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ORIGINAL RESEARCH

Cinobufotalin as an effective adjuvant therapy for advanced gastric cancer: a meta-analysis of randomized controlled trials

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Purpose: This study aimed to investigate the efficacy and safety of combining cinobufotalin and chemotherapy for advanced gastric cancer (GC).

Patients and methods: Literature retrieval was performed in Cochrane Library, Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Wanfang database and Chinese Scientific Journal Database (VIP) before September 2018. The primary reported outcomes including therapeutic efficacy, quality of life (QoL), and adverse events were systematically evaluated.

Results: Data from 27 trials including 1,939 advanced GC patients were included. The results indicated that, compared with chemotherapy alone, the combination of chemotherapy and cinobufotalin significantly improved patients' overall response rate (odds ratio [OR] =1.88, 95% confidence interval [CI] =1.54–2.31, $P<0.00001$) and disease control rate (OR =2.05, 95% CI =1.63–2.58, $P<0.00001$). The QoL of patients also evidently improved after chemotherapy and cinobufotalin combined treatment, as indicated by increased QoL improved rate (OR =2.39, 95% CI =1.81–3.15, $P<0.00001$), Karnofsky Performance Score (OR =7.00, 95% CI =2.25–11.75, $P=0.004$) and pain relief rate (OR =7.00, 95% CI =2.25–11.75, $P=0.004$). Adverse events including nausea and vomiting, diarrhea, leukopenia, hand-foot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity caused by chemotherapy were evidently alleviated ($P<0.05$) when cinobufotalin was administered to GC patients.

Conclusion: Evidence from the meta-analysis suggested that the combination of chemotherapy and cinobufotalin is more effective in treating GC than chemotherapy alone. It alleviates the adverse effects associated with chemotherapy and improves the QoL of GC patients.

Keywords: cinobufotalin, traditional Chinese medicine, chemotherapy, gastric cancer, meta-analysis

Introduction

Gastric cancer (GC) represents the second leading cause of death among all cancer types and caused 782,685 deaths worldwide in 2018.[1] Currently, the incidence of GC has significantly increased, with about 1,033,701 new cases every year.[1] China has a high risk for GC, and the new cases of GC in this region account for about 43% in the world.[2] Despite the improvement of diagnostic and therapeutic methods in the past decades,[3,4] the prognosis of GC is still poor (5-year survival rate <20%) since it is mostly diagnosed at advanced stage.[3,4] Therefore, effective therapeutic approaches should be developed.

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Traditional Chinese medicine has an extensive history and has been more widely used as an effective adjuvant drug for cancer treatment.[5–10] Cinobufotalin is a cardiotonic steroid or bufotalin, which is extracted from the skin secretion of the giant toad.[10–14] Many in vitro studies have shown that cinobufotalin has antitumor activity and enhanced chemotherapeutic effect.[7,10,13,14] Cinobufotalin can inhibit the growth and metastasis of the tumor by inhibiting the expression of vascular endothelial growth factor and epidermal growth factor receptor.[15] Additionally, it can also kill tumor cells by inducing non-apoptotic death possibly depending on cyclophilin-D involved pathway.[12]

Several studies have indicated that chemotherapy combined with cinobufotalin exhibits more prominent therapeutic effects than chemotherapy alone for advanced GC.[16–42] Despite the intensive clinical studies using cinobufotalin and chemotherapy combined therapy in treating GC, its clinical efficacy and safety have not been systematically evaluated. In this study, we conducted a meta-analysis to investigate the treatment efficacy and safety of chemotherapy combined with cinobufotalin in comparison with chemotherapy alone for advanced GC to provide scientific reference for the design of future clinical trials.

Materials and methods

Search strategy and selection criteria

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane Handbook. Original articles were searched across eight electronic databases, including Cochrane Library, Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBM), Wanfang database and Chinese Scientific Journal Database (VIP) before September 2018, with key terms "huachansu" or "cinobufotalin," "cinobufacini," or "cinobufagin" combined with "gastric carcinoma" or "gastric cancer." No language limits were applied.

