

Research Article

The clinical efficacy and safety of kanglaite adjuvant therapy in the treatment of advanced hepatocellular carcinoma: a PRISMA-compliant meta-analysis

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Kanglaite, a type of Chinese medicine preparation, is considered a promising complementary therapy option for advanced hepatocellular carcinoma (HCC). Although an analysis of the published literature has been performed, the exact effects and safety are yet to be systematically investigated. Therefore, we conducted a wide-ranging online search of electronic databases to provide systematic conclusions; data from 31 trials with 2315 HCC patients were included. The results indicated that compared with conventional treatment (CT) alone, the combination of kanglaite with CT markedly prolonged patients' 6-month overall survival (OS, $P=0.003$), 12-month OS ($P<0.0001$), 18-month OS ($P=0.003$), 24-month OS ($P=0.03$) and 36-month OS ($P=0.0006$) and significantly improved the overall response rate (odds ratio (OR) = 2.57, 95% confidence interval (CI) = 2.10–3.16, $P<0.00001$) and disease control rate (OR = 3.10, 95% CI = 2.42–3.97, $P<0.00001$) of patients. The quality of life (QoL), clinical symptoms and immune function of patients were also obviously improved after combined treatment. The incidence rates of nausea and vomiting ($P=0.04$), hepatotoxicity ($P=0.0002$), leukopenia ($P<0.00001$), thrombocytopenia ($P<0.0001$), gastrointestinal side effects ($P=0.01$) and fever ($P<0.0009$) were lower in the group receiving CT and kanglaite than in the group receiving CT alone. In summary, the combination of kanglaite and CT is safe and more effective in treating HCC than is CT alone, and its application in the clinic is worth promoting.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths, and in 2018, 781631 deaths worldwide were attributed to HCC [1]. Recently, the incidence of HCC has significantly increased, with approximately 840000 new cases every year [1]. China is a high-risk region for HCC, with the deaths caused by HCC in this country accounting for approximately 50% of HCC-related deaths worldwide [2]. HCC is a fatal disease with a poor prognosis. Despite the development of diagnostic methods, early detection of HCC remains difficult [3,4]. In most patients, HCC progresses to an advanced stage, with a 5-year survival rate of less than 20% [3]. Surgery and liver transplantation are regarded as the optimal treatment options, but only a small proportion of HCC patients can undergo potentially curative resection [3,4]. In addition, the therapeutic effects of current conventional treatment (CT), such as radiotherapy and chemotherapy for advanced HCC, are still unsatisfactory [3–5]. Therefore, effective comprehensive therapeutic approaches should be developed.

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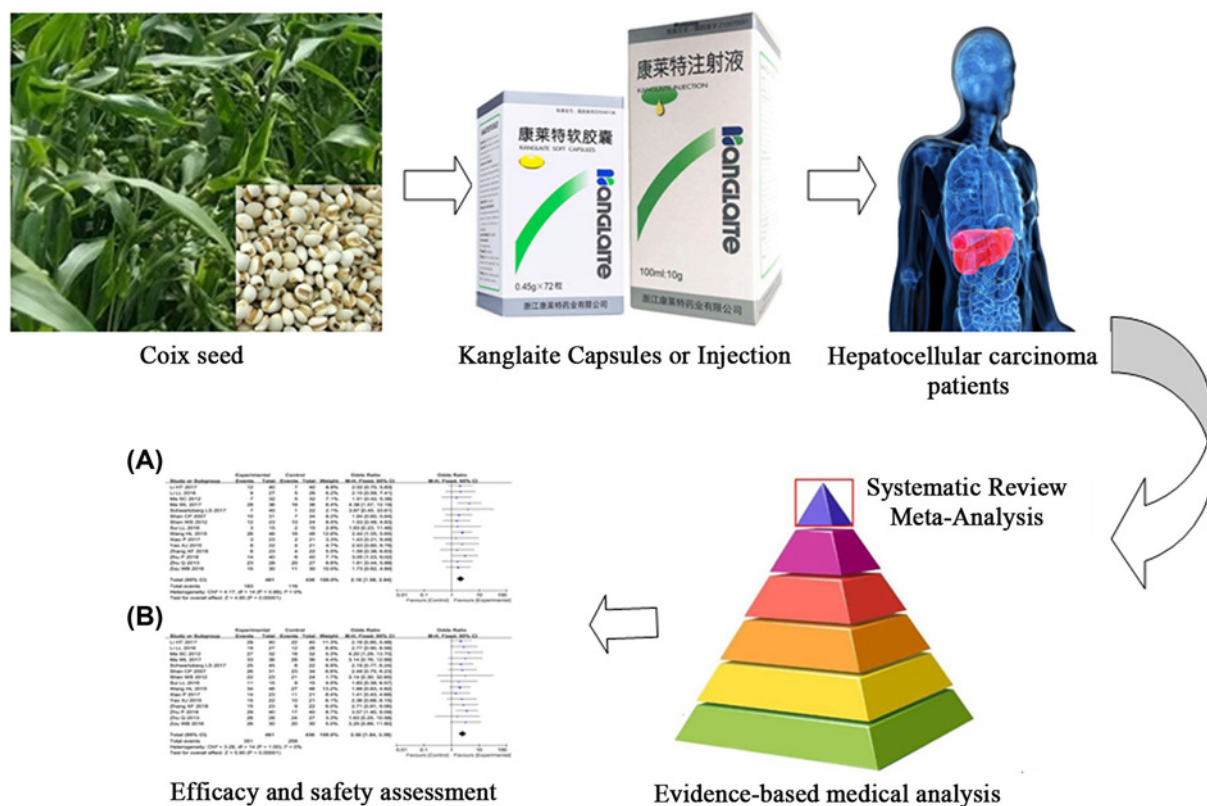


Figure 1. Work flow of the present study
 (A) Efficacy (B) Safety.

Traditional Chinese medicine has been widely applied as an effective complementary medicine for cancer treatment [5,6]. Kanglaite is an extract from Coix seeds, the main active ingredient of which is a triglyceride containing four types of fatty acids [7,8]. Kanglaite was formally approved in 1997 by the Ministry of Health of China for the treatment of malignancies such as HCC, non-small cell lung cancer (NSCLC) and pancreatic cancer (PC) [7,9,10]. Millions of cancer patients in numerous hospitals in China have been treated with kanglaite [7]. Moreover, kanglaite has shown good clinical efficacy in the U.S.A. It is also the first traditional Chinese medicine preparation approved by the U.S. Food and Drug Administration (FDA) for inclusion in clinical trials [11]. Yang et al. [8] demonstrated that kanglaite can effectively reverse the multidrug resistance (MDR) of human HCC and enhance the sensitivity of tumor cells to chemotherapeutic drugs by inducing apoptosis and cell cycle arrest via the PI3K/AKT pathway. Moreover, Huang et al. [12]. found that kanglaite can inhibit HepG2 cell transplantation-induced tumor growth by stimulating anticancer immune responses. In addition, kanglaite can induce cancer cell apoptosis by activating proapoptotic factors, such as p53, Fas and caspase-3 [13,14].

Several studies have indicated that CT combined with kanglaite exhibits more prominent therapeutic effects for advanced HCC than does CT alone [10]. In a meta-analysis comparing hepatic arterial intervention combined with kanglaite and hepatic arterial intervention alone, the former had a significantly higher overall response rate (ORR), though the outcomes discussed were not complete. In fact, overall survival (OS), the disease control rate (DCR), quality of life (QoL), clinical symptoms, immune function and safety were not considered in that analysis [10]. Moreover, the small sample size included may have influenced the analysis of therapeutic effects. Therefore, in the present study, we conducted an up-to-date meta-analysis to investigate the clinical efficacy and safety of CT combined with kanglaite in comparison with CT alone for the treatment of advanced HCC (Figure 1) to provide a scientific basis for the design of future clinical trials.

Materials and methods

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines and Cochrane Handbook. Ethical approval was not necessary because the present study was a meta-analysis.

Search strategy and selection criteria

Nine electronic databases, namely, PubMed, Cochrane Library, Web of Science, Embase, Medline, China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biological Medicine Database (CBM), were searched up to May 2019 using the key terms ‘kanglaite’ or ‘kanglaite injection’ or ‘kanglaite capsule’ or ‘coix seed capsule’ or ‘coix seed injection’ combined with ‘hepatocellular carcinoma’ or ‘hepatocellular cancer’ or ‘hepatocellular tumor’ or ‘liver carcinoma’ or ‘liver cancer’ or ‘hepatocellular tumor’ (Supplementary Table S1).

The inclusion criteria were as follows: (1) controlled trials with advanced HCC patients; (2) studies involving more than 30 HCC patients; (3) studies comparing the clinical outcomes of CT plus kanglaite adjuvant therapy (experimental group) with those of CT alone (control group); and (4) the CT included transcatheter arterial chemoembolization (TACE), transhepatic arterial embolization (TAE), chemotherapy, stereotactic radiotherapy (SRT), support and symptomatic treatment (SST) and targeted therapy.

The exclusion criteria were as follows: (1) patients with mixed malignancies; (2) articles without sufficient available data; and (3) noncontrast articles, case studies and review papers.

Data extraction and quality assessment

Data were independently extracted by two reviewers (Jingjing Liu and Xueni Liu) according to the above inclusion and exclusion criteria; disagreements were adjudicated by the third investigator (Chao Xu). The data extracted comprised the following items: (a) the first author’s name; (b) year of publication; (c) tumor stages or Karnofsky performance score (KPS); (d) number of cases; (e) therapeutic regimens; (f) dosage of kanglaite; and (g) study parameters. To ensure the quality of the meta-analysis, the quality of the included randomized and nonrandomized controlled trials was evaluated according to the Cochrane Handbook tool [15] and Methodological Index for Nonrandomized Studies (MINORS, Supplementary Table S2), respectively [16].

