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Research Article

Efficacy and safety of Chinese patent medicine (Jinlong capsule) in the treatment of advanced hepatocellular carcinoma: a meta-analysis

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Jinlong capsule (JLC), a type of herbal medicine, is considered to be a promising adjuvant therapy for hepatocellular carcinoma (HC). Although an analysis of the published literature has been performed, the exact effects and safety of JLC are yet to be systematically investigated. Therefore, a wide-ranging systematic search of electronic databases to draw conclusions was performed. Data from 29 trials, including 2488 patients with advanced HC, were analyzed. The results indicated that, compared with conventional treatment alone, the combination of conventional treatment and JLC markedly improved overall patient response (odds ratio (OR) 2.06 [95% confidence interval (CI) 1.71–2.49]; $P<0.00001$), disease control rate (DCR) (OR 2.17 [95% CI 1.74–2.71]; $P<0.00001$) and quality of life (QoL) (OR 2.71 [95% CI 2.05–3.58]; $P<0.00001$), and significantly prolonged 6- ($P=0.01$), 12- ($P<0.00001$), 24- ($P=0.001$) and 36-month ($P<0.0001$) overall survival (OS) rates. The immune function of patients was also significantly enhanced after combined conventional therapy and JLC treatment, indicated by clearly increased percentages of $CD3^+$ ($P<0.0001$), $CD4^+$ ($P<0.00001$) and natural killer (NK) cells ($P=0.0003$), and $CD4^+/CD8^+$ ratio ($P<0.00001$). The incidence of leukopenia ($P<0.00001$), hepatotoxicity ($P=0.005$), and myelosuppression ($P=0.0007$) was lower in HC patients injected with JLC, whereas other adverse events did not differ significantly between the two groups ($P>0.05$). In summary, results of this meta-analysis suggest that the combination of conventional treatment and JLC is more effective for the treatment of HC than conventional treatment alone.

Introduction

Hepatocellular carcinoma (HC) is the seventh most common cancer and the third leading cause of cancer-related deaths worldwide [1]. It was estimated that 840000 new cases of HC and 781631 HC-related deaths occurred worldwide in 2018 [1]. Despite advances in diagnostic methods, early detection of HC remains difficult [2]. In most patients, HC progresses to the intermediate and advanced stages, for which the 5-year survival rate is <17% [2,3]. Surgery and liver transplantation are considered to be the optimal treatment options for advanced HC; however, only a small proportion of HC patients are able to undergo potentially curative resection [4]. In addition, the therapeutic effects of current conventional treatments for advanced HC, such as radiotherapy and chemotherapy, remain unsatisfactory [2,5,6]. Therefore, more effective, comprehensive treatment strategies are required.

Jinlong capsule (JLC) is a traditional Chinese medicine with the function of tonifying qi and blood, dredging collaterals and detoxification, and has been widely used as an effective adjuvant drug in cancer treatment [7,8]. It is traditionally prepared from three animals with medicinal properties: Bungarus, Agkistrodon and Gecko [7,8]. The active ingredients of JLC comprise at least 17 amino acids, including

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histidine, serine, arginine, glycine and aspartic acid, among others, which are extracted using modern cryogenic and biochemical separation techniques from freshly prepared animal drugs [8,9].

Research has shown that JLC can effectively reverse multiple-drug resistance in cancer cells and improve the efficacy of chemotherapy [10,11]. Many *in vitro* studies have demonstrated that JLC can suppress cellular mitotic division and inhibit proliferation principally by arresting the cell division cycle at S and G_2/M [8,9]. It can also promote cancer cell apoptosis through activation of the pro-apoptotic proteins BNIP3, Bax and caspase-3, and down-regulating the expression of Bcl-2 for survival [8,9]. Several studies have indicated that conventional treatment combined with JLC is more effective for the treatment of advanced HC than conventional treatment alone [12,13]. Despite intensive studies, the clinical efficacy and safety of the combination of conventional treatment and JLC has not been systematically evaluated. In the present study, we conducted a meta-analysis to investigate the efficacy and safety of conventional treatment combined with JLC compared with conventional treatment alone for advanced HC, to provide a scientific reference for the design of future clinical trials.

Materials and methods

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the Cochrane Handbook. Ethics approval was not necessary due to the nature of the study (i.e. meta-analysis).

Search strategy and selection criteria

A literature search was conducted using eight electronic databases, including the Web of Science, PubMed, Cochrane Library, Embase, Chinese Biological Medicine Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP) and the Wanfang database, for original articles published before February 2019. The search terms included: 'Jinlong capsule' combined with 'liver carcinoma' or 'hepatocellular carcinoma' or 'liver cancer' or 'hepatocellular cancer'.

Studies fulfilling the following criteria were included in the meta-analysis: controlled trials investigating patients with advanced HC; those with >30 HC patients; studies comparing the clinical outcomes of conventional treatment plus JLC adjuvant therapy (experimental group) with conventional treatment alone (control group); and conventional treatments including transcatheter arterial chemoembolization, chemotherapy, radiotherapy, radiofrequency ablation, percutaneous ethanol injection, support and symptomatic treatment and ultrasound therapy.

Studies involving patients with mixed malignancies, non-controlled trials, non-clinical studies, literature reviews, meta-analyses, meeting abstracts, case reports, duplicate studies, experimental models and those with insufficient available data were excluded.

Data extraction and quality assessment

Data were independently extracted by two investigators (H.X. and W.W.) according to the same inclusion criteria; disagreements were adjudicated by a third reviewer (C.D.). The extracted data were as follows: name of the first author; year of publication; tumor stage or Karnofsky Performance score (KPS); number of cases; intervention methods; control group regimens; dose of JLC and study parameters. To ensure the quality of the meta-analysis, the quality of the included randomized and non-randomized controlled trials was evaluated according to the Cochrane Handbook tool [14] and Methodological Index for Nonrandomized Studies (MINORS, Supplementary Table S2), respectively [15].

Outcome definitions

Clinical responses included treatment efficacy, quality of life (QoL), immune function, and adverse events. Treatment efficacy was assessed in terms of overall survival (OS), overall response rate (ORR), and disease control rate (DCR). Patient QoL was evaluated using QoL improved rate (QIR) and KPS. Immune function indicators ($CD3^+$, $CD4^+$, $CD8^+$ and natural killer [NK] cell percentage and $CD4^+/CD8^+$ ratio) and adverse events, including leukopenia, adverse gastrointestinal effects, nausea and vomiting, anorexia, thrombocytopenia, hepatotoxicity, myelosuppression and anemia, were assessed and compared between the two groups.

Statistical analysis

Review Mananger (RevMan) version 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata version 13.0 (StataCorp., College Station, TX, U.S.A.) were used for statistical analyses. Data were mainly expressed as odds ratio (OR) with corresponding 95% confidence interval (CI), and a two-tailed $P<0.05$ was considered to be statistically

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significant. Cochrane's Q test and I^2 statistics were used to assess heterogeneity among the studies: if $P > 0.1$ or $I^2 < 50\%$, fixed-effects model was used for the meta-analysis; otherwise, random-effects model was used [16].

The presence of publication bias was investigated using the Begg's and Egger's tests, and funnel plots. A pooled analysis of publication bias determined that the trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted results were compared with the original pooled OR [17]. Sensitivity analysis was performed to evaluate the impact of different therapeutic regimens, sample size, and type of research on the clinical efficacy of the combination of conventional treatment and JLC.

Results

Search results

The initial search retrieved a total of 328 articles, of which 225 were excluded due to duplication. After title and abstract review, 47 articles were further excluded because they did not include clinical trials (n=23), were unrelated studies (n=17), were reviews and meta-analyses (n=3), or were case reports (n=4), leaving 56 studies as potentially eligible. After detailed assessment of full texts, studies without a control group (n=9), those with <30 HC patients (n=6), inappropriate criteria for the experimental or control groups (n=5), and trials with insufficient data (n=7) were excluded. Ultimately, 29 trials [7,18–45], involving 2488 patients with advanced HC, were included in the final analysis (Figure 1).

Patient characteristics

All included studies were performed in different medical centers in China. In total, 1274 patients with advanced HC were treated using conventional methods in combination with JLC adjuvant therapy, while 1214 patients were treated using conventional methods alone. JLC was manufactured by Beijing Jiansheng Pharmaceutical Co., Ltd. The quality standards of the JLC in the present study were approved by the Chinese State Food and Drug Administration (SFDA), and granted a manufacturing approval number issued by the Chinese SFDA (Z10980041). All pharmaceutical companies involved followed the quality processing procedure outlined in the pharmacopeia. Study and patient characteristics are summarized in Table 1.