Selection Criteria: The inclusion criteria were as follows: (1) controlled trials concerning advanced GC patients, (2) literature comparing the clinical outcomes of chemotherapy plus cinobufotalin adjuvant therapy (experimental group) with chemotherapy treatments alone (control group) and (3) articles involving more than 40 GC patients. On the other hand, the exclusion criteria were as follows: (1) non-contrast articles, case studies and review papers and (2) patients with mixed malignancies.

Data extraction and quality assessment

Data were independently extracted by two investigators (Sun HL, and Bai MH) following the same inclusion criteria; disagreements were adjudicated by the third reviewer (Liu DL). The extracted characteristics were summarized as follows: (I) first author's names, (II) years of publication, (III) study locations, (IV) tumor stages, (V) Karnofsky Performance Score (KPS), (VI) number of cases, (VII) patient ages, (VIII) study parameter types, (IX) therapeutic regimens, (X) enrollment period and (XI) dosage of cinobufotalin. The included trial's quality was evaluated according to the Cochrane Handbook.[43]

Outcome definition

Clinical responses include treatment efficacy, quality of life (QoL) and adverse events. Treatment efficacy was assessed in terms of the overall survival rates (OS rates, defined as the length of time from the start of treatment to death from any cause), complete response (CR) rates, partial response (PR) rates, stable disease (SD) rates, progressive disease (PD) rates, overall response rates (ORRs, ORR=CR + PR) and disease control rates (DCRs, DCR=CR + PR + SD). Patients' QoL was evaluated using QoL improved rate (QIR), KPS and pain relief rate (PRR). Adverse events including nausea and vomiting, diarrhea, leucopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, oral mucositis, alopecia, hand-foot syndrome, anemia, gastrointestinal adverse effects, peripheral neurotoxicity, neutropenia and myelosuppression were also assessed.

Statistical analysis

RevMan 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 13.0 (Stata Corp., College Station, TX, USA) software were the main statistical analysis tools in this study. $P<0.05$ was considered statistically significant. Analysis model was determined by heterogeneity among studies assessed using Cochran's Q test, and publication bias was analyzed using Begg's and Egger's regression asymmetry tests and presented using funnel plots.[44] $I^2<50\%$ or $P>0.1$ indicated that the studies were homogenous. Treatment effects were mainly represented by odds ratio (OR) presented with a 95% confidence

interval (CI). Pooled analysis with publication bias determined that trim and fill method would be applied to coordinate the estimates of unpublished studies, and the adjusted results were compared with the original pooled OR.[45] Sensitivity analysis was performed to evaluate the impact of different therapeutic regimens, drug forms of cinobufotalin, sample sizes and research types on clinical efficacy.

Results

Search results

A total of 493 articles were identified and initially retrieved, and 275 papers were excluded due to duplication. After title and abstract review, 163 articles were further excluded because they did not include clinical trials (n=127) and were unrelated studies (n=34) or published before 2000 (n=2), leaving 55 studies as potentially relevant. After detailed assessment of full texts, articles without control group (n=8), studies with case reports (n=6), reviews or meta-analysis (n=5), and trials with insufficient data (n=9) were excluded. Finally, 27 trials[16–42] involving 1,939 advanced GC patients were included in this analysis (Figure 1).

Patient characteristics

After selection, all included studies were performed in different medical centers of China since 2000. In total, 972 advanced GC patients were treated with chemotherapy in combination with cinobufotalin adjuvant therapy, while 967 patients were treated with chemotherapy alone. Detailed information of the involved studies and GC patients is shown in Tables 1 and 2.

Quality assessment

The assessment of bias risk is shown in Figure 2. A total of 24 studies were determined as having low risk, and the remaining 3 studies were not true randomized controlled