Outcome definition

The clinical responses assessed included treatment efficacy, QoL, clinical symptoms, immune function and adverse events. Treatment efficacy was evaluated in terms of the OS rate, ORR and DCR. QoL was assessed using the KPS scale. The clinical symptoms of the patients included the following indicators: appetite, hepatalgia, abdominal distension, fatigue and jaundice. Immune function indicators (percentages of CD3⁺, CD4⁺, CD8⁺ and NK cells and the CD4⁺/CD8⁺ ratio) and the decrease rate of α -fetoprotein (AFP) in HCC patients were determined and compared between the kanglaite and nonkanglaite groups. Adverse events, including nausea and vomiting, hepatotoxicity, nephrotoxicity, leukopenia, thrombocytopenia gastrointestinal adverse effects, anemia, fever, myelosuppression and alopecia, were also assessed.

Statistical analysis

Statistical analysis was performed with RevMan 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 13.0 (Stata Corp., College Station, TX, U.S.A.) software. All data are expressed as odds ratios (ORs) and 95% confidence intervals (CIs), and $P < 0.05$ indicated a significant difference. Heterogeneity among the studies was assessed by Cochran’s Q test; $I^2 < 50\%$ or $P > 0.1$ indicated a lack of heterogeneity among the studies [17]. When the level of heterogeneity was small ($I^2 < 50\%$), a fixed-effects model was applied for OR estimation; otherwise, a random-effects model was selected.

Publication bias was analyzed with Begg’s and Egger’s regression tests, and the results are presented in funnel plots. Pooled analysis of publication bias determined that the trim-and-fill method should be applied to coordinate the estimates from unpublished studies; the adjusted results were compared with the original pooled OR [18,19]. Sensitivity analysis was conducted to evaluate the impacts of different therapeutic regimens, kanglaite dosages, sample sizes and research types on clinical efficacy.

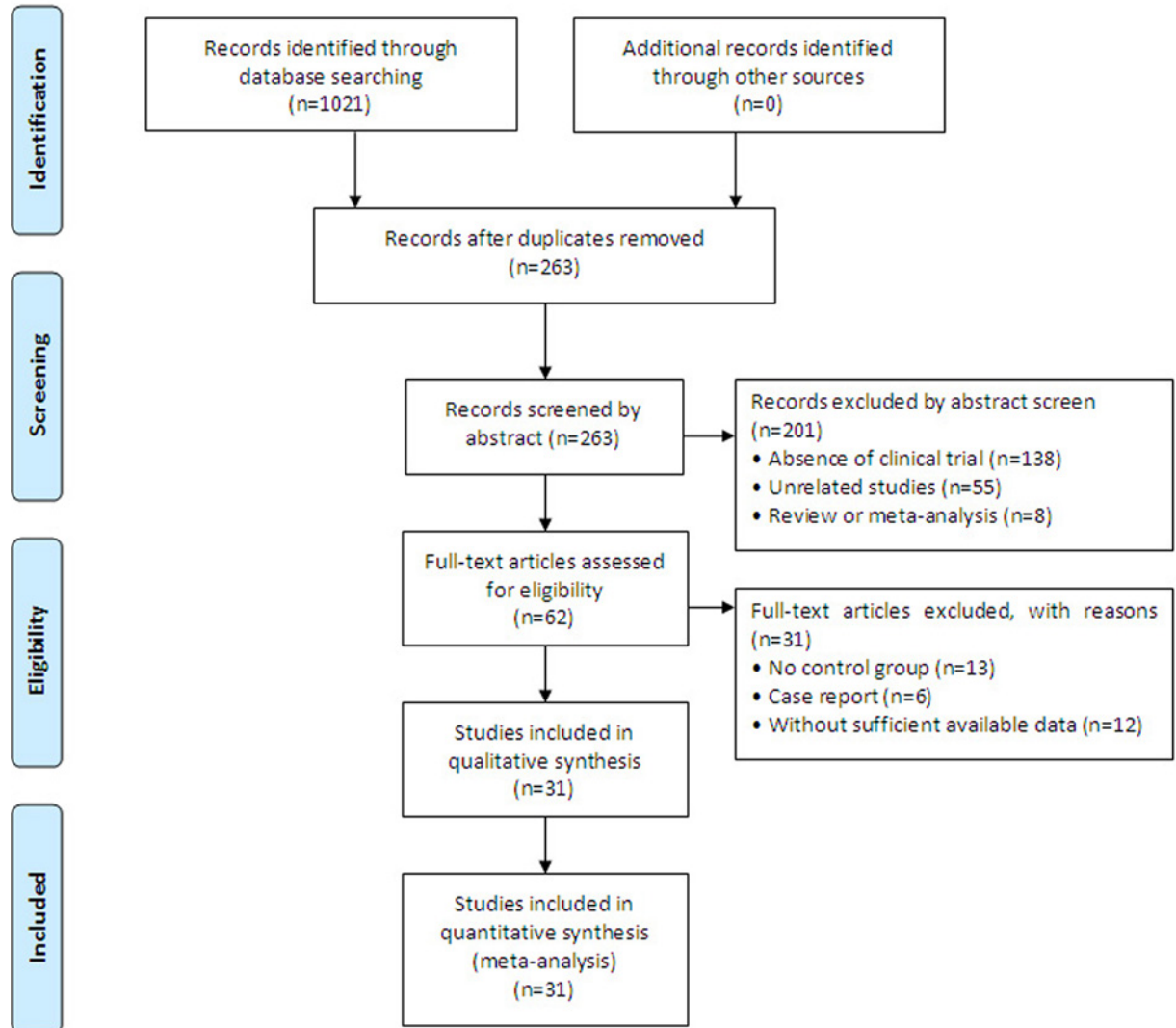


Figure 2. Study selection process for the meta-analysis

Results

Search results

In total, 1021 articles were initially identified. Of those, 758 papers were excluded because they were duplicates. After title and abstract review, 201 articles were further excluded because they were not clinical trials ($n=138$), were unrelated studies ($n=55$), or were reviews or meta-analyses ($n=8$), leaving 62 studies that were potentially relevant. After a detailed assessment of the full text articles, those without a control group ($n=13$), studies that were case reports ($n=6$), and trials with insufficient data ($n=12$) were excluded. Ultimately, 31 trials [20–50] involving 2315 advanced HCC patients were included in this analysis (Figure 2).

Patient characteristics

All included trials were performed in different medical centers in China. In total, 1219 advanced HCC patients were treated with CT combined with kanglaite adjuvant therapy; 1096 patients were treated with CT alone. All included trials except one [27] clearly stated the dosage of kanglaite administered. Detailed information on the involved studies and HCC patients is shown in Table 1. The kanglaite used was manufactured by Zhejiang Kanglaite Pharmaceutical Co., Ltd. The Quality Standards of kanglaite in the present study were approved by the Chinese State Food and Drug Administration (SFDA) and were granted a Manufacturing Approve Number issued by Chinese SFDA (Z20040138