Quality assessment

Quality assessment of the risk of bias is shown in Supplementary Figure S1 and Table S1. The results revealed that the literature retrieved for the present study was of good quality.

Therapeutic efficacy assessments ORR and DCR

Twenty-five clinical trials [7,18–21,23–30,32–36,38,39,41–45], involving 2161 patients, compared ORR and DCR between the two groups. As shown in Figures 2 and 3, the pooled results revealed that patients who underwent combination therapy experienced significantly improved ORR (OR 2.06 [95% CI 1.71–2.49]; P<0.00001) and DCR (OR 2.17 [95% CI 1.74–2.71]; P<0.00001) compared with those who received conventional treatment(s) alone. The fixed-effect model was selected due to slight heterogeneity among the studies.

Long-term survival

Eight clinical trials [18,22,23,26,28,31,35,42] with 1014 HC patients reported OS (Figure 4). Meta-analysis revealed that the 6- (OR 1.63 [95% CI 1.11–2.39]; P=0.01), 12- (OR 2.05 [95% CI 1.54–2.73]; P<0.00001), 24- (OR 2.45 [95% CI 1.44–4.19]; P=0.001) and 36-month OS (OR 2.41 [95% CI 1.56–3.74]; P<0.0001) of patients in the combined treatment group were significantly prolonged compared with the control group. There was statistical heterogeneity in 24-month OS (P=0.03, $I^2 = 58\%$) according to the heterogeneity test. Therefore, a random-effects model was used to pool this meta-analysis. Otherwise, the fixed-effect model was used.

QoL assessment

Ten trials [18,21,24,26,29,31,32,42,43,45] with 1040 participants evaluated QIR, and three trials [7,27,34], including 208 patients, reported KPS data (Figure 5). Results demonstrated that the QoL of HC patients in the combined group was significantly better than that of the control group, indicated by significantly increased QIR (OR 2.71 [95% CI 2.05–3.58]; P<0.00001) and KPS (OR 9.33 [95% CI 4.26–14.40]; P=0.0003). QIR (P=0.86, $I^2 = 0\%$) was not heterogeneous among the studies; therefore, a fixed-effect model was used to analyze OR. Otherwise, a random-effect model was used.

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

Included studies	Tumor stage/KPS	Patients Con/Exp	Intervening methods	Control group regimens	Dosage of JLC	Parameter types
Dong, H.T. (2008) [18]	II–IV	66/67	Con+JLC vs Con	TACE (THP, 5-Fu)	1.0 g/time, 3 times/day	OS, ORR, AE, QoL
Jia, C.H. (2008) [19]	I–III	30/30	Con+JLC vs Con	TACE (MMC)	1.0 g/time, 3 times/day	ORR, DCR, IF
Jiang, C.Y. (2013) [20]	II–III	33/30	Con+JLC vs Con	TACE (THP, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, AE
Li, B. (2013) [21]	ND	73/74	Con+JLC vs Con	TACE (E-ADM, 5-Fu, DDP, MMC, CL)	1.0 g/time, 3 times/day	ORR, DCR, QoL
Li, H. (2007) [22]	ND	30/55	Con+JLC vs Con	TACE, RFA; PEI	1.0g/time, 3 times/day	OS
Liang, T.J. (2005) [23]	ND	108/116	Con+JLC vs Con	TACE (E-ADM, MMC, Carboplatin)	1.0 g/time, 3 times/day	OS, ORR, DCR
Liu, Z.Y. (2015) [24]	>60	80/80	Con+JLC vs Con	TACE (THP, MMC, 5-Fu, HCPT)	1.0 g/time, 3 times/day	ORR, DCR, QoL
Meng, P. (2016) [25]	ND	58/58	Con+JLC vs Con	TACE (E-ADM, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, IF
Sun, J.H. (2006) [26]	ND	64/64	Con+JLC vs Con	SST	1.0 g/time, 3 times/day	OS, ORR, DCR, AE, QoL,
Tang, W.H. (2015) [27]	ND	20/20	Con+JLC vs Con	SST	2.0 g/time, 1 time/day	ORR, DCR, QoL
Wang, H.B. (2013) [28]	ND	42/43	Con+JLC vs Con	3-DCRT	1.0 g/time, 3 times/day	OS, ORR, DCR, AE
Wang, X.H. (2009) [29]	I–III	30/30	Con+JLC vs Con	TACE (DDP, MMC, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, QoL, AE
Wu, G.L. (2010) [7]	≥60	45/53	Con+JLC vs Con	TACE (Oxaliplatin, HCPT, THP)	1.0 g/time, 3 times/day	ORR, DCR, QoL
Xiao, Z.Y. (2009) [30]	≥60	26/26	Con+JLC vs Con	3-DCRT	1.0 g/time, 3 times/day	ORR, DCR, AE
Xie, B. (2008) [31]	I–II	61/61	Con+JLC vs Con	Surgery, CT (5-Fu)	1.0 g/time, 3 times/day	OS, QoL, IF
Xie, Y.F. (2003) [32]	I–III	31/31	Con+JLC vs Con	TACE (DDP, MMC, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, QoL, AE
Xiong, T.Q. (2010) [33]	≥60	26/26	Con+JLC vs Con	SST, KAI, SFJ	1.0 g/time, 3 times/day	ORR, DCR, AE
Yang, P.Y. (2013) [34]	≥60	36/34	Con+JLC vs Con	TACE (E-ADM, DDP, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, QoL
Ye, X. (2008) [35]	II–IV	40/54	Con+JLC vs Con	HIFU	1.0 g/time, 3 times/day	OS, ORR, DCR
Yin, L.J. (2008) [36]	≥60	48/48	Con+JLC vs Con	GKS	1.0 g/time, 3 times/day	ORR, DCR, AE
Yuan, T.W. (2013) [37]	60–80	30/30	Con+JLC vs Con	TACE (DDP, MMC, 5-Fu)	1.0 g/time, 3 times/day	IF
Zeng, B.Z. (2010) [38]	I–III	30/31	Con+JLC vs Con	TACE (E-ADM, DDP, MMC)	1.0 g/time, 3 times/day	ORR, DCR, AE, IF
Zeng, C.S. (2012) [39]	II–III	30/30	Con+JLC vs Con	TACE (THP, DDP, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR
Zeng, C.S. (2014) [40]	II–III	30/30	Con+JLC vs Con	TACE (THP, DDP, 5-Fu)	1.0 g/time, 3 times/day	AE, IF
Zhang, S.Z. (2012) [41]	≥50	22/22	Con+JLC vs Con	SST	1.0 g/time, 3 times/day	ORR, DCR, AE
Zhang, X.Q. (2012) [42]	III–IV	77/74	Con+JLC vs Con	TACE (DDP, 5-Fu)	1.0 g/time, 3 times/day	OS, ORR, DCR, QoL, AE
Zhang, X.Q. (2012) [43]	>70	13/14	Con+JLC vs Con	TACE (Oxaliplatin, Gemcitabine)	1.0 g/time, 3 times/day	ORR, DCR, QoL, AE, IF
Zheng, C. (2018) [44]	II–III	28/30	Con+JLC vs Con	TACE (DDP, MMC, 5-Fu)	1.0 g/time, 3 times/day	ORR, DCR, AE, IF
Zhu, X. (2003) [45]	30–60	25/25	Con+JLC vs Con	SST	1.0 g/time, 3 times/day	ORR, DCR, QoL

Con, Control group (Conventional treatment alone group); Exp, Experimental group (Conventional treatment and JLC combined group). Abbreviations: AE, adverse event; CL, calcium levofolinate; CT, chemotherapy; DDP, Cisplatin; E-ADM, epirubicin; Fu, Fluorouracil; GKS, γ knife surgery; HCPT, hydroxycamptothecin; HIFU, high-intensity focused ultrasound therapy; IF, immune function; KAI, Kang Ai injection; MMC, mitomycin C; ND, non-determined; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SFJ, compound injection of sophora flavescens; SST, support and symptomatic treatment; TACE, transcatheter arterial chemoembolization; THP, pirarubicin; 3-DCRT, three-dimensional conformal radiotherapy.