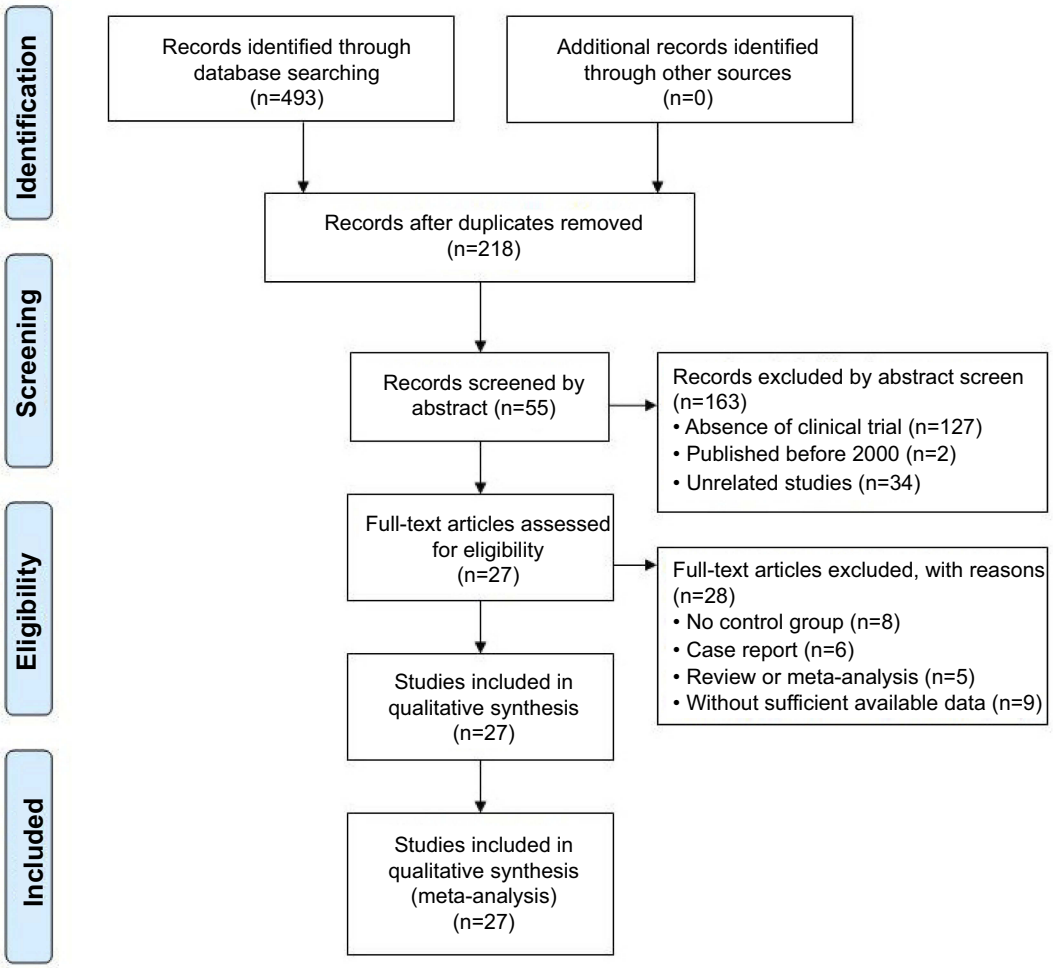

Figure 1 Flow diagram of the selection process.