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

Included studies	Tumor stage/KPS	Patients Con/Exp	Therapeutic regimen		Dosage of kanglaite	Parameter types
			Experimental	Control (drugs)		
Ao, M. (2017)	≥60	38/38	Con+ kanglaite ¹	TACE (DDP, 5-Fu, E-ADM)	20 g/time, 1 time/day	ORR, DCR, AE
Feng, Y.Z. (2001)	II–IV	21/11	Con+KLT ¹	TAE	20 g/time, 1 time/day	ORR, DCR, IF
Hu, J.B. (2003)	II–IV	25/31	Con+KLT ¹	TACE (DDP, 5-Fu, THP)	20 g/time, 1 time/day	ORR, DCR, AE, CS, AFP, QoL
Jiang, Y.B. (2006)	I–III	51/105	Con+KLT ¹	TACE (DDP, 5-Fu, ADM)	20 g/time, 1 time/day	ORR, DCR, CS, QoL
Li, D.J. (2009)	II–III	32/30	Con+KLT ²	TACE (DDP, 5-Fu, ADM)	2.7 g/time, 4 times/day	OS, ORR, DCR, AE, AFP, QoL
Li, M. (2015)	II–III	23/24	Con+KLT ¹	CT (Oxaliplatin)	20 g/time, 1 time/day	OS, ORR, DCR, IF, CS, QoL
Li, Y. (2014)	I–IV	75/75	Con+KLT ¹	CT (Meccnu, ADM, 5-Fu)	20 g/time, 1 time/day	OS, ORR, DCR, AE, QoL
Liang, S.M. (2006)	II–III	25/31	Con+KLT ¹	TAE	unknown	ORR, DCR, CS, AFP
Lu, D.P. (2017)	Unknown	43/51	Con+KLT ¹	TACE (Oxaliplatin, 5-Fu)	20 g/time, 1 time/day	OS, ORR, DCR, QoL
Lu, H. (2006)	I–III	24/24	Con+KLT ¹	TACE (DDP, 5-Fu, MMC)	20 g/time, 1 time/day	OS, ORR, DCR, AE, QoL
Lv, D.Z. (2004)	II–III	38/38	Con+KLT ¹	TACE (unknown), SST	20 g/time, 1 time/day	IF, CS, QoL
Ma, W.L. (2017)	Unknown	43/43	Con+KLT ¹	CT (FOLFOX)	20 g/time, 1 time/day	ORR, DCR, IF
Qin, G.Y. (1998)	Unknown	20/18	Con+KLT ¹	TACE (DDP, 5-Fu, THP)	10–20 g/time, 1 time/day	ORR, DCR, CS
Qin, Y.T. (2001)	Unknown	42/52	Con+KLT ¹	SST	20 g/time, 1 time/day	IF
Shao, L. (2017)	II–III	25/25	Con+KLT ¹	SRT	20 g/time, 1 time/day	ORR, AE, QoL
Wang, C.H. (2001)	I–III	50/50	Con+KLT ¹	TACE (DDP, ADM, HCPT)	10 g/time, 1 time/day	ORR, DCR
Wang, X.F. (2012)	III–IV	24/34	Con+KLT ¹	TACE (unknown) FOLFOX	10 g/time, 1 time/day	ORR, AE, QoL
Wei, Q.C. (2009)	Unknown	24/24	Con+KLT ¹	SST	10 g/time, 1 time/day	QoL
Wu, D.H. (2009)	II–III	30/30	Con+KLT ¹	CT (Oxaliplatin, FUDR)	20 g/time, 1 time/day	ORR, DCR, AE, CS, QoL
Wu, J.L. (2015)	Unknown	60/60	Con+KLT ¹	TACE (unknown)	10 g/time, 1 time/day	ORR, DCR, QoL
Xi, D.S. (2001)	I–III	20/20	Con+KLT ¹	CT (E-ADM, 5-Fu, HCPT, ACTD)	20 g/time, 1 time/day	ORR, DCR, AE
Xu, J. (2018)	Unknown	54/54	Con+KLT ¹	CT (Meccnu, ADM, 5-Fu)	20 g/time, 1 time/day	ORR, DCR
Xu, X.H. (2010)	II–III	37/38	Con+KLT ¹	CT (Capecitabine)	20 g/time, 1 time/day	OS, ORR, DCR, AE, CS
Yang, T. (2013)	≥60	30/60	Con+KLT ¹	TACE (DDP, 5-Fu, E-ADM)	10 g/time, 1 time/day	ORR, DCR, AE, CS, QoL
Ye, X. (2003)	III–IV	17/19	Con+KLT ¹	TACE (DDP, 5-Fu, ADM, MMC)	20 g/time, 1 time/day	ORR, DCR, AE, CS, AFP, QoL
Yin, R.R. (2009)	Unknown	32/40	Con+KLT ¹	TACE (unknown)	10 g/time, 1 time/day	ORR, DCR
Yu, Z.H. (2016)	≥50	20/20	Con+KLT ¹	Thalidomide	20 g/time, 1 time/day	OS, ORR, DCR, AE, QoL
Zhang, Y. (2012)	>50	31/31	Con+KLT ¹	SST	10 g/time, 1 time/day	AFP, QoL
Zhang, Y.J. (2017)	II–III	48/49	Con+KLT ¹	TACE (DDP, 5-Fu, ADM, MMC)	20 g/time, 1 time/day	ORR, DCR, AE, AFP, QoL
Zhou, S.F. (2018)	III–IV	54/54	Con+KLT ¹	Sorafenib	20 g/time, 1 time/day	ORR, DCR, IF
Zhu, X.F. (2006)	I–IV	40/40	Con+KLT ¹	TACE (DDP, 5-Fu, THP)	20 g/time, 1 time/day	ORR, DCR, CS, QoL

Con, control group (CTs alone group); Exp, experimental group (CTs and kanglaite group). Abbreviations: ACTD, actinomycin D; ADM, adriamycin; AE, adverse event; CF, calcium folinate; CS, clinical symptom; DDP, cisplatin; E-ADM, epirubicin; FOLFOX, oxaliplatin+CF+5-Fu; HCPT, hydroxy-camptothecin; IF, immune function; MMC, mitomycin C; ORR, overall response rate; THP, pirarubicin; 5-Fu, 5-Fluorouracil.

¹Kanglaite injection.

²Kanglaite capsules.

and Z10970091). All pharmaceutical companies involved followed the quality processing procedure outlined in Chinese Pharmacopeia.

Quality assessment

The quality assessment of the risk of bias is shown in Figure 3 and Supplementary Table S3. The results showed that the literature recruited in the present study was of good quality.

Therapeutic efficacy assessments

As shown in Figures 4–6, pooled results showed that compared with those who underwent CT alone, patients who underwent combined therapy had significantly improved 6-, 12-, 18-, 24- and 36-month OS (6-month OS: OR = 2.85, 95% CI = 1.42–5.71, $P=0.003$; 12-month OS: OR = 2.25, 95% CI = 1.51–3.36, $P<0.0001$; 18-month OS: OR =

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ao M 2017	+	+	+	+	+	+	+
Feng YZ 2001	+	+	+	+	+	+	+
Hu JB 2003	+	+	+	+	+	+	+
Jiang YB 2006	+	+	+	+	+	+	+
Liang SM 2006	+	+	+	+	+	+	+
Lu DJ 2009	+	+	+	+	+	+	+
Li Y 2014	+	+	+	+	+	+	+
Lu DP 2017	+	+	+	+	+	+	+
Lu H 2006	+	+	+	+	+	+	+
Lv DZ 2004	+	+	+	+	+	+	+
Ma WL 2017	+	+	+	+	+	+	+
Shao L 2017	+	+	+	+	+	+	+
Wang CH 2001	+	+	+	+	+	+	+
Wang XF 2012	+	+	+	+	+	+	+
Wu DH 2009	+	+	+	+	+	+	+
Xi DS 2001	+	+	+	+	+	+	+
Xu XH 2010	+	+	+	+	+	+	+
Yang T 2013	+	+	+	+	+	+	+
Ye X 2003	+	+	+	+	+	+	+
Yu ZH 2016	+	+	+	+	+	+	+
Zhang Y 2012	+	+	+	+	+	+	+
Zhang YJ 2017	+	+	+	+	+	+	+
Zhou SF 2018	+	+	+	+	+	+	+
Zhu XF 2006	+	+	+	+	+	+	+

Figure 3. Risk of bias summary: review of the authors' judgments about each risk of bias item for the included randomized controlled studies

Each color represents a different level of bias: red indicates high risk, green indicates low risk and yellow indicates an unclear risk of bias.

3.52, 95% CI = 1.54–8.09, $P=0.003$; 24-month OS: OR = 10.96, 95% CI = 1.33–90.60, $P=0.03$; 36-month OS: OR = 2.70, 95% CI = 1.53–4.75, $P=0.0006$, ORR (OR = 2.57, 95% CI = 2.10–3.16, $P<0.00001$) and DCR (OR = 3.10, 95% CI = 2.42–3.97, $P<0.00001$). Fixed-effect models were applied to analyze the OR rate because of the low degree of heterogeneity.

Detection of AFP

Six clinical trials [22,24,27,44,47,48] with 369 patients reported data on the AFP decrease rate between the two groups. As shown in Figure 7, the AFP decrease rate was significantly lower in patients receiving the combination treatment than in those receiving the CT alone (OR = 2.74, 95% CI = 1.70–4.41, $P<0.0001$). As no obvious heterogeneity was found among the included articles, a fixed-effects model was used to pool data.

QoL assessment

Nineteen trials [23–26,28–30,34,36–39,42–44,46–48,50] with 1449 patients reported QoL according to the KPS scale (Figure 8). According to the results, the QoL of HCC patients in the combined group was significantly better than that of patients in the control group (OR = 3.80, 95% CI = 3.01–4.80, $P<0.00001$). A fixed-effect model was used due to the low level of heterogeneity.

Assessment of clinical symptoms

The clinical symptoms of HCC patients receiving combined therapy were significantly improved compared with those of patients treated with CT alone (Supplementary Figure S1, OR = 5.36, 95% CI = 3.21–8.94, $P<0.00001$), as indicated by increased appetite and reductions in hepatalgia, abdominal distension, fatigue and jaundice (Supplementary Figure S1, appetite: OR = 5.50, 95% CI = 1.72–17.61, $P=0.004$; hepatalgia: OR = 2.95, 95% CI = 1.74–5.00, $P<0.0001$; abdominal distension: OR = 3.52, 95% CI = 1.33–9.31, $P=0.01$; fatigue: OR = 4.60, 95% CI = 1.89–11.22, $P=0.0008$; jaundice: OR = 1.42, 95% CI = 0.41–4.95, $P=0.59$), though the improvement in jaundice was not significant.

Immune function evaluation

The immune status of patients between kanglaite and nonkanglaite groups was examined in six controlled studies [21,25,30,31,33,49]. As presented in Figure 9, the percentages of CD3⁺, CD4⁺ and CD8⁺ cells and the CD4⁺/CD8⁺ ratio were significantly higher in the combined treatment group than in the control group (CD3⁺: OR = 9.12, 95% CI = 6.69–11.56, $P<0.00001$; CD4⁺: OR = 7.01, 95% CI = 4.32–9.69, $P<0.00001$; CD8⁺: OR = 0.99, 95% CI = 0.23–1.76, $P=0.01$; CD4⁺/CD8⁺: OR = 0.33, 95% CI = 0.19–0.47, $P<0.00001$). However, the proportions of NK (CD3⁻CD56⁺) cells did not differ significantly between the two groups (OR = 13.16, 95% CI = -3.25–29.56, $P=0.12$). The percentage of CD8⁺ cells was not heterogeneous among the studies; thus, a fixed-effect model was used to analyze the OR. Otherwise, random-effects models were used.