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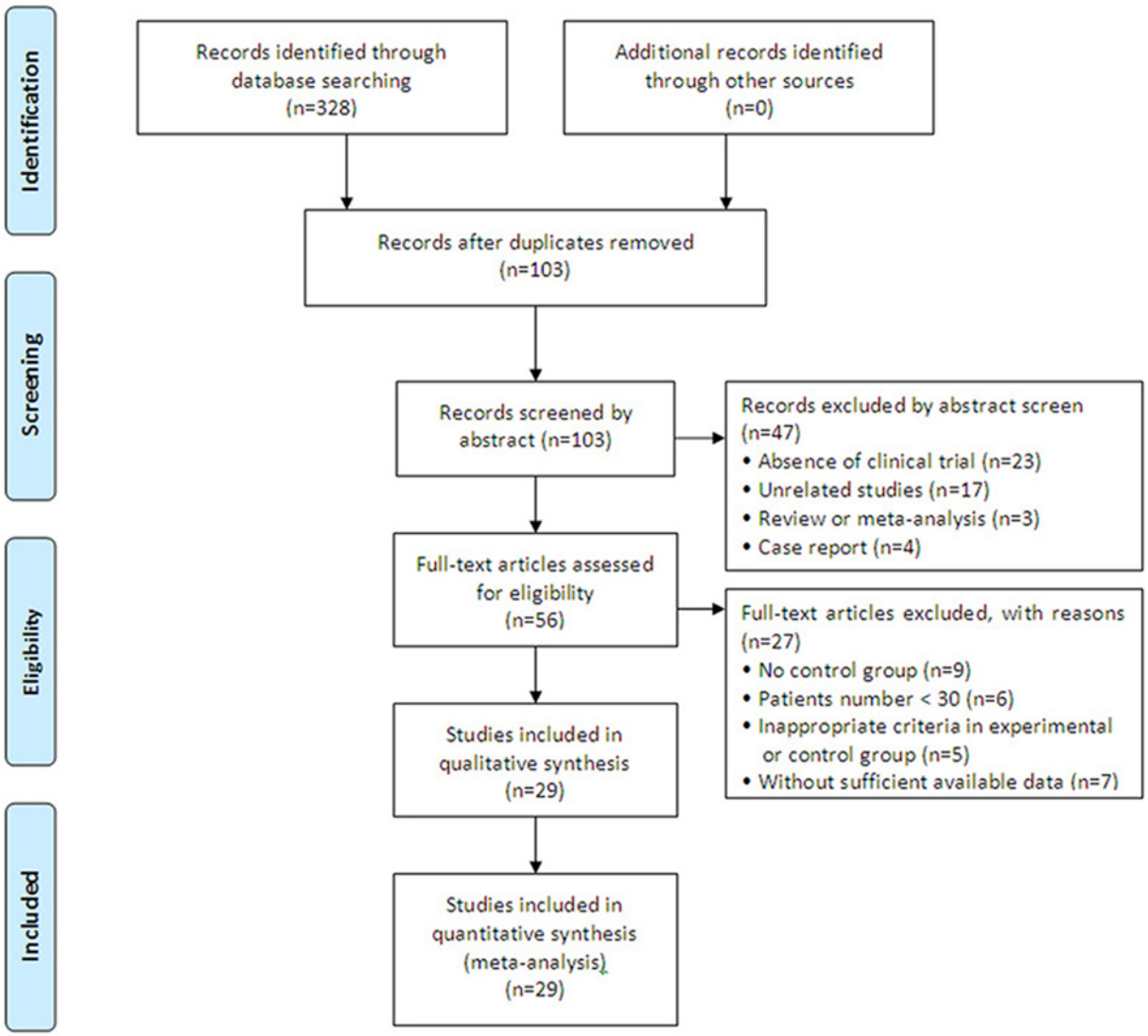

Figure 1. Study selection process for the meta-analysis

Immune function evaluation

Immune status of the patients was examined between the two groups in nine controlled studies [19,25,31,32,37,38,40,43,44]. The percentages of $CD3^+$, $CD4^+$ and NK cells, and $CD4^+/CD8^+$ ratio in the combined treatment group were significantly increased compared with those in the conventional treatment alone group, ($CD3^+$, OR 13.69 [95% CI 7.40–19.98], $P<0.0001$; $CD4^+$, OR 8.04 [95% CI 4.94–11.13], $P<0.00001$; NK, OR 6.29 [95% CI 2.88–9.69], $P=0.0003$; and $CD4^+/CD8^+$, OR 0.39 [95% CI 0.27–0.51], $P<0.00001$), whereas the proportions of $CD8^+$ were clearly decreased (OR −5.62 [95% CI −7.68 to −3.56]; $P<0.00001$) (Figure 6). A random-effects model was used to pool this meta-analysis due to significant heterogeneity.

Assessment of adverse events

As shown in Table 2 and Supplementary Figure S2, patients treated with JLC and conventional methods exhibited lower incidences of leukopenia, hepatotoxicity and myelosuppression (leukopenia, OR 0.49 [95% CI 0.36–0.67], $P<0.00001$; hepatotoxicity, OR 0.29 [95% CI 0.12–0.69, $P=0.005$; and myelosuppression, OR 0.26 [95% CI 0.12–0.56], $P=0.0007$), whereas analysis of gastrointestinal side effects, nausea and vomiting, anorexia, thrombocytopenia and anemia (gastrointestinal side effects, OR 0.69 [95% CI 0.44–1.07], $P=0.10$; nausea and vomiting, OR 0.81 [95% CI 0.45–1.48], $P=0.49$; anorexia, OR 0.89 [95% CI 0.35–2.29], $P=0.81$; thrombocytopenia, OR 0.76 [95% CI 0.28–2.06],

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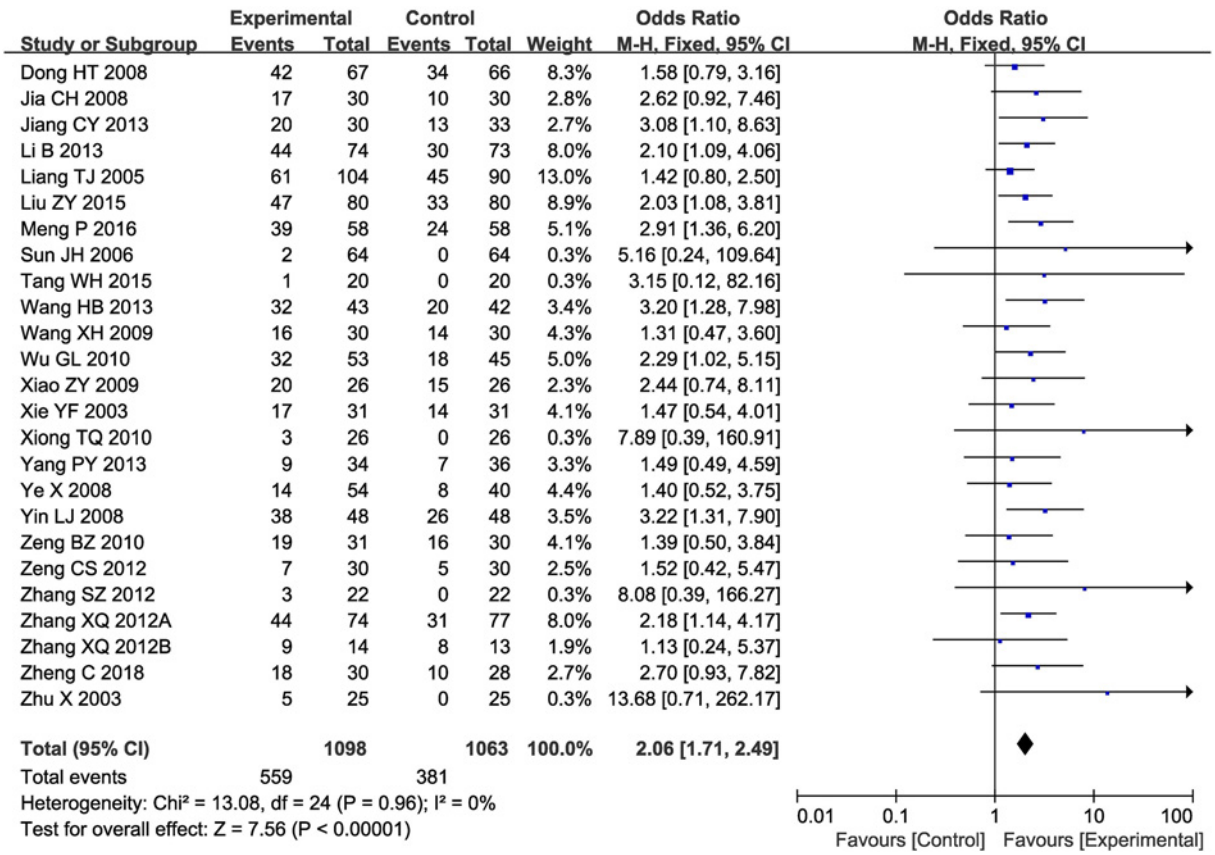

Figure 2. Forest plot of the comparison of ORR between the experimental and control groups

Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group. The 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			
Leukopenia	392	393	Fixed	8	0.37	0.49	0.36–0.67	<0.00001
Gastrointestinal adverse effects	195	195	Fixed	0	0.85	0.69	0.44–1.07	0.10
Nausea and vomiting	185	184	Fixed	0	1.00	0.81	0.45–1.48	0.49
Anorexia	112	112	Fixed	0	0.92	0.89	0.35–2.29	0.81
Thrombocytopenia	73	72	Fixed	0	0.84	0.76	0.28–2.06	0.59
Hepatotoxicity	60	61	Fixed	0	0.37	0.29	0.12–0.69	0.005
Myelosuppression	62	61	Fixed	0	1.00	0.26	0.12–0.56	0.0007
Anemia	73	72	Fixed	0	0.85	0.68	0.29–1.60	0.38

Control group, Conventional treatments alone group; Experimental group, Conventional treatments and JLC combined group.

