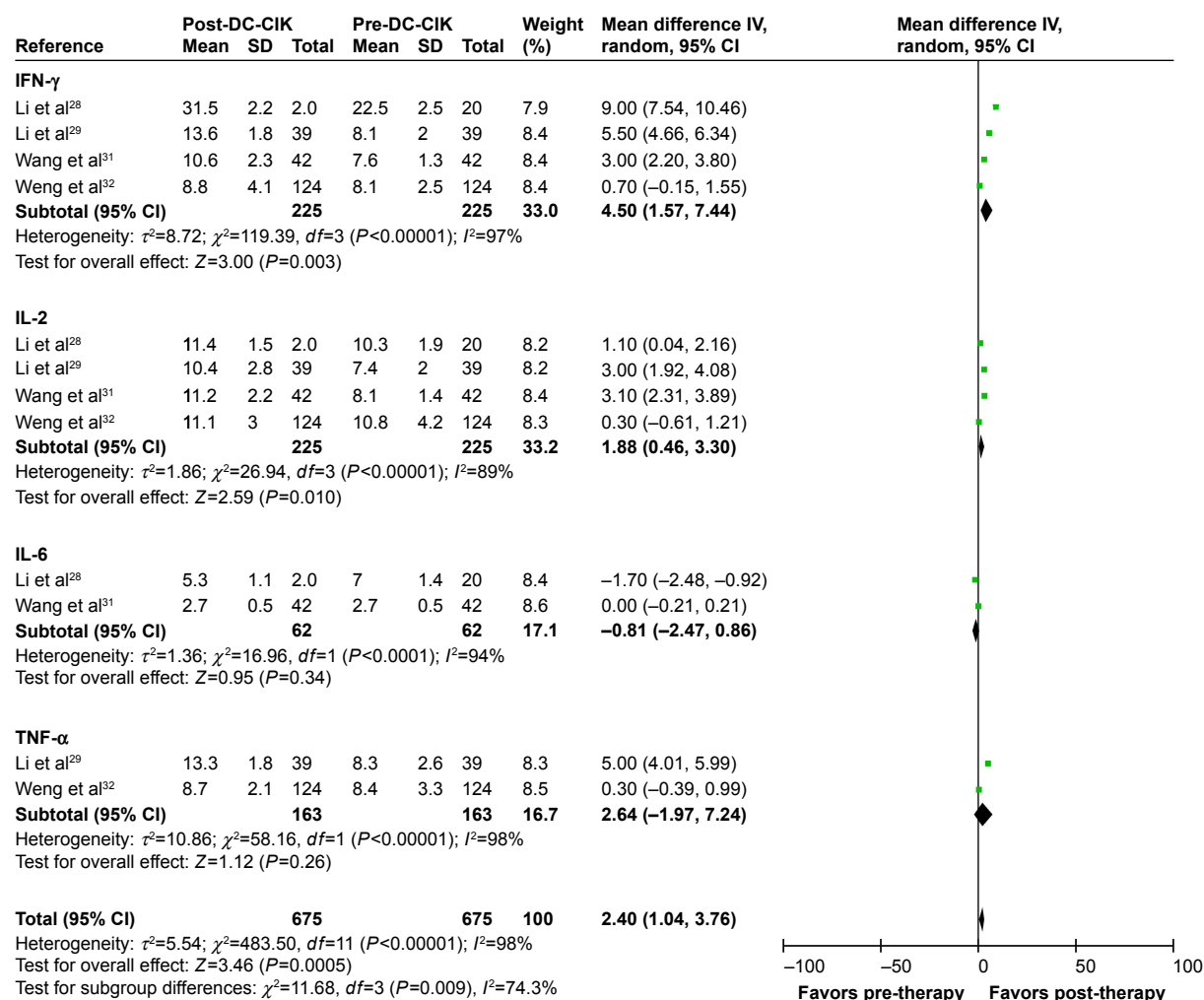


Figure 7 Forest plot of the comparison of cytokines in pre- and post-DC-CIK immunotherapy. The patient data were obtained before (pre-DC-CIK) and after DC-CIK treatment (post-DC-CIK). The random-effects meta-analysis model (IV method) was used.