Assessment of adverse events

As shown in Table 2 and Supplementary Figure S2, compared with patients treated with CT alone, those treated

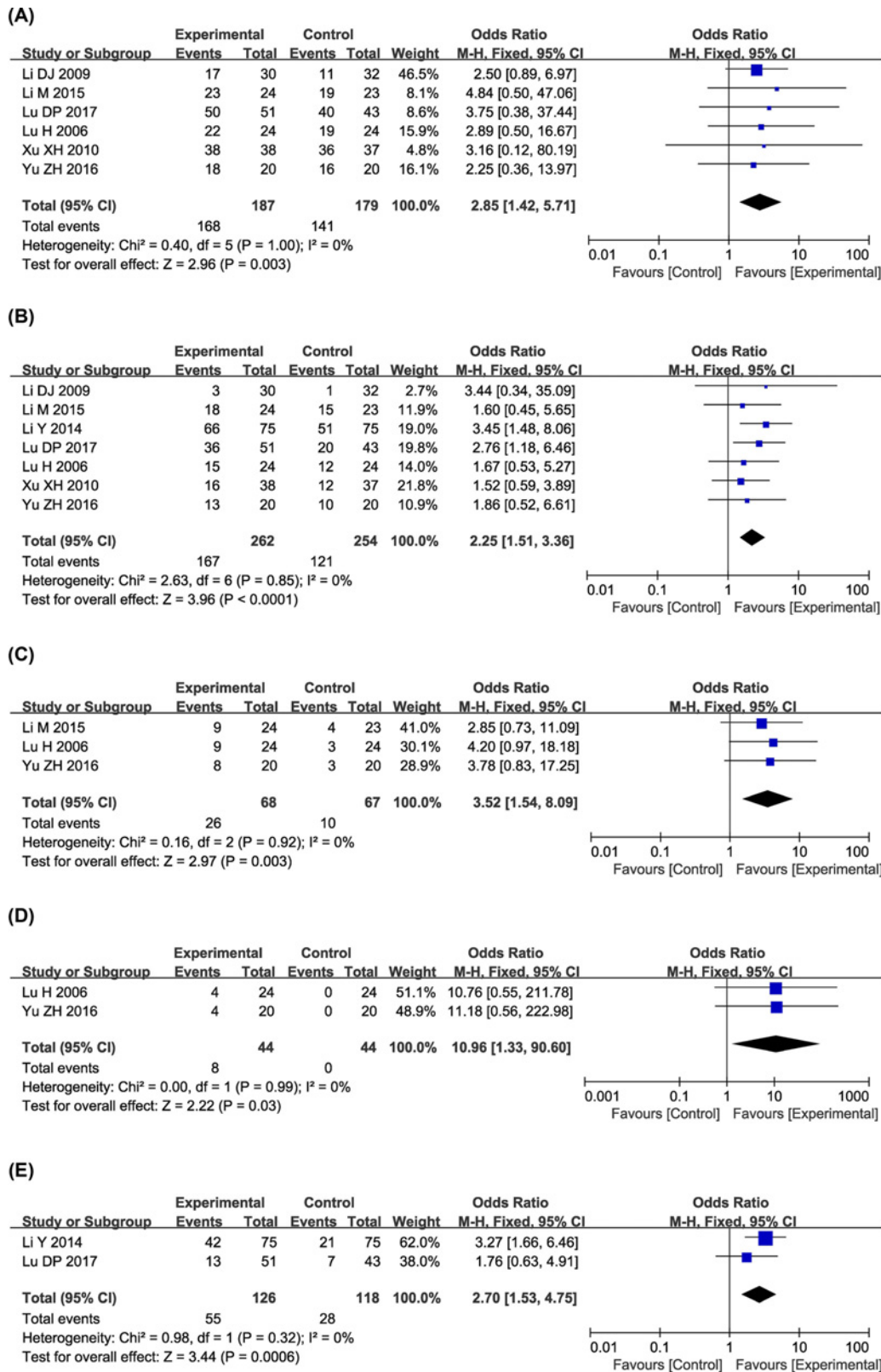


Figure 4. Comparisons of OS between control and experimental group

Forest plot of the comparison of 6-month (A); 12-month (B); 18-month (C); 24-month (D); and 36-month (E), OS between the experimental and control groups. Control group, CT alone group; experimental group, CTs and kanglaite group. A fixed effects meta-analysis model (Mantel–Haenszel method) was used.

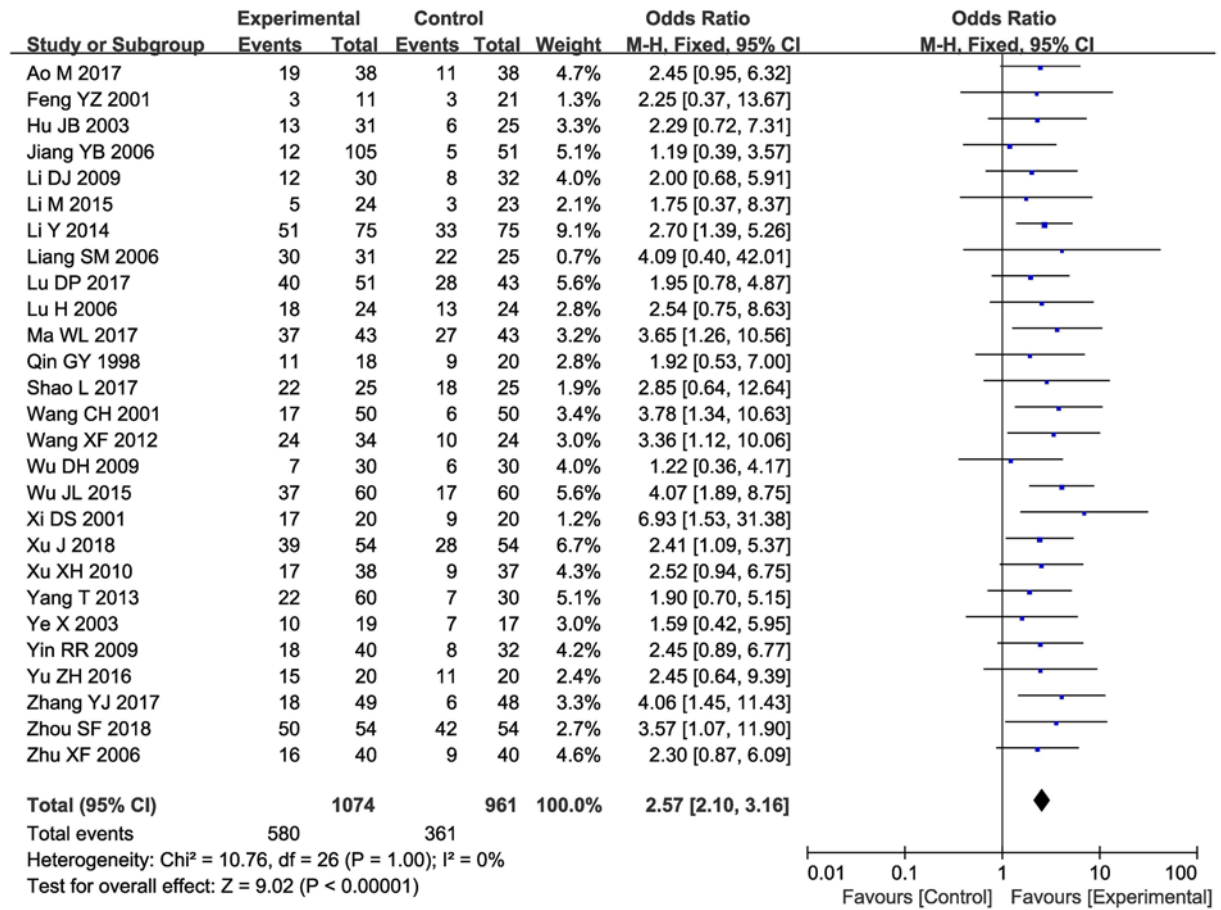


Figure 5. Forest plot of the comparison of overall response rates between the experimental and control groups
 Control group, CTs alone group; experimental group, CTs and kanglaite group. A fixed effects meta-analysis model (Mantel-Haenszel method) was used.

Table 2 Comparison of adverse events between the experimental and control groups

Adverse events	Experimental group	Control group	Analysis method	Heterogeneity		OR	95% CI	P-value
	Number of patients (n) ref	Number of patients (n) ref		I ² (%)	P-value			
Nausea and vomiting	291	281	Fixed	0	0.53	0.62	0.39–0.97	0.04
Hepatotoxicity	217	201	Fixed	0	0.70	0.40	0.25–0.66	0.0002
Nephrotoxicity	90	82	Fixed	—	—	0.16	0.01–3.56	0.25
Leukopenia	164	155	Fixed	0	0.94	0.28	0.17–0.47	<0.00001
Thrombocytopenia	150	144	Fixed	0	0.79	0.21	0.10–0.42	<0.0001
Gastrointestinal adverse effects	185	152	Fixed	0	0.64	0.43	0.22–0.84	0.01
Anemia	71	65	Fixed	0	0.64	0.75	0.33–1.73	0.50
Fever	98	97	Fixed	10	0.33	0.37	0.20–0.66	0.0009
Myelosuppression	135	105	Fixed	0	0.71	0.64	0.34–1.19	0.16
Alopecia	129	129	Fixed	0	0.72	0.64	0.34–1.24	0.19

Control group, CTs alone group; Experimental group, CTs and kanglaite group.