P=0.59; and anemia, OR 0.68 [95% CI 0.29–1.60, *P*=0.38) did not differ significantly between the two groups. A fixed-effect model was used to analyze OR rate due to low heterogeneity.

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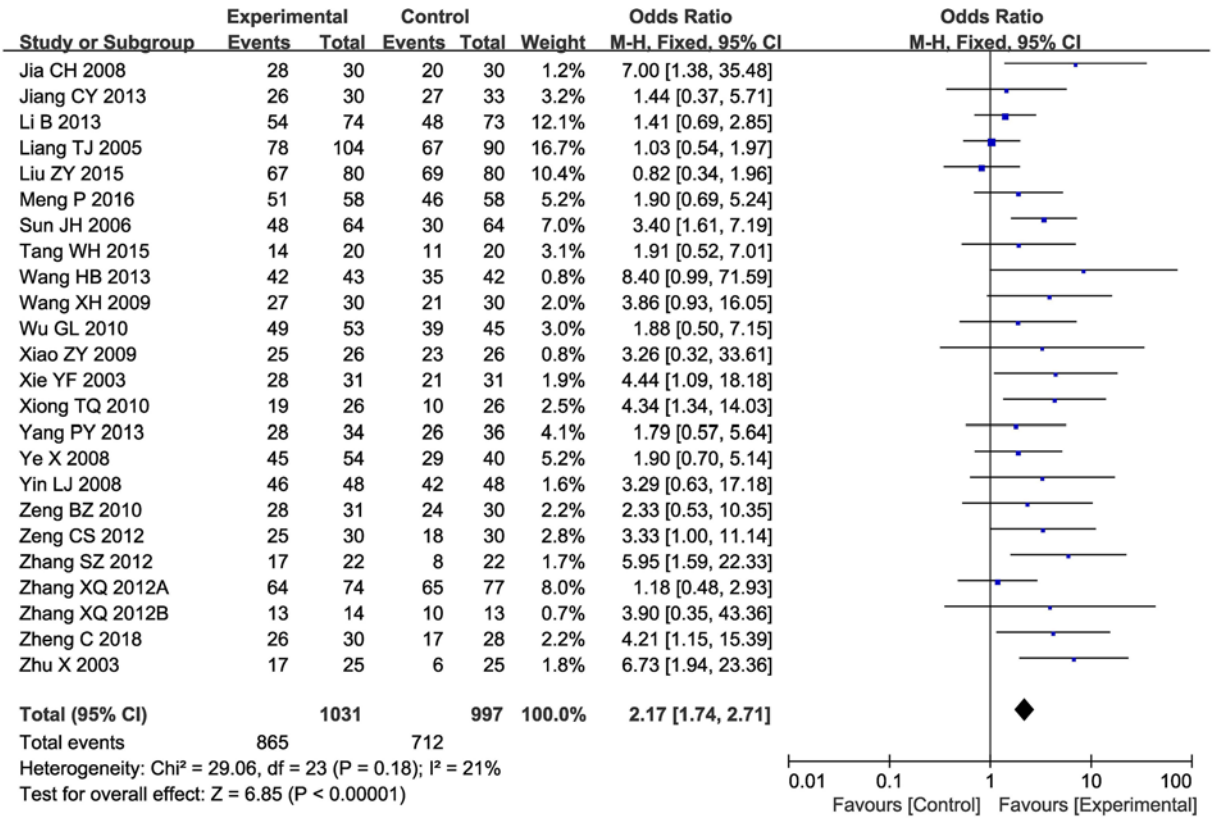

Figure 3. Forest plot of the comparison of DCR between the experimental and control groups

Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

Publication bias

Publication bias was visually assessed using funnel plots (Supplementary Figure S3) and quantified using Egger's test and Begg's regression test (Supplementary Table S2). The funnel plots were symmetrical for 12- and 24-month OS, and $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and leukopenia, but were asymmetrical for ORR, DCR and QIR. To determine whether bias affected the pooled risk of ORR, DCR and QIR, a trim-and-fill analysis was performed. The adjusted OR indicated a trend similar to the results of the primary analysis (Supplementary Table S2), reflecting the reliability of the primary conclusions.

Sensitivity analysis

A subgroup analysis was conducted to explore the source of heterogeneity for ORR and DCR. As shown in Supplementary Table S3, results revealed that no significant difference was found between the therapeutic regimens, sample size, and types of studies.

Discussion

JLC, a type of traditional Chinese medicine, has been clinically applied as an adjuvant therapy for decades. Several studies have reported that addition of JLC could be beneficial to patients with advanced HC [12,13]. Although there was a statistical analysis of published clinical trials, the exact therapeutic effects are yet to be systematically evaluated because of small sample sizes and different protocols among various studies. Therefore, in the present analysis, we performed a wide-ranging online search according to strict inclusion and exclusion criteria, to draw a clear and systematic conclusion.

Data from 29 trials [7,18–45] including 2488 patients with advanced HC were included in our meta-analysis. JLC in all the included studies was manufactured by Beijing Jiansheng Pharmaceutical Co., Ltd. The dosages of JLC were 2.0–3.0 g per day via oral administration. The pooled results revealed that the combination of JLC and conventional

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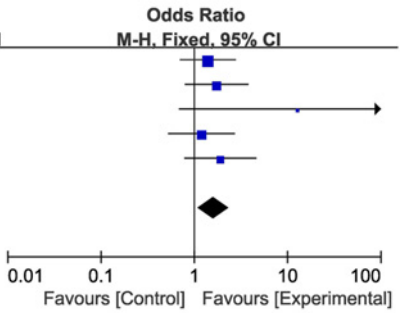
(A)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dong HT 2008	41	67	35	66	33.1%	1.40 [0.70, 2.78]
Liang TJ 2005	104	116	90	108	23.3%	1.73 [0.79, 3.79]
Wang HB 2013	43	43	37	42	1.0%	12.76 [0.68, 238.44]
Xie B 2008	47	61	45	61	25.0%	1.19 [0.52, 2.73]
Zhang XQ 2012A	65	74	61	77	17.6%	1.89 [0.78, 4.60]
Total (95% CI)		**361**		**354**	**100.0%**	**1.63 [1.11, 2.39]**
Total events	300		268			

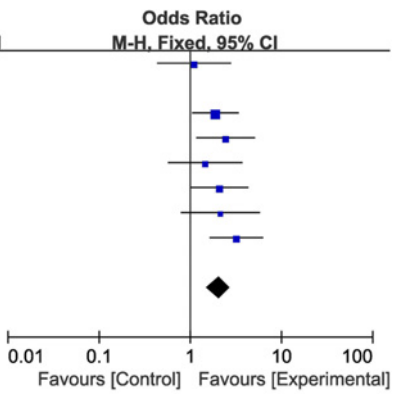
Heterogeneity: Chi² = 2.77, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)



(B)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dong HT 2008	11	67	10	66	12.8%	1.10 [0.43, 2.80]
Li H 2007	55	55	30	30		Not estimable
Liang TJ 2005	90	116	70	108	24.7%	1.88 [1.04, 3.39]
Sun JH 2006	30	64	17	64	13.7%	2.44 [1.16, 5.12]
Wang HB 2013	32	43	28	42	11.0%	1.45 [0.57, 3.72]
Xie B 2008	39	61	28	61	15.4%	2.09 [1.01, 4.32]
Ye X 2008	40	49	25	37	8.0%	2.13 [0.79, 5.79]
Zhang XQ 2012A	53	74	34	77	14.4%	3.19 [1.62, 6.28]
Total (95% CI)		**529**		**485**	**100.0%**	**2.05 [1.54, 2.73]**
Total events	350		242			