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

Included studies	Nation	Tumor stage	KPS	Patients Con/Exp	Age (year)		Parameter types
					Con	Exp	
Cha XT (2016)[16]	China	ND	>70	20/20	ND	ND	ORR, DCR, AE
Chen GF (2012)[17]	China	IV	ND	86/62	71.8±18.6 (mean)	73.1±22.3 (mean)	ORR, DCR, QoL, AE
Chen HM(2009)[18]	China	III–IV	KPS≥60	33/34	49.6 (median)	50.6 (median)	ORR, DCR
Cui P (2009)[19]	China	ND	65 (mean)	23/32	ND	ND	ORR, DCR, QoL, AE
Guo CJ (2011)[20]	China	IV	≥50	43/43	ND	ND	ORR, DCR, QoL
Guo XY (2013)[21]	China	III–IV	≥65	38/42	64.8±3.7 (mean)	66.4±4.2 (mean)	ORR, DCR, QoL
Huang Q (2014)[22]	China	ND	≥60	20/26	55.8±4.9 (mean)	57.4±5.6 (mean)	ORR, DCR, QoL
Li W (2016)[23]	China	ND	ND	74/76	66.8±1.4 (mean)	66.6±1.5 (mean)	ORR, DCR, AE
Li YX (2012)[24]	China	ND	ND	74/74	ND	ND	ORR, DCR, QoL, AE
Lu B (2016)[25]	China	ND	>60	30/30	74.8±6.2 (mean)	73.7±5.1 (mean)	ORR, DCR, QoL, AE
Lu CH (2014)[26]	China	ND	71 (mean)	31/31	ND	ND	ORR, DCR
Tian B (2012)[27]	China	III–IV	KPS>60	22/23	ND	ND	ORR, DCR, AE
Wang F (2014)[28]	China	ND	ND	58/58	58.8 (mean)	58.4 (mean)	ORR, DCR, QoL, AE
Wang WM (2010)[29]	China	ND	>60	23/20	ND	ND	ORR, DCR, AE
Wang YH (2009)[30]	China	III–IV	>60	32/36	ND	ND	ORR, DCR, AE
Wang ZF (2012)[31]	China	ND	>60	24/24	59.1 (median)	58.7 (median)	ORR, DCR, QoL
Xiao XN (2018)[32]	China	III–IV	58 (mean)	31/34	ND	ND	ORR, DCR, QoL, AE
Xu DM (2015)[33]	China	ND	>60	30/30	65.0±3.9 (mean)	66.3±4.6 (mean)	ORR, DCR, QoL, AE
Xu YM (2016)[34]	China	ND	≥60	30/30	49.9 (median)	45.8 (median)	ORR, DCR, QoL, AE
Yang B (2017)[35]	China	ND	>60	34/34	53 (mean)	51 (mean)	ORR, DCR
Yang F (2018)[36]	China	ND	ND	25/25	50 (median)	54 (median)	ORR, DCR, QoL, AE
Zhang CW (2001)[37]	China	III–IV	>70	32/35	66 (median)	64 (median)	ORR, DCR, AE
Zhang RG (2004)[38]	China	IV	≥40	43/43	48 (median)	49 (median)	OS, ORR, DCR, AE
Zhang Y (2005)[39]	China	IV	≥40	29/28	54 (median)	57 (median)	OS, ORR, AE
Zheng YL (2007)[40]	China	III–IV	68 (mean)	20/20	ND	ND	OS, QoL
Zhu WK (2012)[41]	China	III–IV	≥70	32/32	62.8 (mean)	61.7 (mean)	ORR, DCR, QoL, AE
Zou HP (2012)[42]	China	III–IV	ND	30/30	56.5 (median)	59.1 (median)	ORR, DCR, AE

Notes: Con, control group (chemotherapy alone group); Exp, experimental group (chemotherapy and cinobufotalin combined group).
Abbreviations: ND, non determined; KPS, karnofsky performance score; ORR, overall response rate; DCR, disease control rate; QoL, quality of life; AE, adverse events.