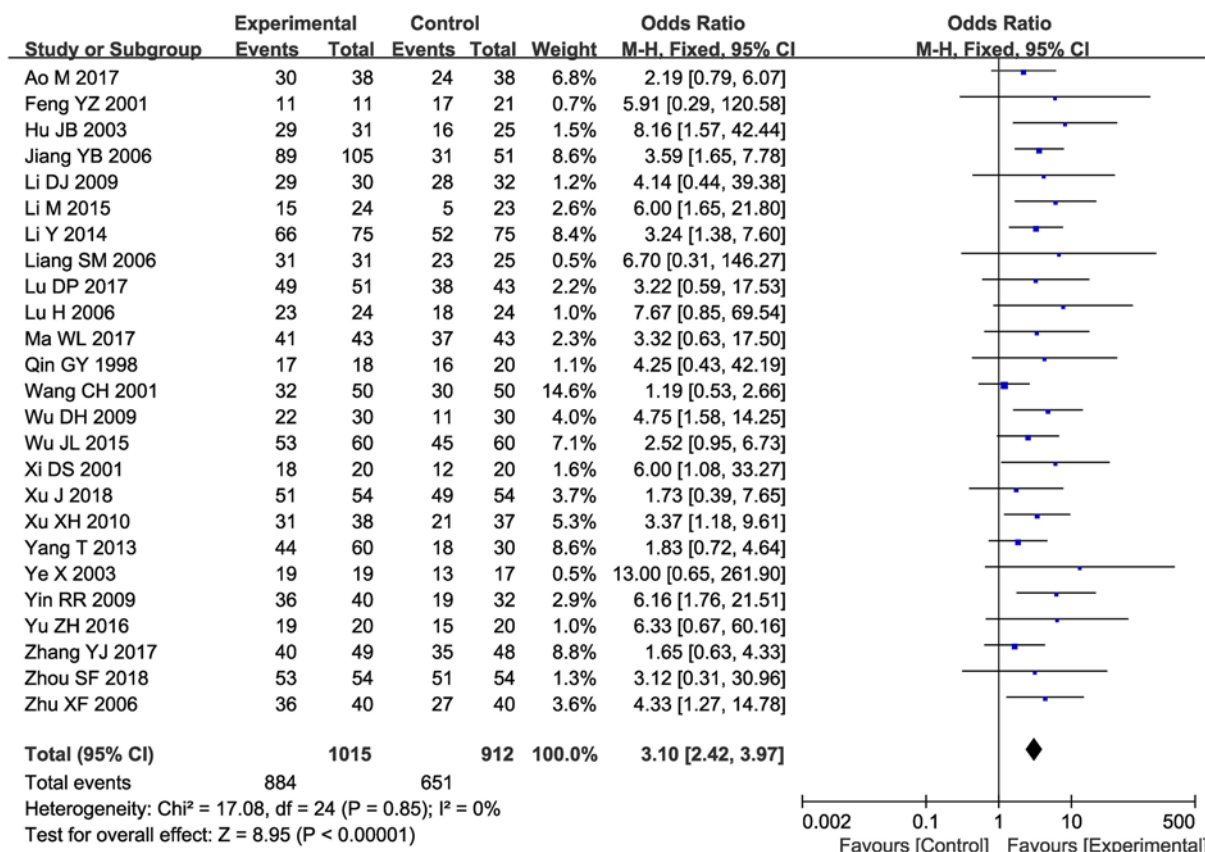


Figure 6. Forest plot of the comparison of DCRs between the experimental and control groups

Control group, CTs alone group; experimental group, CTs and kanglaite group. A fixed effects meta-analysis model (Mantel–Haenszel method) was used.

with kanglaite and CT displayed lower incidence rates of nausea and vomiting [24,26,34,36,42,48,50], hepatotoxicity [20,22,24,34,36,44,50] leukopenia [22,34,44,48,50], thrombocytopenia [22,34,49,50], gastrointestinal side effects [20,25,29,43,44,46] and fever [24,44,48] (nausea and vomiting: OR = 0.62, 95% CI = 0.39–0.97, *P* = 0.04; hepatotoxicity: OR = 0.40, 95% CI = 0.25–0.66, *P* = 0.0002; leukopenia: OR = 0.28, 95% CI = 0.17–0.47, *P* < 0.00001; thrombocytopenia: OR = 0.21, 95% CI = 0.10–0.42, *P* < 0.0001; gastrointestinal side effects: OR = 0.43, 95% CI = 0.22–0.84, *P* = 0.01; fever: OR = 0.37, 95% CI = 0.20–0.66, *P* = 0.0009). In contrast, the incidence rates of nephrotoxicity [22,44,50], anemia [22,50], myelosuppression [26,43] and alopecia [26,49] (nephrotoxicity: OR = 0.16, 95% CI = 0.01–3.56, *P* = 0.25; anemia: OR = 0.75, 95% CI = 0.33–1.73, *P* = 0.50; myelosuppression: OR = 0.64, 95% CI = 0.34–1.19, *P* = 0.16; alopecia: OR = 0.64, 95% CI = 0.34–1.24, *P* = 0.19) did not differ significantly between the two groups. Fixed-effect models were used in these analyses due to the low level of heterogeneity.

Publication bias

Publication bias was assessed visually with funnel plots. As illustrated in Figure 10, the funnel plots were symmetrical for ORR and QoL but asymmetrical for DCR.

We also assessed publication bias by Begg’s and Egger’s regression tests, and DCR was found to have bias (Begg = 0.059; Egger = 0.005). Conversely, no significant publication bias was found for ORR (Begg = 0.802; Egger = 0.680) or QIR (Begg = 0.675; Egger = 0.630). To determine if the bias affected the pooled risk for DCR, we conducted a trim-and-fill analysis. The adjusted OR indicated the same trend as was indicated by the result of the primary analysis (before: *P* < 0.0001, after: *P* < 0.0001), reflecting the reliability of our primary conclusions.

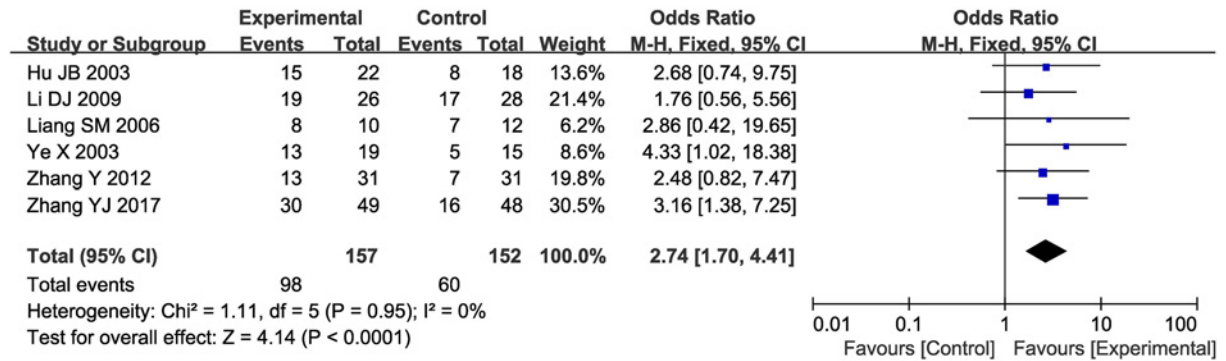


Figure 7. Forest plot of the comparison of the AFP decrease rate between the experimental and control groups
 Control group, CTs alone group; experimental group, CTs and kanglaite group. A fixed effects meta-analysis model (Mantel-Haenszel method) was used.

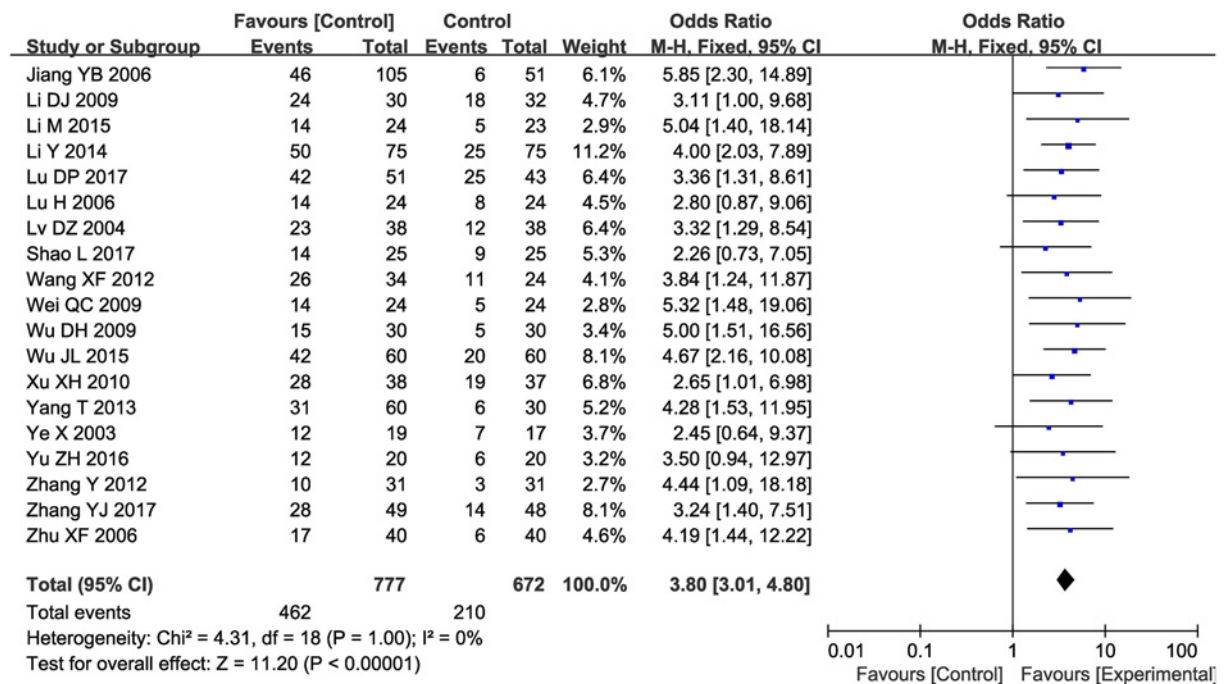


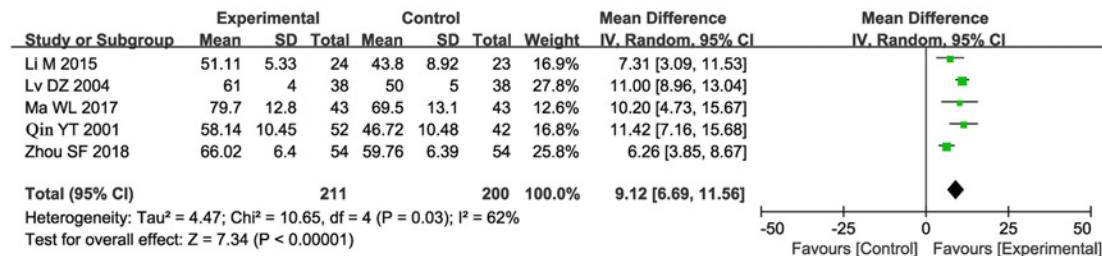
Figure 8. Forest plot of the comparison of QoL scores between the experimental and control groups
 Control group, CTs alone group; experimental group, CTs and kanglaite group. A fixed effects meta-analysis model (Mantel-Haenszel method) was used.