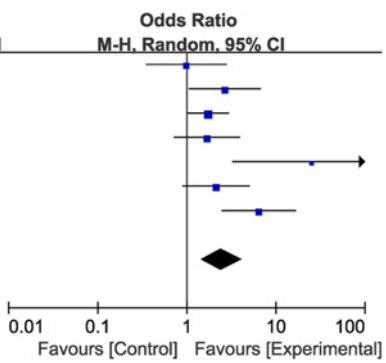
Heterogeneity: Chi² = 4.17, df = 6 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)



(C)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Dong HT 2008	8	67	8	66	13.2%	0.98 [0.35, 2.79]
Li H 2007	40	55	15	30	14.7%	2.67 [1.05, 6.76]
Liang TJ 2005	55	116	37	108	20.9%	1.73 [1.01, 2.97]
Wang HB 2013	25	43	19	42	15.8%	1.68 [0.71, 3.97]
Xie B 2008	18	61	1	61	5.4%	25.12 [3.23, 195.37]
Ye X 2008	29	49	15	37	15.6%	2.13 [0.89, 5.07]
Zhang XQ 2012A	26	74	6	77	14.3%	6.41 [2.45, 16.74]
Total (95% CI)		**465**		**421**	**100.0%**	**2.45 [1.44, 4.19]**
Total events	201		101			

Heterogeneity: Tau² = 0.28; Chi² = 14.14, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 3.29 (P = 0.001)



(D)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Li H 2007	34	55	11	30	20.3%	2.80 [1.11, 7.02]
Liang TJ 2005	23	116	11	108	34.1%	2.18 [1.01, 4.72]
Wang HB 2013	15	43	7	42	17.2%	2.68 [0.96, 7.47]
Ye X 2008	18	49	8	37	21.5%	2.10 [0.79, 5.58]
Zhang XQ 2012A	5	74	2	77	6.8%	2.72 [0.51, 14.47]
Total (95% CI)		**337**		**294**	**100.0%**	**2.41 [1.56, 3.74]**
Total events	95		39			

Heterogeneity: Chi² = 0.30, df = 4 (P = 0.99); I² = 0%
Test for overall effect: Z = 3.94 (P < 0.0001)

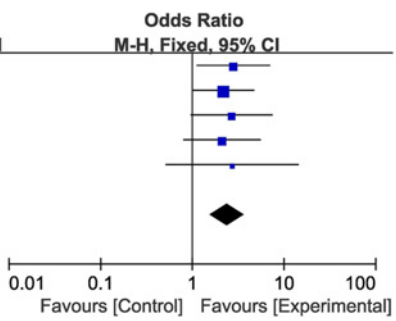


Figure 4. Comparisons of OS between experimental and control group

Forest plot of the comparison of 6- (**A**), 12- (**B**), 24- (**C**) and 36-month (**D**) OS between the experimental and control groups. Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group.

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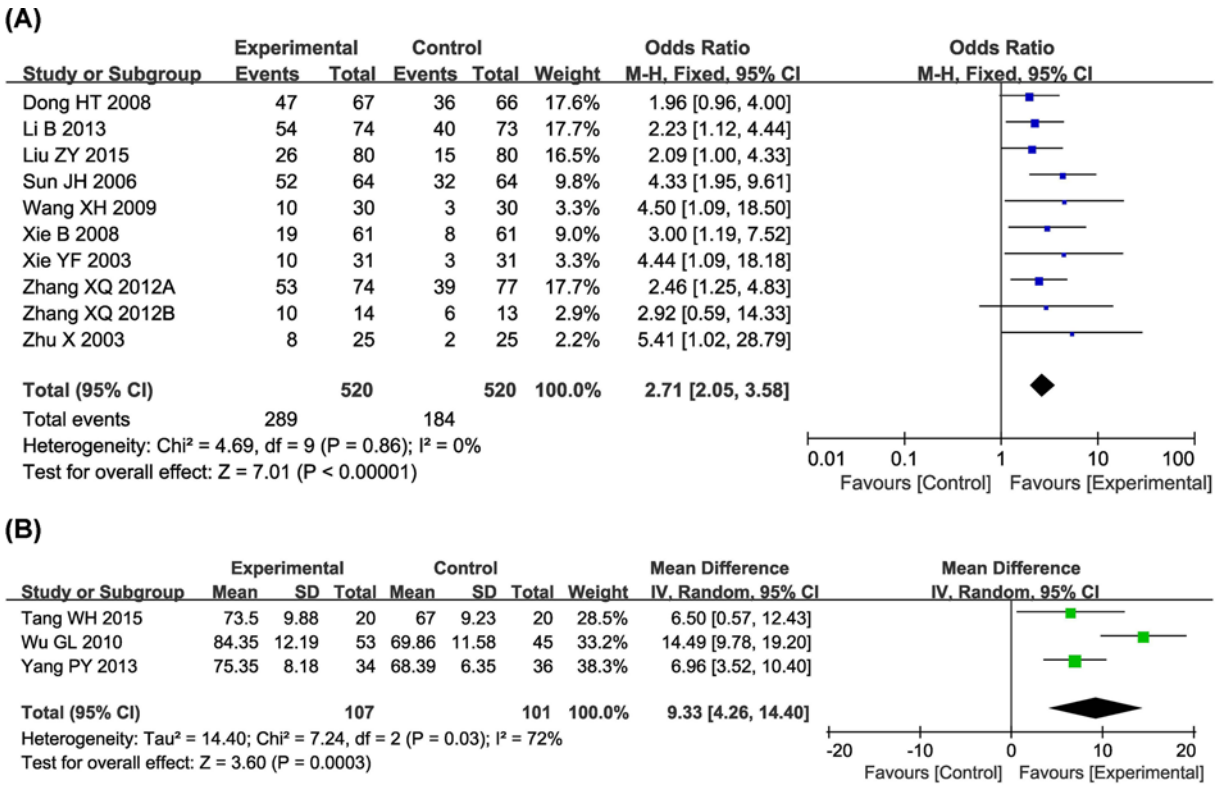

Figure 5. Comparisons of QoL between experimental and control group

Forest plot of the comparison of QIR (**A**) and KPS (**B**) between the experimental and control groups. Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group.

treatment for HC achieved more beneficial effects compared with those treated solely with conventional therapy. Compared with conventional treatment alone, JLC could significantly improve ORR, DCR and QoL in patients with HC ($P<0.05$). The study also assessed whether JLC could prolong the long-term survival rates of HC patients, and the results showed that the 6-, 12-, 24- and 36-month OS of patients were significantly prolonged compared with the control group. These results indicated that using JLC could improve the short- and long-term curative effects of conventional treatment for advanced HC. However, the analysis of therapeutic effects may have been influenced by several factors. Therefore, we performed a subgroup analysis to determine the influence of different therapeutic regimens, sample sizes, study type and evaluation criteria on ORR and DCR. Subgroup analysis revealed that the therapeutic efficacy of JLC did not appear to be affected by these factors. However, there were limited studies and insufficient sample sizes for these investigations, which may have resulted in insufficient assessment. Therefore, these results need to be confirmed by new evidence.

The immunosuppressed status of cancer patients has been reported previously [2]. Therefore, immune system reconstruction is one of several critical aspects in effectively treating malignancies. Many studies have reported that JLC can enhance the ability of the body's immunity and resistance to tumors [12]. Our analysis demonstrated that the percentages of $CD3^+$, $CD4^+$ and NK cells, and $CD4^+/CD8^+$ ratio, were significantly increased in HC patients treated with JLC, indicating that immune function in HC patients was improved after JLC adjuvant therapy.

Safety is the top priority of clinical treatment. Although JLC is cytotoxic to tumor cells, it may also be toxic to normal cells. As such, we analyzed 16 trials [18,20,26,28–30,32,33,36,38–44], involving 1192 patients, to evaluate adverse events according to World Health Organization standards. Meta-analysis revealed that patients who underwent JLC plus conventional treatment demonstrated a lower risk for leukopenia, hepatotoxicity and myelosuppression compared with conventional treatment alone, whereas analysis of other toxic side effects did not differ significantly. Therefore, JLC appears to be a safe auxiliary anti-tumor medicine for individuals with HC.