Table 2 Information on cinobufotalin combined with chemotherapy

Included studies	Therapeutic regimen		Enrollment Period	Dosage of cinobufotalin
	Experimental group	Control group		
Cha XT (2016)[16]	Oxaliplatin+Tegafur+CF/SF+Cinobufotalin[a]	Oxaliplatin+Tegafur+CF/SF	January 2013–March 2016	750 mg/time, 3 times/day
Chen GF (2012)[17]	Capecitabine+Cinobufotalin[b]	Capecitabine	October 2006–October 2010	10 ml/time, 3 times/day
Chen HM (2009)[18]	Paclitaxel+Cisplatin+5-Fu+Cinobufotalin[b]	Paclitaxel+Cisplatin+5-Fu	October 2005–December 2007	30 ml/time, 1 time/day
Cui P (2009)[19]	FOLFOX+Cinobufotalin[b]	FOLFOX	2004–2006	30 ml/time, 1 time/day
Guo CJ (2011)[20]	Docetaxel+Cinobufotalin[b]	Docetaxel	March 2005–March 2010	20 ml/time, 1 time/day
Guo XY (2013)[21]	FOLFOX+Cinobufotalin[c]	FOLFOX	January 2009–May 2010	1200 mg/time, 4 times/day
Huang Q (2014)[22]	XELOX+Cinobufotalin[b]	XELOX	August 2009–August 2013	50 ml/time, 1 time/day
Li W (2016)[23]	Capecitabine+Cinobufotalin[b]	Capecitabine	January 2012–January 2015	10-20 ml/time, 1 time/day
Li YX (2012)[24]	Capecitabine+Cinobufotalin[b]	Capecitabine	January 2006–July 2011	10 ml/time, 1 time/day
Lu B (2016)[25]	Capecitabine+Cinobufotalin[a]	Capecitabine	January 2010–December 2012	500 mg/time, 3 times/day,
Lu CH (2014)[26]	FOLFOX+Cinobufotalin[b]	FOLFOX	2009–2013	20 ml/time, 1 time/day
Tian B (2012)[27]	FOLFOX+Cinobufotalin[b]	FOLFOX	2004–2006	30 ml/time, 1 time/day
Wang F (2014)[28]	Cisplatin+5-Fu+Cinobufotalin[a]	Cisplatin+5-Fu	ND	500 mg/time, 3 times/day,
Wang WM (2010)[29]	S-1+Cinobufotalin[a]	S-1	October 2011–October 2013	500 mg, 3 times/day
Wang YH (2009)[30]	FOLFOX+Cinobufotalin[b]	FOLFOX	December 2004–May 2008	10-20 ml/time, 1 time/day
Wang ZF (2012)[31]	FOLFOX+Cinobufotalin[b]	FOLFOX	December 2003–May 2008	20 ml/time, 1 time/day
Xiao XN (2018)[32]	FOLFOX+Cinobufotalin[b]	FOLFOX	January 2008–December 2010	10-20 ml/time, 1 time/day
Xu DM (2015)[33]	Docetaxel+Cisplatin+Cinobufotalin[b]	Docetaxel+Cisplatin	2013–2016	20 ml/time, 1 time/day
Xu YM (2016)[34]	Capecitabine+Cinobufotalin[b]	Capecitabine	June 2010–June 2011	20 ml/time, 1 time/day
Yang B (2017)[35]	FOLFOX+Cinobufotalin[a]	FOLFOX	January 2014–April 2015	750 mg/time, 3 times/day,
Yang F (2018)[36]	XELOX+Cinobufotalin[b]	XELOX	January 2015–June 2017	20 ml/time, 1 time/day
Zhang CW (2001)[37]	EOF+Cinobufotalin[a]	EOF	May 2014–May 2015	200-500 mg/time, 3 times/day
Zhang RG (2004)[38]	Etoposide+Leucovorin+5-Fu+Cinobufotalin[b]	Etoposide+Leucovorin+5-Fu	March 1999–December 2000	20 ml/time, 1 time/day
Zhang Y (2005)[39]	HCPT+CF+5-Fu+Cinobufotalin[b]	HCPT+CF+5-Fu	July 1998–June 2003	20 ml/time, 1 time/day
Zheng YL (2007)[40]	FOLFOX+Cinobufotalin[b]	FOLFOX	March 2002–February 2003	50 ml/time, 1 time/day
Zhu WK (2012)[41]	Oxaliplatin+Capecitabine+Cinobufotalin[b]	Oxaliplatin+Capecitabine	March 2010–MArch 2011	30 ml/time, 1 time/day
Zou HP (2012)[42]	EOF+Cinobufotalin[b]	EOF	May 2008–May 2011	20 ml/time, 1 time/day

Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. a, cinobufotalin capsule; b, cinobufotalin injection; c, cinobufotalin tablet; S-1, Gimeracil and Oteracil Porassium Capsules.

Abbreviations: ND, non determined; CF, Calcium folinate; SF, Sodium folinate; Fu, Fluorouracil; HCPT, Hydroxycamptothecin; FOLFOX, Oxaliplatin+CF+5-Fu; XELOX, Oxaliplatin+Capecitabine; EOF, Epirubicin+Oxaliplatin+5-Fu.