Sensitivity analysis

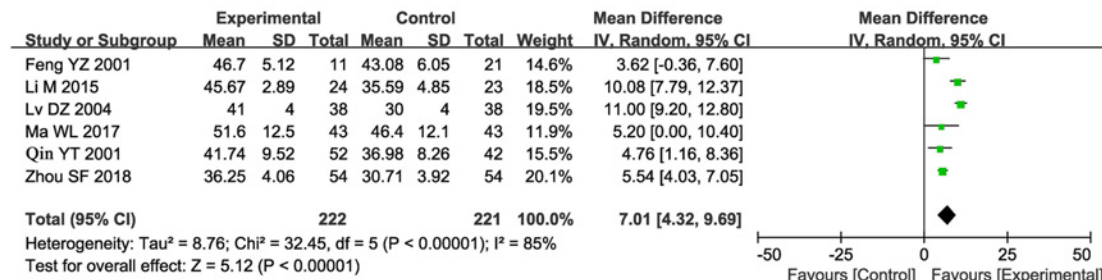
A sensitivity analysis was conducted, and one trial [24] was excluded because the type of kanglaite was in capsule form in the present study. The results of this analysis were similar to those obtained from the overall analysis of the pooled trials.

To explore the sources of ORR, DCR and QoL heterogeneity, we also conducted subgroup analyses with respect to therapeutic regimen, kanglaite dosage, sample size and type of study. As shown in Table 3, our analysis revealed no significant differences between different dosages of kanglaite, sample sizes and types of studies. Moreover, our results showed that kanglaite increased ORR and DCR among HCC patients only when combined with TACE/CT regimens.

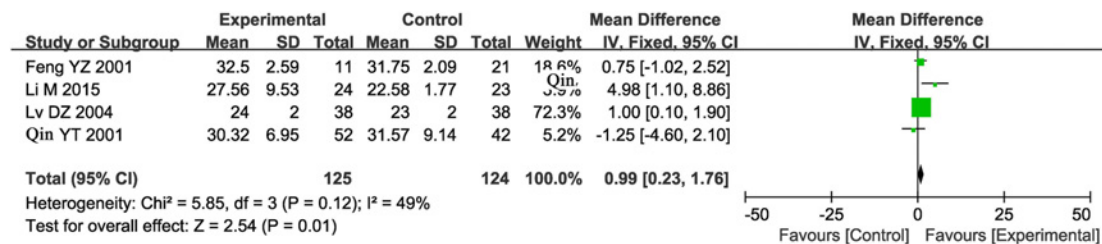
(A)



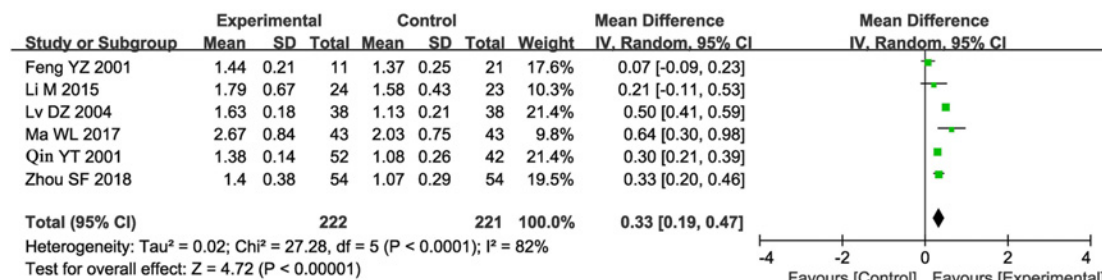
(B)



(C)



(D)



(E)

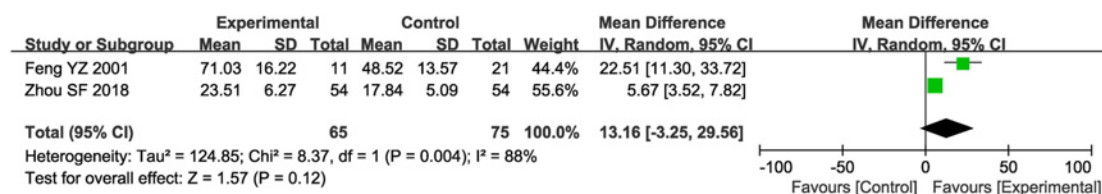


Figure 9. Comparisons of immune function between control and experimental group

Forest plot of the comparison of immune function (CD3⁺ (A); CD4⁺ (B); CD8⁺ (C); CD3⁻CD56⁺ (D); and CD4⁺/CD8⁺ (E)) between the experimental and control groups. Control group, CTs alone group; experimental group, CTs and kanglaite group.

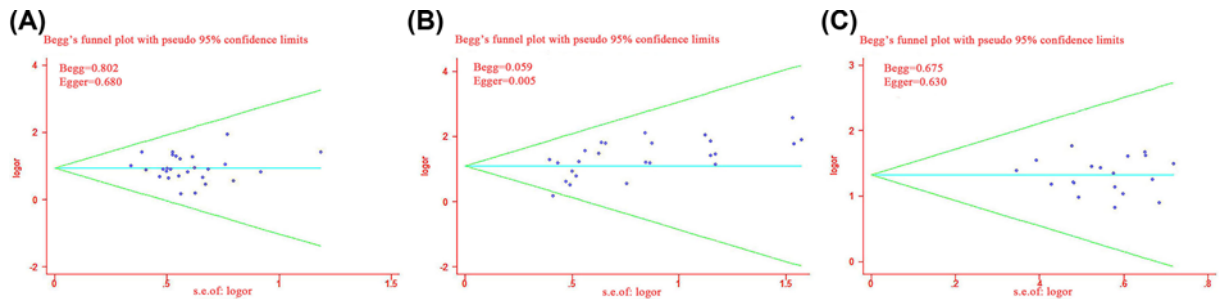


Figure 10. Funnel plot of publication bias
Funnel plot of the ORR (A); DCR (B); and QoL (C).

Discussion

The disadvantages of current CT for malignancies, such as drug resistance and toxic side effects, are a substantial burden for cancer patients [3,5]. Clinicians have been exploring complementary and alternative treatments to improve patients' survival time, QoL and immune function and to reduce side effects caused by radiochemotherapy [3,5,10]. Kanglaite, a type of traditional Chinese medicine, has been clinically applied as an adjuvant therapy for decades [12,51]. Many studies have reported that the addition of kanglaite may be beneficial for HCC patients [14]. Although statistical analyses of the published literature have been performed, the exact therapeutic effects have not been systematically investigated. In this analysis, we conducted a wide-ranging online search with strict inclusion and exclusion criteria to provide clear and systematic conclusions.

The meta-analysis was performed with 27 articles [20–29,31,32,34–36,38–46,48–50] to evaluate the clinical efficacy of the addition of kanglaite to CT. Our analysis found that compared with CT alone, the combination of kanglaite and CT significantly improved survival time at 6, 12, 18, 24 and 36 months ($P < 0.05$), suggesting that the addition of kanglaite to CT might prolong the survival time of HCC patients with advanced disease. The analysis considered ORR, DCR, QoL and clinical symptoms, all of which showed significant improvements in the combined group compared with the control group. Moreover, AFP is commonly used to predict the recurrence, metastasis and prognosis of HCC after comprehensive treatments [52,53], and our analysis showed that AFP was clearly reduced after treatment with the combination of CT and kanglaite. All these results indicate that using kanglaite might enhance the curative effects of CT for advanced HCC.

The immunosuppressed status of cancer patients has been reported, and immune system reconstruction is a critical approach for effectively treating malignancies. Our analysis showed that the percentages of CD3⁺, CD4⁺ and CD8⁺ cells and the CD4⁺/CD8⁺ ratio were significantly increased when kanglaite was administered to HCC patients, indicating that the immune function of HCC patients was improved by kanglaite-mediated therapy.

The meta-analysis evaluated the incidence rates of side effects after therapy, clearly showing reductions in nausea and vomiting, hepatotoxicity, leukopenia, thrombocytopenia, gastrointestinal side effects and fever ($P < 0.05$) in the combined group compared with the control group. Therefore, kanglaite is a safe auxiliary antitumor medicine for advanced HCC and can effectively alleviate some of the adverse events associated with CT.

This analysis of therapeutic effects may have been influenced by several factors. In our study, no differences were found between different dosages of kanglaite, sample sizes and research types. Moreover, the results of subgroup analyses indicated that kanglaite increased HCC patient ORR and DCR only when combined with TACE/CT regimens. Nonetheless, recent studies on the impacts of these factors on the curative effect of kanglaite adjuvant therapy remain insufficient, and further investigations should be performed.