There were some limitations to our analysis. First, as an important Chinese patent medicine, JLC is mainly applied in China, which may lead to unavoidable regional bias. Second, several results demonstrated significant heterogeneity among the included trials, which may be due to the different tumor stages and ages of the HC patients and duration of

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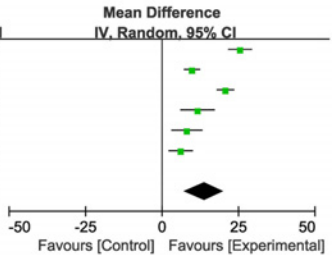
(A)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jia CH 2008	67.3	8.9	30	41.8	6.3	30	16.8%	25.50 [21.60, 29.40]
Meng P 2016	68.09	7.65	58	58.33	6.98	58	17.4%	9.76 [7.09, 12.43]
Yuan TW 2013	55.8	5.2	30	35.1	6.1	30	17.3%	20.70 [17.83, 23.57]
Zeng CS 2014	55.62	11.02	30	44.03	11.11	30	15.7%	11.59 [5.99, 17.19]
Zhang XQ 2012B	65.54	7.25	14	57.45	6.21	13	16.1%	8.09 [3.01, 13.17]
Zheng C 2018	66.34	8.18	30	60.29	7.25	28	16.7%	6.05 [2.08, 10.02]
Total (95% CI)			**192**			**189**	**100.0%**	**13.69 [7.40, 19.98]**

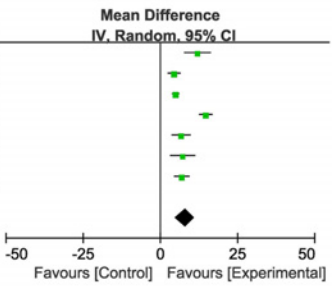
Heterogeneity: Tau² = 57.36; Chi² = 85.13, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.27 (P < 0.0001)



(B)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jia CH 2008	40	9.5	30	28	7.5	30	12.4%	12.00 [7.67, 16.33]
Meng P 2016	40.21	5.87	58	35.77	5.61	58	15.2%	4.44 [2.35, 6.53]
Xie B 2008	25.01	1.87	61	20.09	4.21	61	15.9%	4.92 [3.76, 6.08]
Yuan TW 2013	41.3	5.1	30	26.6	3.3	30	15.1%	14.70 [12.53, 16.87]
Zeng CS 2014	37.52	6.06	30	30.81	6.25	30	14.0%	6.71 [3.59, 9.83]
Zhang XQ 2012B	36.75	5.29	14	29.54	5.46	13	12.7%	7.21 [3.15, 11.27]
Zheng C 2018	40.55	4.71	30	33.62	5.1	28	14.7%	6.93 [4.40, 9.46]
Total (95% CI)			**253**			**250**	**100.0%**	**8.04 [4.94, 11.13]**

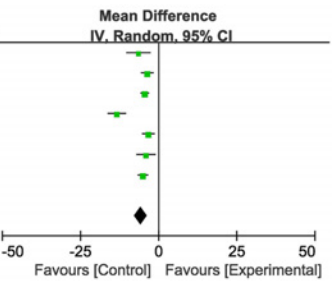
Heterogeneity: Tau² = 15.27; Chi² = 71.39, df = 6 (P < 0.00001); I² = 92%
Test for overall effect: Z = 5.09 (P < 0.00001)



(C)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jia CH 2008	23.7	8.2	30	30.2	7.2	30	10.9%	-6.50 [-10.40, -2.60]
Meng P 2016	31.6	5.44	58	35.27	5.69	58	15.3%	-3.67 [-5.70, -1.64]
Xie B 2008	23.97	2.16	61	28.45	4.94	61	16.6%	-4.48 [-5.83, -3.13]
Yuan TW 2013	25.1	5.2	30	38.5	6.3	30	13.2%	-13.40 [-16.32, -10.48]
Zeng CS 2014	22.96	4.13	30	26.26	3.89	30	15.3%	-3.30 [-5.33, -1.27]
Zhang XQ 2012B	32.34	4.57	14	36.43	3.53	13	12.8%	-4.09 [-7.16, -1.02]
Zheng C 2018	22.48	3.16	30	27.56	3.4	28	16.0%	-5.08 [-6.77, -3.39]
Total (95% CI)			**253**			**250**	**100.0%**	**-5.62 [-7.68, -3.56]**

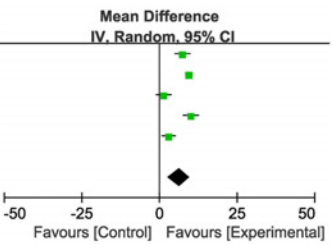
Heterogeneity: Tau² = 6.17; Chi² = 37.55, df = 6 (P < 0.00001); I² = 84%
Test for overall effect: Z = 5.34 (P < 0.00001)



(D)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jia CH 2008	14.6	6.4	30	7.22	3.18	30	19.5%	7.38 [4.82, 9.94]
Xie B 2008	26.84	3.41	61	17.39	3.37	61	21.4%	9.45 [8.25, 10.65]
Xie YF 2003	12.4	5.22	31	11.05	5.02	31	19.6%	1.35 [-1.20, 3.90]
Yuan TW 2013	31.3	4.2	30	21.2	6	30	19.4%	10.10 [7.48, 12.72]
Zeng CS 2014	31.3	4.59	30	28.33	4.24	30	20.1%	2.97 [0.73, 5.21]
Total (95% CI)			**182**			**182**	**100.0%**	**6.29 [2.88, 9.69]**

Heterogeneity: Tau² = 13.76; Chi² = 51.94, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.62 (P = 0.0003)



(E)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jia CH 2008	1.87	0.45	30	0.86	0.14	30	12.1%	1.01 [0.84, 1.18]
Xie B 2008	1.05	0.06	61	0.71	0.17	61	15.7%	0.34 [0.29, 0.39]
Xie YF 2003	1.31	0.24	31	1	0.12	31	14.6%	0.31 [0.22, 0.40]
Yuan TW 2013	1.31	0.59	30	1.05	0.35	30	9.5%	0.26 [0.01, 0.51]
Zeng BZ 2010	1.35	0.23	31	1.03	0.12	30	14.7%	0.32 [0.23, 0.41]
Zeng CS 2014	1.56	0.39	30	1.31	0.57	30	9.4%	0.25 [0.00, 0.50]
Zhang XQ 2012B	1.28	0.34	14	1.03	0.34	13	9.1%	0.25 [-0.01, 0.51]
Zheng C 2018	1.81	0.19	30	1.48	0.13	28	14.9%	0.33 [0.25, 0.41]
Total (95% CI)			**257**			**253**	**100.0%**	**0.39 [0.27, 0.51]**

Heterogeneity: Tau² = 0.02; Chi² = 62.05, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 6.47 (P < 0.00001)

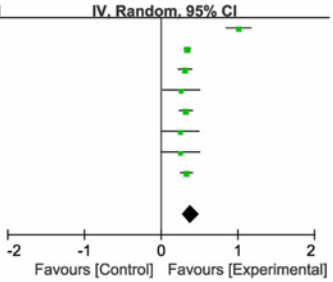


Figure 6. Comparisons of immune function between experimental and control group

Forest plot of the comparison of immune function indicators including $CD3^+$ (**A**), $CD4^+$ (**B**), $CD8^+$ (**C**) and NK (**D**) cells percentage and $CD4^+/CD8^+$ ratio (**E**) between the experimental and control groups. Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group.

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treatment. However, based on the currently available literature, there are insufficient data to perform more statistical analysis to evaluate correlations. Third, our results may have inherent bias due to unclear randomization methods, allocation concealment and blinding in some of the included trials. Finally, there were limited studies and sample sizes for immune function and safety evaluation; therefore, analytical bias is possible. All these limitations may have resulted in insufficient evaluations of the outcome indicators.

Conclusion

In summary, findings of this meta-analysis indicate that the combination of JLC and conventional treatment is effective in treating patients with advanced HC. The clinical application of JLC not only clearly enhanced the therapeutic effects of conventional treatment, but also effectively improved QoL and immune function in patients with HC. Thus, we anticipate that our study will provide valuable evidence for further evaluation of JLC. On the other hand, the low quality of some of the included publications increased the risk of bias, which, to some extent, affects the reliability of this research. Therefore, additional studies with high-quality evidence to verify the effectiveness of JLC-mediated therapy for HC are warranted.

Author Contribution

C.W.D. and H.X. conceived and designed the methods, extracted the original data and drafted the manuscript. H.X., W.W. and M.Y. performed statistical analysis. H.X. and C.W.D. interpreted the results. C.W.D. 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

Bcl-2, B-cell lymphoma-2; BNIP3, B-cell lymphoma-2/adenovirus E1B nineteen kilodalton interacting protein-3; CI, confidence interval; DCR, disease control rate; HC, hepatocellular carcinoma; JLC, Jinlong Capsule; KPS, Karnofsky Performance Score; NK, natural killer; OR, odds ratio; ORR, overall response rate; OS, overall survival; QIR, quality of life improved rate; QoL, quality of life; SFDA, State Food and Drug Administration.