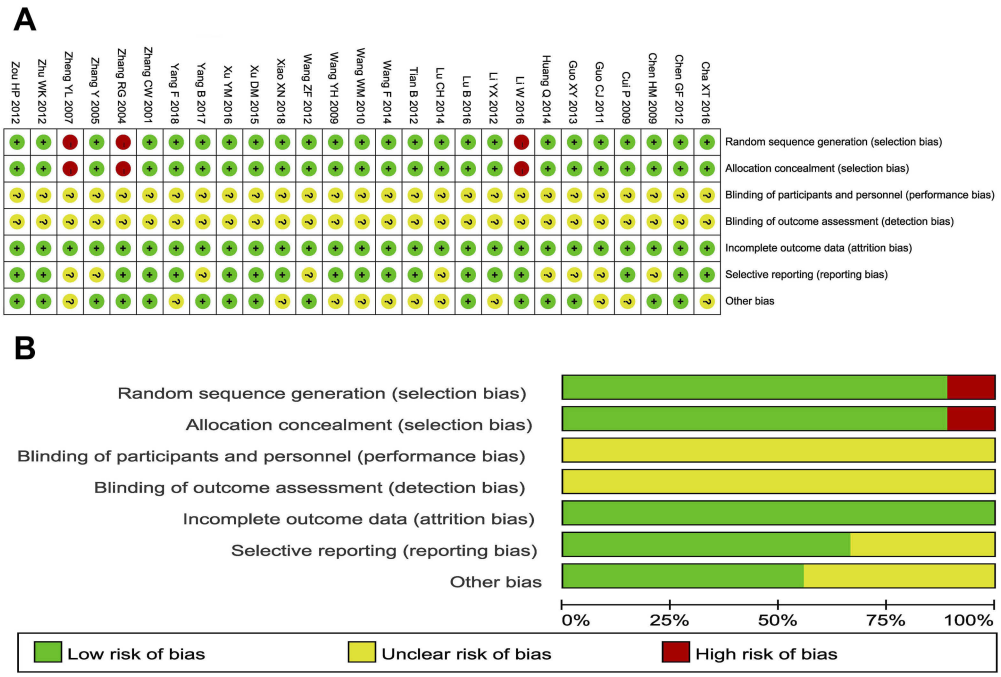

Figure 2 (**A**) Risk of bias summary: review of authors' judgments about each risk of bias item for included studies. (**B**) Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all included studies. Each color represents a different level of bias: red for high-risk, green for low-risk and yellow for unclear-risk of bias.

trials. All included trials did not provide clear description of performance and detection risks. The attrition risks of involved trials were low; 9 trials were considered as having unclear risk owing to selective reporting.

Therapeutic efficacy assessment

As shown in Figures 3 and 4, Figure S1 and Table 3, the pooled results showed that patients who underwent combined therapy had significantly improved CR, PR, ORR and DCR (CR, OR =1.69, 95% CI =1.11–2.57, P=0.01; PR, OR =1.69, 95% CI =1.38–2.08, P<0.00001; ORR, OR =1.88, 95% CI =1.54–2.31, P<0.00001; DCR, OR =2.05, 95% CI =1.63–2.58, P<0.00001) and significantly decreased PD (OR =0.49, 95% CI =0.39–0.61, P<0.00001), whereas SD and 6- and 12-months OS rates had no significant

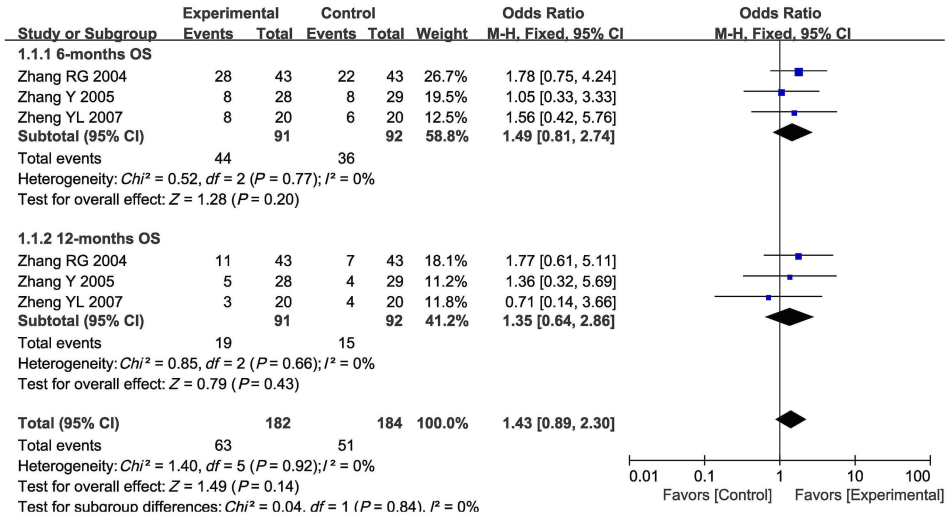

Figure 3 Forest plot of the comparison of 6-months (**A**) and 12-months (**B**) overall survival (OS) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