There are some limitations in our analysis. First, as an important Chinese herbal preparation, kanglaite is mainly used in China, which may result in unavoidable regional bias and subsequently influence the clinical application of kanglaite worldwide. Currently, four clinical trials in the U.S.A. in which malignancies are being treated by kanglaite in conjunction with conventional regimens have been registered on ClinicalTrials.gov (one for prostate cancer, NCT01483586; one for NSCLC, NCT01640730; one for PC, NCT00733850; and one for refractory solid tumors, NCT00031031). Schwartzberg et al. (NCT00733850) [7] reported that compared with gemcitabine alone, kanglaite injection combined with gemcitabine significantly improved the progression-free survival, median OS and QoL of PC patients. Regardless, to date, no trial meeting our inclusion criteria has been published outside China. We will continue to pay close attention to global studies in further analyses. Second, confounding factors such as smoking and alcohol history may have an impact on the efficacy of kanglaite-mediated therapy. However, our data were extracted

Table 3 Subgroup analyses of ORR, DCR and QoL between the experimental and control groups

Parameter	Factors at study level	Experimental group	Control group	Analysis method	Heterogeneity		OR	95% CI	P-value
		Number of patients (n) ref	Number of patients (n) ref		I ² (%)	P-value			
ORR	Therapeutic regimen								
	kanglaite+TACE	649	534	Fixed	0	0.95	2.49	1.91–3.25	<0.00001
	kanglaite+CT	284	282	Fixed	0	0.71	2.62	1.81–3.78	<0.00001
	kanglaite+TAE	42	46	Fixed	0	0.69	2.88	0.71–11.78	0.14
	Dosage of kanglaite								
	200 ml/day	751	688	Fixed	0	0.98	2.47	1.93–3.15	<0.00001
	100 ml/day	244	196	Fixed	0	0.78	3.09	2.01–4.73	<0.00001
	Study sample size								
	>60	787	687	Fixed	0	0.96	2.64	2.07–3.36	<0.00001
	≤60	287	274	Fixed	0	0.96	2.41	1.63–3.56	<0.0001
Type of control trials									
RCT	878	772	Fixed	0	0.99	2.53	2.01–3.20	<0.00001	
Non-RCT	196	189	Fixed	0	0.78	2.72	1.76–4.21	<0.00001	
DCR	Therapeutic regimen								
	kanglaite+TACE	615	510	Fixed	0	0.48	2.74	2.02–3.72	<0.00001
	kanglaite+CT	284	282	Fixed	0	0.90	3.71	2.36–5.82	<0.00001
	kanglaite+TAE	42	46	Fixed	0	0.95	6.26	0.72–54.47	0.10
	Dosage of kanglaite								
	200 ml/day	726	663	Fixed	0	0.96	3.56	2.63–4.81	<0.00001
	100 ml/day	210	172	Fixed	40	0.17	2.07	1.30–3.30	0.002
	Study sample size								
	>60	787	687	Fixed	0	0.80	2.58	1.95–3.40	<0.00001
	≤60	228	225	Fixed	0	1.00	6.14	3.47–10.88	<0.00001
Type of control trials									
RCT	819	723	Fixed	0	0.79	2.99	2.28–3.94	<0.00001	
Non-RCT	196	189	Fixed	0	0.60	3.59	2.01–6.40	<0.0001	
QoL	Therapeutic regimen								
	kanglaite+TACE	510	407	Fixed	0	0.99	3.81	2.83–5.14	<0.00001
	kanglaite+CT	167	165	Fixed	0	0.82	3.88	2.43–6.20	<0.00001
	kanglaite+SST	55	55	Fixed	0	0.85	4.89	1.89–12.61	0.001
	Dosage of kanglaite								
	200 ml/day	538	471	Fixed	0	0.99	3.62	2.75–4.78	<0.00001
	100 ml/day	209	169	Fixed	0	1.00	4.48	2.80–7.17	<0.00001
	Study sample size								
	>60	577	485	Fixed	0	0.99	3.89	2.94–5.14	<0.00001
	≤60	200	187	Fixed	0	0.96	3.58	2.33–5.50	<0.00001
Type of control trials									
RCT	669	565	Fixed	0	1.00	3.63	2.81–4.68	<0.00001	
Non-RCT	108	107	Fixed	0	0.98	4.88	2.71–8.76	<0.00001	

Control group, CTs alone group; Experimental group, CTs and kanglaite group. Abbreviation: kanglaite, Kanglaite.

from publications where this information was not sufficiently provided. Therefore, based on currently available literature, there are insufficient data to perform a statistical analysis to evaluate correlations. We will focus on this concern in future studies. Third, as the sources of our data were published articles instead of raw records from clinical trials, analytical bias may exist. Finally, significant heterogeneity among the included trials was found in some cases, which may be due to the different ages of the HCC patients, tumor stages and durations of treatment. However, based on the currently available literature, there are insufficient data to perform more statistical analyses to evaluate these correlations.

Conclusions

In conclusion, the findings of this meta-analysis indicate that kanglaite combined with CT is effective in treating advanced HCC. The clinical application of kanglaite not only clearly enhances the therapeutic effects of CT but also effectively improves the QoL and immune function of HCC patients. However, the low quality of some of the included publications increases the risk of bias, which to some extent affects the reliability of the research. The clinical efficacy of kanglaite-mediated adjuvant therapy for advanced HCC still needs to be verified in methodologically rigorous trials.

Author Contribution

Jingjing Liu and Chao Xu conceived and designed the methods, extracted the original data and drafted the manuscript. Xueni Liu, Jing Ma and Ke Li performed the statistical analysis. Jingjing Liu and Chao Xu interpreted the results. Chao Xu revised the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

AFP, α -fetoprotein; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CT, conventional treatment; DCR, disease control rate; HCC, hepatocellular carcinoma; KPS, Karnofsky performance score; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, overall response rate; OS, overall survival; PC, pancreatic cancer; QoL, quality of life; SFDA, Chinese State Food and Drug Administration; TACE, transcatheter arterial chemoembolization; TAE, transhepatic arterial embolization.

References

- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **68**, 394–424, <https://doi.org/10.3322/caac.21492>
- Chen, W., Zheng, R., Baade, P.D., Zhang, S., Zeng, H., Bray, F. et al. (2016) Cancer statistics in China, 2015. *CA Cancer J. Clin.* **66**, 115–132, <https://doi.org/10.3322/caac.21338>
- Guo, N., Miao, Y. and Sun, M. (2018) Transcatheter hepatic arterial chemoembolization plus cinobufotalin injection adjuvant therapy for advanced hepatocellular carcinoma: a meta-analysis of 27 trials involving 2,079 patients. *Onco Targets Ther.* **11**, 8835–8853, <https://doi.org/10.2147/OTT.S182840>
- Wang, H., Yu, Z. and Liu, H. (2018) Alternative treatment strategies to sorafenib in patients with advanced hepatocellular carcinoma: a meta-analysis of randomized Phase III trials. *Onco Targets Ther.* **11**, 5195–5201, <https://doi.org/10.2147/OTT.S171918>
- Shi, Z., Song, T., Wan, Y., Xie, J., Yan, Y., Shi, K. et al. (2017) A systematic review and meta-analysis of traditional insect Chinese medicines combined chemotherapy for non-surgical hepatocellular carcinoma therapy. *Sci. Rep.* **7**, 4355, <https://doi.org/10.1038/s41598-017-04351-y>
- Qi, F., Zhao, L., Zhou, A., Zhang, B., Li, A., Wang, Z. et al. (2015) The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. *Biosci. Trends* **9**, 16–34, <https://doi.org/10.5582/bst.2015.01019>
- Schwartzberg, L.S., Arena, F.P., Bienvenu, B.J., Kaplan, E.H., Camacho, L.H., Campos, L.T. et al. (2017) A randomized, open-label, safety and exploratory efficacy study of kanglaite injection (KLTi) plus gemcitabine versus gemcitabine in patients with advanced pancreatic cancer. *J. Cancer* **8**, 1872–1883, <https://doi.org/10.7150/jca.15407>
- Yang, C., Hou, A., Yu, C., Dai, L., Wang, W., Zhang, K. et al. (2018) Kanglaite reverses multidrug resistance of HCC by inducing apoptosis and cell cycle arrest via PI3K/AKT pathway. *Onco Targets Ther.* **11**, 983–996, <https://doi.org/10.2147/OTT.S153814>
- Liu, X., Yang, Q., Xi, Y., Yu, K., Wang, W., Zhao, X. et al. (2014) Kanglaite injection combined with chemotherapy versus chemotherapy alone in the treatment of advanced non-small cell lung carcinoma. *J. Cancer Res. Ther.* **10**, 46–51, <https://doi.org/10.4103/0973-1482.139758>
- Fu, F., Wan, Y. and Wu, T. (2014) Kanglaite injection combined with hepatic arterial intervention for unresectable hepatocellular carcinoma: a meta-analysis. *J. Cancer Res. Ther.* **10**, 38–41, <https://doi.org/10.4103/0973-1482.139753>
- Zhang, X.W., Liu, L., Zhang, X.Z. and Bo, P. (2017) Kanglaite inhibits the expression of drug resistance genes through suppressing PVT1 in cisplatin-resistant gastric cancer cells. *Exp. Ther. Med.* **14**, 1789–1794, <https://doi.org/10.3892/etm.2017.4650>
- Huang, X., Qin, J. and Lu, S. (2014) Kanglaite stimulates anticancer immune responses and inhibits HepG2 cell transplantation induced tumor growth. *Mol. Med. Rep.* **10**, 2153–2159, <https://doi.org/10.3892/mmr.2014.2479>
- Lu, Y., Wu, L.Q., Dong, Q. and Li, C.S. (2009) Experimental study on the effect of Kang-Lai-Te induced apoptosis of human hepatoma carcinoma cell HepG2. *Hepatobil. Pancreat. Dis. Int.* **8**, 267–272
- Lu, Y., Li, C.S. and Dong, Q. (2008) Chinese herb related molecules of cancer-cell-apoptosis: a minireview of progress between kanglaite injection and related genes. *J. Exp. Clin. Cancer Res.* **27**, 31, <https://doi.org/10.1186/1756-9966-27-31>