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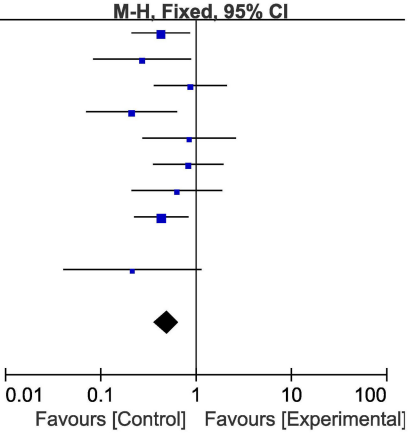
Dong HT 2008
Jiang CY 2013
Li B 2013
Meng P 2016
Tang WH 2015
Wang XH 2009
Wu GL 2010
Xiao ZY 2009
Xie B 2008
Xie YF 2003
Yang PY 2013
Ye X 2008
Yin LJ 2008
Yuan TW 2013
Zeng CS 2012
Zeng CS 2014
Zeng BZ 2010
Zhang SZ 2012
Zhang XQ 2012B
Zheng C 2018
Zhu X 2003
Random sequence generation (selection bias)
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

Supplementary Figure 1. Risk of bias summary: review of authors' judgments about each risk of bias item for included studies. **Note:** Each color represents a different level of bias: red for high-risk, green for low-risk, and yellow for unclear-risk of bias.

A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dong HT 2008	32	67	45	66	19.9%	0.43 [0.21, 0.86]
Jiang CY 2013	5	30	14	33	9.3%	0.27 [0.08, 0.89]
Wang HB 2013	15	43	16	42	8.8%	0.87 [0.36, 2.11]
Wang XH 2009	8	30	19	30	11.7%	0.21 [0.07, 0.63]
Xiao ZY 2009	9	26	10	26	5.5%	0.85 [0.27, 2.62]
Yin LJ 2008	15	48	17	48	9.8%	0.83 [0.35, 1.94]
Zeng CS 2014	8	30	11	30	6.8%	0.63 [0.21, 1.88]
Zhang XQ 2012A	35	74	52	77	22.5%	0.43 [0.22, 0.83]
Zhang XQ 2012B	14	14	13	13		Not estimable
Zheng C 2018	2	30	7	28	5.7%	0.21 [0.04, 1.14]
Total (95% CI)		**392**		**393**	**100.0%**	**0.49 [0.36, 0.67]**
Total events	143		204			

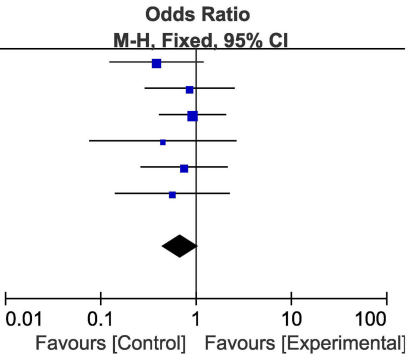
Heterogeneity: Chi² = 8.65, df = 8 (P = 0.37); I² = 8%
Test for overall effect: Z = 4.58 (P < 0.00001)



B

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jiang CY 2013	6	30	13	33	21.4%	0.38 [0.12, 1.20]
Xiao ZY 2009	12	26	13	26	15.1%	0.86 [0.29, 2.55]
Yin LJ 2008	20	48	21	48	26.4%	0.92 [0.41, 2.06]
Zeng BZ 2010	2	31	4	30	8.2%	0.45 [0.08, 2.65]
Zeng CS 2014	10	30	12	30	17.3%	0.75 [0.26, 2.15]
Zheng C 2018	4	30	6	28	11.6%	0.56 [0.14, 2.26]
Total (95% CI)		**195**		**195**	**100.0%**	**0.69 [0.44, 1.07]**
Total events	54		69			

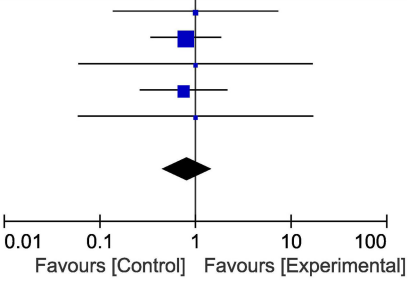
Heterogeneity: Chi² = 1.98, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)



C

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sun JH 2006	2	64	2	64	8.2%	1.00 [0.14, 7.33]
Wang HB 2013	19	43	21	42	50.0%	0.79 [0.34, 1.86]
Xiong TQ 2010	1	26	1	26	4.1%	1.00 [0.06, 16.89]
Zeng CS 2012	10	30	12	30	33.7%	0.75 [0.26, 2.15]
Zhang SZ 2012	1	22	1	22	4.0%	1.00 [0.06, 17.07]
Total (95% CI)		**185**		**184**	**100.0%**	**0.81 [0.45, 1.48]**
Total events	33		37			

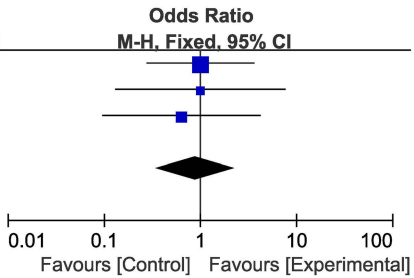
Heterogeneity: Chi² = 0.11, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.49)



D

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sun JH 2006	5	64	5	64	50.2%	1.00 [0.27, 3.64]
Xiong TQ 2010	2	26	2	26	20.1%	1.00 [0.13, 7.69]
Zhang SZ 2012	2	22	3	22	29.7%	0.63 [0.10, 4.22]
Total (95% CI)		**112**		**112**	**100.0%**	**0.89 [0.35, 2.29]**
Total events	9		10			

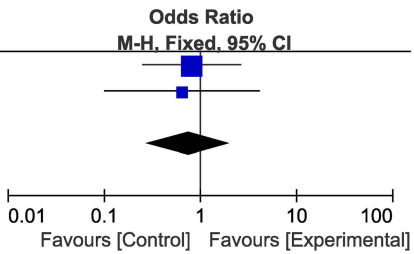
Heterogeneity: Chi² = 0.17, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



E

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Wang HB 2013	6	43	7	42	68.5%	0.81 [0.25, 2.65]
Zeng CS 2014	2	30	3	30	31.5%	0.64 [0.10, 4.15]
Total (95% CI)		**73**		**72**	**100.0%**	**0.76 [0.28, 2.06]**
Total events	8		10			

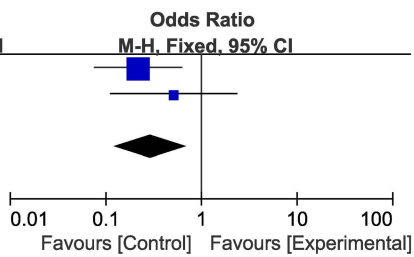
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



F

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jiang CY 2013	11	30	24	33	75.7%	0.22 [0.07, 0.63]
Zheng C 2018	3	30	5	28	24.3%	0.51 [0.11, 2.37]
Total (95% CI)		**60**		**61**	**100.0%**	**0.29 [0.12, 0.69]**
Total events	14		29			

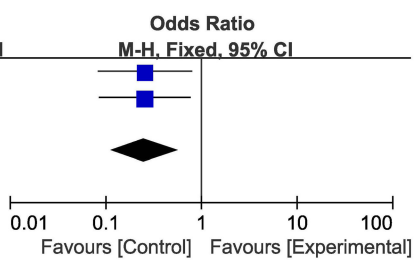
Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)



G

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Xie YF 2003	6	31	15	31	49.0%	0.26 [0.08, 0.80]
Zeng BZ 2010	7	31	16	30	51.0%	0.26 [0.08, 0.77]
Total (95% CI)		**62**		**61**	**100.0%**	**0.26 [0.12, 0.56]**
Total events	13		31			

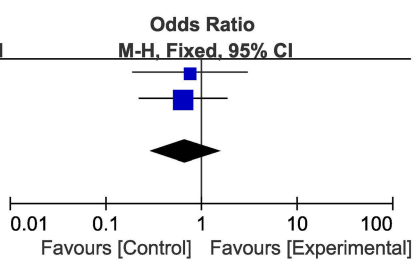
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 3.37 (P = 0.0007)