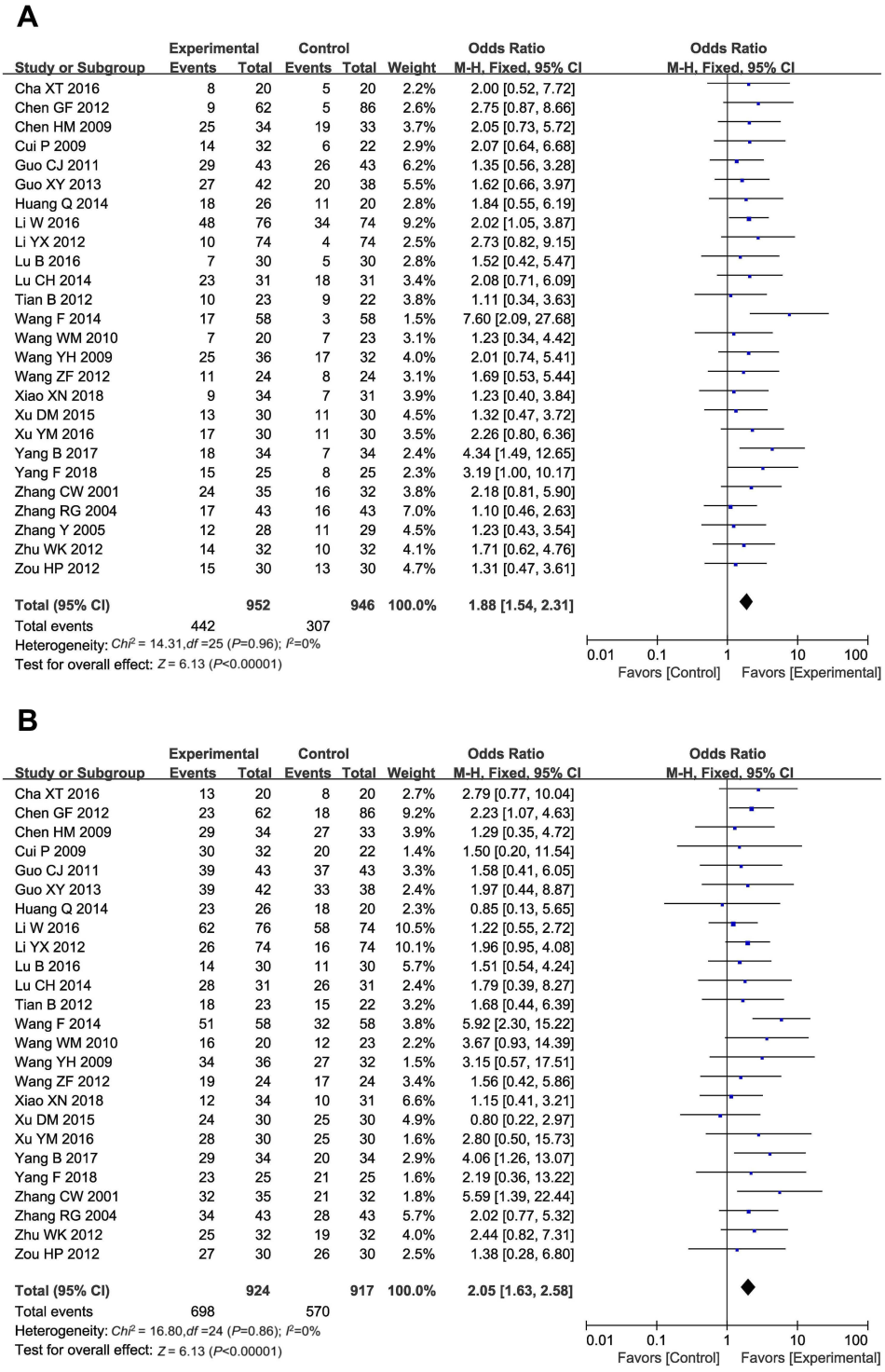

Figure 4 Forest plot of the comparison of overall response rate (ORR, **A**) and disease control rate (DCR, **B**) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