Abbreviations: DC-CIK, dendritic cells and cytokine-induced killer cells; SD, standard deviation; IV, inverse variance; CI, confidence interval.

Safety is a key factor to be considered in clinical treatment. Patients in combination group showed milder adverse events than those treated by FOLFOX alone. FOLFOX caused myelosuppression and gastrointestinal adverse reactions which were alleviated by DC-CIK immunotherapy ($P<0.05$), but relief from other adverse events was not obtained. DC-CIK immunotherapy also enhanced the efficiency of FOLFOX in treating CRC. Compared to patients treated by FOLFOX alone, patients treated with combined therapy showed markedly increased 2-year OS, ORR, and DCR. Tumor markers, as the main factor for evaluation of therapeutic effects and prediction of recurrence and prognosis,^{36–39} also showed promising results with combined therapy. The levels of CEA, CA199, and CA242 were decreased after DC-CIK immunotherapy, although changes in the latter two were not statistically significant.

Immune reconstitution is important for treating malignancies.⁶ CD4⁺ T cells assist in the recruitment of

CD8⁺ T cells and activate macrophages through the secretion of immune-regulatory cytokines, including IL-2, IL-12, and IFN- γ , thereby inducing tumor cell death.^{6,40} This also indicates a synergistic relationship between CD4⁺ and CD8⁺ cells in immune responses.⁴⁰ It was found that the ratios of T-lymphocyte subsets were disordered in tumor patients.^{6,40} This analysis showed significantly increased percentages of CD3⁺ and CD4⁺ cells and CD4⁺/CD8⁺ ratio upon DC-CIK treatment, indicating that the immune function of CRC patients was improved upon DC-CIK immunotherapy. Moreover, the antitumor activity of immune cells was associated with higher percentages of CD3⁺CD56⁺ and CD3⁺CD56⁺ cells⁶ and lower percentages of CD4⁺CD25⁺ regulatory T cells.⁴¹ In this meta-analysis, no significant difference was found in the percentages of CD8⁺, CD3⁺CD56⁺, CD3⁺CD56⁺, and CD4⁺CD25⁺ T cells between pre- and post-immunotherapy. This may be related to the various DC-CIK transfusion dosages and different time points of lymphocyte