- 15 Zeng, X., Zhang, Y., Kwong, J.S., Zhang, C., Li, S., Sun, F. et al. (2015) The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J. Evid. Based Med.* **8**, 2–10, <https://doi.org/10.1111/jebm.12141>
- 16 Slim, K., Nini, E., Forestier, D., Kwiatkowski, F., Panis, Y. and Chipponi, J. (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J. Surg.* **73**, 712–716, <https://doi.org/10.1046/j.1445-2197.2003.02748.x>
- 17 Jackson, D., White, I.R. and Riley, R.D. (2012) Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat. Med.* **31**, 3805–3820, <https://doi.org/10.1002/sim.5453>
- 18 Lin, L., Chu, H., Murad, M.H., Hong, C., Qu, Z., Cole, S.R. et al. (2018a) Empirical comparison of publication bias tests in meta-analysis. *J. Gen. Intern. Med.* **33**, 1260–1267, <https://doi.org/10.1007/s11606-018-4425-7>
- 19 Lin, L. and Chu, H. (2018b) Quantifying publication bias in meta-analysis. *Biometrics* **74**, 785–794, <https://doi.org/10.1111/biom.12817>
- 20 Ao, M., Xiao, X. and Ao, Y.Z. (2017) Observation on effect and adverse reactions of thalidomide combined with kanglite injections in treating primary liver cancer. *Doctor* **2**, 9–10
- 21 Feng, Y.Z., Zhao, W.H., Ma, Z.M., Zhou, X.R., Wang, M. and Sheng, J.M. (2001) Transcatheter hepatic artery infusion with coix seed extract injection (kanglite) in the treatment of advanced HCC. *China J. Cancer Prev. Treat.* **8**, 310–311
- 22 Hu, J.B., Wong, J., Liu, S.L., Guan, L.L., Zhou, J. and Liu, Y.J. (2003) Therapeutic effect observation of kanglaite combined with interventional chemoembolization in the treatment of middle and advanced hepatocellular carcinoma. *ShanXi Oncol. Med.* **11**, 48–49
- 23 Jiang, Y.B. (2006) The efficacy of kanglaite injection in the treatment of primary Liver cancer. *J. Modern Oncol.* **14**, 485–486
- 24 Li, D.J., Xu, X.H., Bao, D., Xue, F. and Dai, D.L. (2009) Effects of kanglaite capsules combined with transcatheter arterial chemoembolization (TACE) on patients with mid or late-stage primary hepatocellular carcinoma (HCC). *Chin. German J. Clin. Oncol.* **8**, 65–68, <https://doi.org/10.1007/s10330-008-0142-8>
- 25 Li, M., Wang, Y. and Hui, S. (2015) Therapeutic effect of kanglaite injection on 47 patients with advanced primary hepatocellular carcinoma. *Pharmacol. Clin. Chin. Mater. Med.* **31**, 197–199
- 26 Li, Y., Zhao, X.M., Xu, H.L., Li, J. and Sun, H. (2014) Clinical efficacy and influence of kanglaite combined with chemotherapy on the activity of immune cells in patients with liver cancer. *Progress Modern Biomed* **14**, 2103–2106
- 27 Liang, S.M., Wang, J. and Song, J. (2006) Kanglaite combined with interventional chemoembolization in the treatment of middle and advanced hepatocellular carcinoma. *Chin. J. Modern Appl. Pharm.* **23**, 825–826
- 28 Lu, D.P., Wang, Y.Q., Zhao, W.L. and Qi, Z.P. (2017) Clinical study of kanglaite combined with transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma. *World Clin. Med.* **11**, 70–72
- 29 Lu, H., Zhou, J.S., Xu, X. and Deng, N. (2006) Effects of transcatheter arterial chemoembolization combined with kanglaite injection on patients with advanced unresectable hepatocellular carcinoma. *Central Plains Med. J.* **33**, 3–4
- 30 Lv, D.Z. and Zhao, C.Y. (2004) Therapeutic effect observation of kanglaite injection in the treatment of hepatocellular carcinoma after interventional therapy. *New Med* **35**, 415–416
- 31 Ma, W.L., Yan, Y.F. and Wang, X.P. (2017) Efficacy of kanglaite injection combined with chemotherapy for the treatment of hepatocellular carcinoma and its effect on immune system. *Int. J. Immunol.* **40**, 409–412
- 32 Qin, G.Y. and Zhang, Y.Y. (1998) Therapeutic effect of kanglaite injection combined with intra-arterial chemotherapy in the treatment of mid and advanced primary liver cancer. *Zhejiang J. Integr. Tradit. Chin. West Med.* **8**, 196–198
- 33 Qin, Y.T., Wei, C.Y. and Li, T. (2001) The effect of KLT (Kang Lai Te) on immune function in patients with advanced primary hepatocarcinoma. *China J. Cancer Prev. Treat.* **8**, 23–24
- 34 Shao, L., Shi, Y.X., Zhu, H.X., Ma, M., Niu, T.T. and Li, C.T. (2017) Clinical study of stereotactic radiotherapy combined with kanglaite injection in the treatment of primary hepatocellular carcinoma. *Clin. J. Med. Officers* **45**, 313–315
- 35 Wang, C.H. and Wang, Z.Y. (2001) The role of kanglaite in the multidisciplinary treatment of primary hepatocellular carcinoma. *ShanXi Oncol. Med* **9**, 211–212
- 36 Wang, X.F. (2012) Clinical observation of kanglaite injection in the treatment of middle and advanced hepatocellular carcinoma. *Psychol. Doctor* **11**, 56
- 37 Wei, Q.C., Meng, Q.C. and Yan, Z.S. (2009) Research on the interference of intravenous kanglaite on quality of life in patients with advanced hepatocellular carcinoma. *J. Modern Oncol.* **17**, 1740–1741
- 38 Wu, D.H., Chen, N.J., Chen, Y.Y. and Lai, Y.Q. (2009) Clinical observation of kanglaite injection in the treatment of middle and advanced primary hepatocellular carcinoma. *Proc. Clin. Med.* **18**, 2041–2042
- 39 Wu, J.L. (2015) Clinical observation of kanglaite injection combined with interventional chemotherapy in the treatment of middle and advanced hepatocellular carcinoma. *China Naturopath.* **23**, 60–61
- 40 Xi, D.S., Li, H. and Huang, Y.P. (2001) Kanglaite for 20 cases of primary hepatocellular carcinoma. *Herald Med.* **20**, 568
- 41 Xu, J. and Lu, M.Y. (2018) Effect of kanglaite injection combined with chemotherapy on patients with hepatic carcinoma and its influence on immune system. *Diet Health* **5**, 50
- 42 Xu, X.H., Su, J. and Fu, X.Y. (2010) Clinical observation of kanglaite injection combined with capecitabine in the treatment of middle and advanced primary hepatocellular carcinoma. *Lishizhen Med. Mater. Med. Res.* **21**, 1479–1480
- 43 Yang, T., Cao, J.M. and Xu, J. (2013) Clinical analysis of TACE combined with kanglaite injection in the treatment of primary hepatocellular carcinoma. *Med. J. Liaoning* **27**, 249–251
- 44 Ye, X., Zhang, T., Song, B.Y., Cheng, P., Liu, J.H. and Zhou, K. (2003) Combining kanglaite and TACE in treatment of unresectable hepatocellular carcinoma. *Chin. J. Clin. Med.* **4**, 23–25
- 45 Yin, R.R. (2009) Interventional therapy combined with kanglaite injection in the treatment of middle and advanced hepatocellular carcinoma. *China Foreign Med. Treat.* **28**, 78

- 46 Yu, Z.H. (2016) Therapeutic effect and adverse reactions of thalidomide combined with kanglaite injection in the treatment of primary hepatocellular carcinoma. *Clin. J. Med. Liter.* **3**, 1143–1146
- 47 Zhang, Y., Jia, Y.J. and Chen, J. (2012) Clinical observation in kanglaite Injection on serum alpha-fetoprotein and physical conditions of advanced hepatocellular carcinoma patients. *Drugs Clinic* **27**, 477–479
- 48 Zhang, Y.J., Cao, J.H., Xu, X.D., Yang, X.B. and Yin, J.H. (2017) A clinical study on kanglaite combined with interventional chemotherapy in the treatment of primary hepatocellular carcinoma. *Antitumor Pharm.* **7**, 104–108
- 49 Zhou, S.F. and Sun, H.X. (2018) Effects of kanglaite and sorafenib on T-cell subsets and quality of life in patients with advanced hepatocellular carcinoma. *China J. Modern Med.* **28**, 125–128
- 50 Zhu, X.F. (2006) The clinical observation of the effect of kanlaite injection combined with chemoembolization primary on middle and advanced stage liver cancer. *J. Basic Clin. Oncol.* **19**, 132–134
- 51 Zhang, P., Meng, X., Tang, X., Ren, L. and Liang, J. (2019) The effect of a coix seed oil injection on cancer pain relief. *Support. Care Cancer* **27**, 461–465, <https://doi.org/10.1007/s00520-018-4313-z>
- 52 Sauzay, C., Petit, A., Bourgeois, A.M., Barbare, J.C., Chauffert, B., Galmiche, A. et al. (2016) Alpha-foetoprotein (AFP): a multi-purpose marker in hepatocellular carcinoma. *Clin. Chim. Acta* **463**, 39–44, <https://doi.org/10.1016/j.cca.2016.10.006>
- 53 Erdal, H., Gul Utku, O., Karatay, E., Celik, B., Elbeg, S. and Dogan, I. (2016) Combination of DKK1 and AFP improves diagnostic accuracy of hepatocellular carcinoma compared with either marker alone. *Turk. J. Gastroenterol.* **27**, 375–381, <https://doi.org/10.5152/tjg.2016.15523>