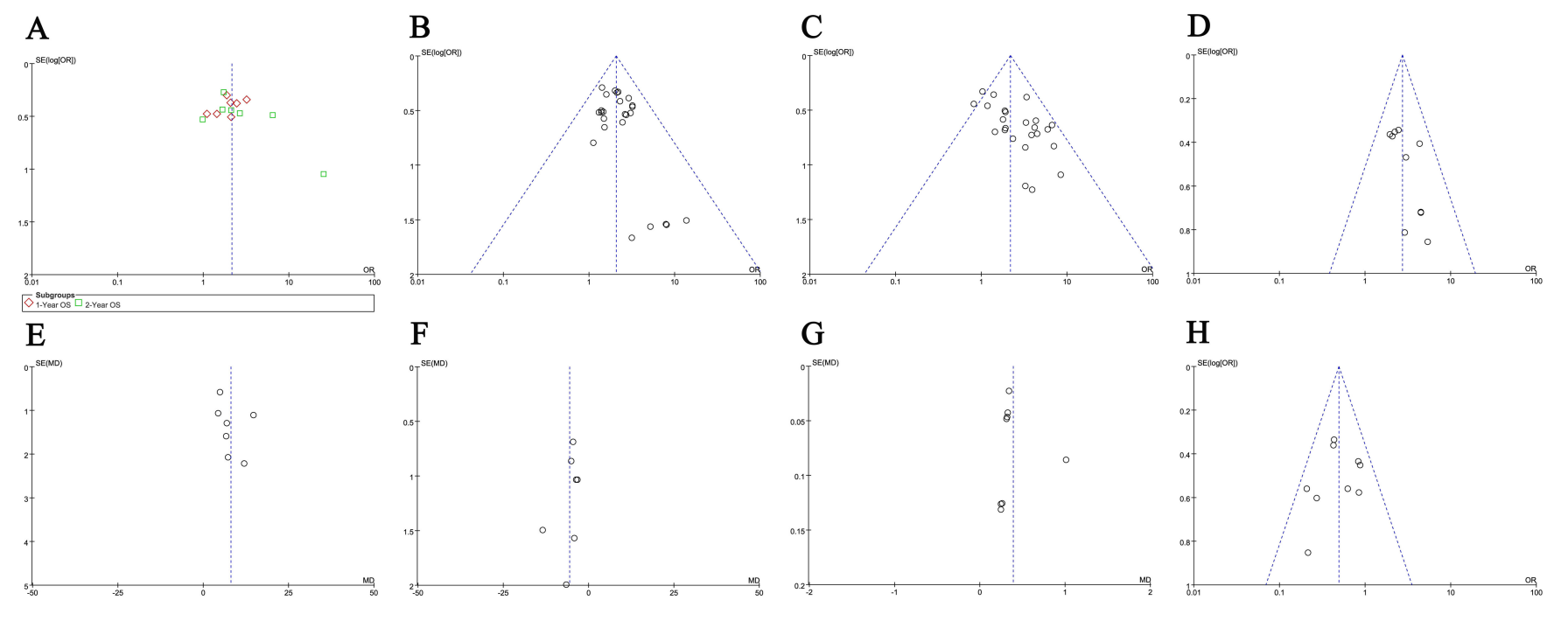
H

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Wang HB 2013	4	43	5	42	35.3%	0.76 [0.19, 3.05]
Zeng CS 2014	9	30	12	30	64.7%	0.64 [0.22, 1.87]
Total (95% CI)		**73**		**72**	**100.0%**	**0.68 [0.29, 1.60]**
Total events	13		17			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)



Supplementary Figure 2. Forest plot of the comparison of adverse effects including leukopenia (A), gastrointestinal adverse effects (B), nausea and vomiting (C), anorexia (D), thrombocytopenia (E), hepatotoxicity (F), myelosuppression (G) and anemia (H) between the experimental and control group. Control group, conventional treatment alone group; Experimental group, conventional treatment and JLC combined group; JLC, Jinlong capsule. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.


A
SE(log[OR])
OR
Subgroups
1-Year OS
2-Year OS
B
SE(log[OR])
OR
C
SE(log[OR])
OR
D
SE(log[OR])
OR
E
SE(MD)
MD
F
SE(MD)
MD
G
SE(MD)
MD
H
SE(log[OR])
OR

Supplementary Figure 3. Funnel plot of 12- and 24-month overall survival (OS, A), overall response rate (ORR, B), disease control rate (DCR, C), quality of life improved rate (QIR, D), $CD4^+$ (E), $CD8^+$ (F), $CD4^+/CD8^+$ (G), and leukopenia (H).

Supplementary Table 1. Quality assessment of non-randomized comparative studies

Study	Non-randomized studies								Additional criteria in comparative study				Total
	A	B	C	D	E	F	G	H	I	J	K	L	
Jia CH 2008[19]	2	1	2	1	2	1	2	0	2	2	2	2	19
Li H 2007[23]	2	1	2	1	1	2	2	0	2	2	2	2	19
Liang TJ 2005[24]	2	1	2	1	2	2	2	0	2	2	2	2	20
Liu ZY 2015[25]	2	1	2	1	2	1	2	0	2	2	2	2	19
Sun JH 2006[27]	2	1	2	2	2	2	2	0	2	2	2	2	21
Wang HB 2013[29]	2	1	2	2	2	2	2	0	2	2	2	2	21
Xiong TQ 2010[34]	2	1	2	2	2	1	2	0	2	2	2	2	20
Zhang XQ 2012[43]	2	1	2	2	2	2	2	0	2	2	2	2	21

Notes: The items are scored 0 (not reported), 1 (reported but inadequate) and 2 (reported and adequate).

A: A clearly stated aim; B: Inclusion of consecutive patients; C: Prospective collection of data; D: Endpoints appropriate to the aim of the study; E: Unbiased assessment of the study endpoint; F: Follow-up period appropriate to the aim of the study; G: Loss to follow up less than 5%; H: Prospective calculation of the study size; I: An adequate control group; J: Contemporary groups; K: Baseline equivalence of groups; L: Adequate statistical analyses.

Supplementary Table 2. Publication bias on therapeutic efficacy indexes (OS, ORR, DCR and QIR), immune function indexes ($CD4^+$, $CD8^+$, and $CD4^+/CD8^+$) and leucopenia.

Publication Bias	**Therapeutic efficacy indexes**					**Immune function indexes**			**Adverse events**
	12-month OS	24-month OS	ORR	DCR	QIR	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$	Leucopenia
Begg	0.764	0.133	0.168	0.035	0.107	0.133	0.548	0.902	0.675
Egger	0.301	0.161	0.049	0.001	0.036	0.321	0.331	0.603	0.542
Trim and fill analysis									
before			$P < .0001$	$P < .0001$	$P < .0001$				
after			$P < .0001$	$P < .0001$	$P < .0001$				

Notes: Parameters discussed in over 7 papers were conducted bias analyses.

Abbreviations: OS: overall survival; ORR: overall response rate; DCR: disease control rate; QIR: quality of life improved rate.

Supplementary Table 3. Subgroup analyses of ORR and DCR between the experimental and control group.

Parameter	Factors at study level	Patients Con/Exp	Analysis method	Heterogeneity I^2 (%)	Heterogeneity *P*-value	Odds Ratio	95% CI	*P*-value
ORR	**Therapeutic regimen**							
	JLC+TACE	739/719	Fixed	0	0.96	1.93	1.56-2.38	<0.00001
	JLC+SST	157/157	Fixed	0	0.97	7.37	1.91-28.36	0.004
	JLC+RT	117/116	Fixed	0	0.93	3.02	1.72-5.31	0.0001
	Study sample size							
	>80	719/683	Fixed	0	0.83	2.06	1.64-2.59	<0.00001
	<80	379/380	Fixed	0	0.89	2.06	1.48-2.88	<0.0001
	Type of control trials							
	RCTs	677/654	Fixed	0	0.93	2.06	1.63-2.61	<0.00001
	non-RCTs	421/409	Fixed	0	0.69	2.07	1.52-2.82	<0.00001
DCR	**Therapeutic regimen**							
	JLC+TACE	672/653	Fixed	6	0.39	1.66	1.26-2.18	0.0003
	JLC+SST	157/157	Fixed	0	0.65	3.90	2.42-6.29	<0.00001
	JLC+RT	117/116	Fixed	0	0.76	4.50	1.46-13.86	0.009
	Study sample size							
	>80	652/617	Fixed	24	0.23	1.62	1.22-2.15	0.0009
	<80	379/380	Fixed	0	0.91	3.46	2.40-4.99	<0.00001
	Type of control trials							
	RCTs	610/588	Fixed	0	0.83	2.48	1.84-3.33	<0.00001
	non-RCTs	421/409	Random	63	0.01	2.09	1.11-3.94	0.02

Notes: Con, Control group (Conventional treatment alone group); Exp, Experimental group (Conventional treatment and JLC combined group).

Abbreviations: ORR: overall response rate; DCR: disease control rate; JLC: Jinlong capsule; TACE: transcatheter arterial chemoembolization; SST: Support and symptomatic treatment; RT: Radiotherapy; RCTs; randomized controlled trials.