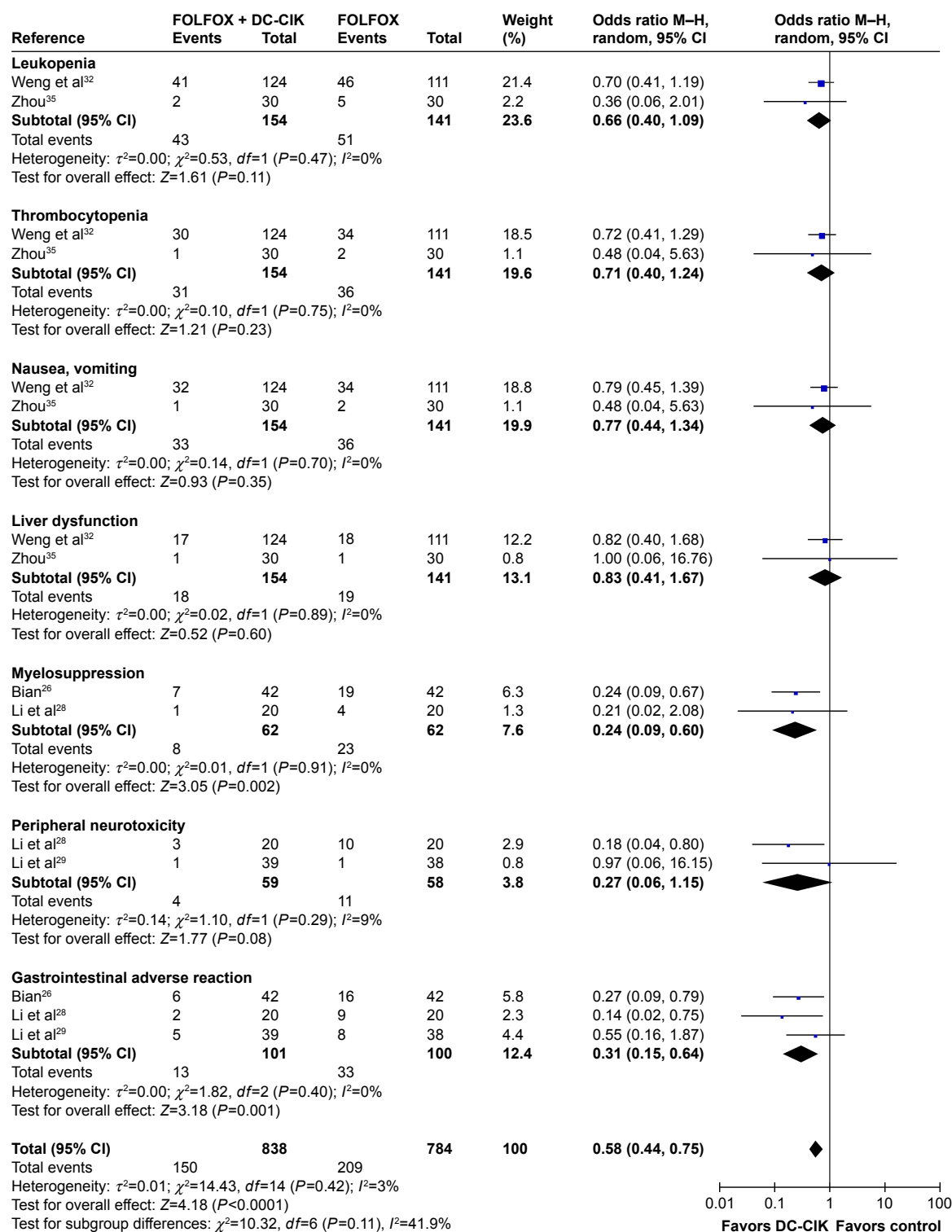


Figure 8 Forest plot of the comparison of adverse effects between the patients who received FOLFOX + DC-CIK therapy and those who received FOLFOX alone. The random-effects meta-analysis model (Mantel-Haenszel method) was used.

Abbreviations: FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; DC-CIK, dendritic cells and cytokine-induced killer cells; M-H, Mantel-Haenszel method; CI, confidence interval.

subset tests among these trials.⁸ Furthermore, the balance between Th1 and Th2 cells is crucial in immunotherapy.⁷ Th1 cytokines, including IFN- γ , IL-2, and TNF- α , enhance the cytotoxicity of CIK, whereas Th2 cytokines, such as IL-6

and IL-10, are associated with tumor immune escape.^{42,43} The present analysis showed that after DC-CIK immunotherapy, the levels of IFN- γ and IL-2 were significantly increased, whereas no significant differences were observed in TNF- α

and IL-6, indicating an important role of IFN- γ and IL-2 in DC-CIK immunotherapy.

Limitations

There are some limitations in our study. The 10 trials meeting the selection criteria were all conducted on a Chinese population. This may be because the large number of Chinese CRC patients has made CRC a research focus in China and led to there being many papers on it. Although the effectiveness of DC-CIK immunotherapy in various malignant tumors has been widely reported,^{44–46} its usage in CRC is still rare outside of China. One German trial was included in this meta-analysis originally, but it was excluded due to insufficient data.⁴⁷ We will keep up with the future research and carry out further analyses of studies conducted both in and outside of China. Moreover, this analysis did not go through an open external evaluation, which may have led to an overestimation of treatment effects. Finally, the different treatment dosages and cycles of DC-CIK immunotherapy may have led to different clinical responses,¹⁹ but we were not able to obtain accurate information from some of the involved trials. Due to the above-mentioned limitations of this meta-analysis, further studies are needed to verify the safety and efficacy of the combined therapy strategy.

Conclusion

Taken together, this study confirms that FOLFOX regimen plus DC-CIK immunotherapy is a safe and effective treatment for CRC patients. It markedly prolongs patient's survival time and improves the efficacy of CRC treatment by reconstructing the patient's immune system. Therefore, the combination of FOLFOX chemotherapy regimen and DC-CIK immunotherapy is a promising treatment option for CRC patients.

Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

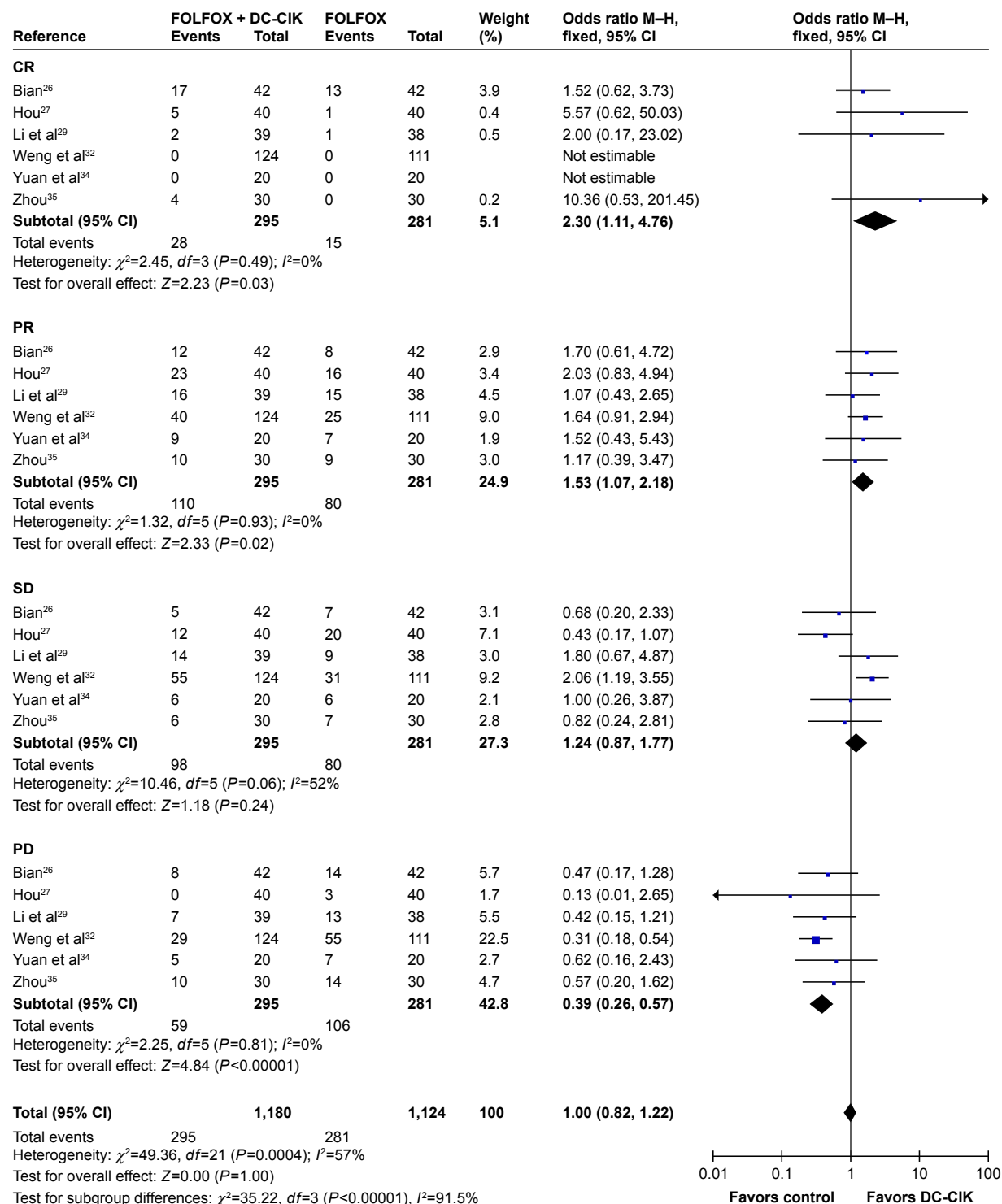


Figure S1 Forest plot of the comparison of CR, PR, SD, and PD between the patients who received FOLFOX + DC-CIK therapy and those who received FOLFOX alone. The fixed-effects meta-analysis model (Mantel-Haenszel method) was used.

Abbreviations: CR, complete response rate; PR, partial response rate; SD, stable disease rate; PD, progressive disease rate; FOLFOX, oxaliplatin, 5-fluorouracil, and leucovorin; DC-CIK, dendritic cells and cytokine-induced killer cells; M-H, Mantel-Haenszel method; CI, confidence interval.

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