differences in patients who received chemotherapy alone (SD, OR =0.94, 95% CI =0.76–1.15, *P*=0.53; 6-months OS, OR =1.49, 95% CI =0.81–2.74, *P*=0.20; 12-months OS, OR =1.35, 95% CI =0.64–2.86, *P*=0.43). Fixed effect models were used to analyze OR rate because of low heterogeneity.

Table 3 Comparison of CR, PR, SD, PD, ORR and DCR between the experimental and control group

Parameter	Experimental group	Control group	Analysis method	Heterogeneity		Odds Ratio (OR)	95% CI	P-value
	No. patients (n)	No. patients (n)		I^2 (%)	P-value			
CR	924	917	Fixed	0	1.00	1.69	1.11 to 2.57	0.01
PR	924	917	Fixed	0	0.95	1.69	1.38 to 2.08	<0.00001
SD	924	917	Fixed	0	0.62	0.94	0.76 to 1.15	0.53
PD	924	917	Fixed	0	0.86	0.49	0.39 to 0.61	<0.00001
ORR	952	946	Fixed	0	0.96	1.88	1.54 to 2.31	<0.00001
DCR	924	917	Fixed	0	0.86	2.05	1.63 to 2.58	<0.00001

Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

Quality of life assessment

QoL was evaluated in this analysis. Result showed that QoL of patients in the combined group was significantly better than that of the control group, indicated by increased QIR, KPS and PRR (Figure 5, QIR, OR =2.39, 95% CI =1.81–3.15, $P<0.00001$; KPS, OR =7.00, 95% CI =2.25–11.75, $P=0.004$; PRR, OR =4.06, 95% CI =2.24–7.35, $P<0.00001$).

Adverse event assessment

As shown in Table 4 and Figure S2, patients treated with cinobufotalin and chemotherapy combined therapy showed lower incidences of nausea and vomiting, diarrhea, leucopenia, hand-foot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity (nausea and vomiting, OR =0.55, 95% CI =0.41–0.74, $P<0.0001$; diarrhea, OR =0.65, 95% CI =0.46–0.90, $P=0.010$; leucopenia, OR =0.62, 95% CI =0.47–0.82, $P=0.0008$; hand-foot syndrome, OR =0.57, 95% CI =0.41–0.79, $P=0.0007$; anemia, OR =0.69, 95% CI =0.48–0.99, $P=0.05$; gastrointestinal side effects, OR =0.56, 95% CI =0.32–1.00, $P=0.05$; peripheral neurotoxicity, OR =0.32, 95% CI =0.20–0.50, $P<0.00001$), whereas analysis on thrombocytopenia, hepatotoxicity, nephrotoxicity, oral mucositis, alopecia, neutropenia and myelosuppression (thrombocytopenia, OR =0.69, 95% CI =0.44–1.11, $P=0.13$; hepatotoxicity, OR =0.53, 95% CI =0.24–1.16, $P=0.11$; nephrotoxicity, OR =0.56, 95% CI =0.16–1.95, $P=0.36$; oral mucositis, OR =0.62, 95% CI =0.28–1.34, $P=0.22$; alopecia, OR =0.61, 95% CI =0.24–1.56, $P=0.30$; neutropenia, OR =0.45, 95% CI =0.14 −1.42, $P=0.17$; myelosuppression, OR =0.38, 95% CI =0.08–1.84, $P=0.23$) did not differ significantly between the two groups.

Publication bias

Funnel plots drawn for the studies on primary outcomes (CR, PR, SD, PD, ORR, DCR and adverse events) were approximately symmetrical, which indicated generally controlled publication bias and reliability of our primary conclusions (Figure 6 and S3).

We also assessed publication bias using Begg's and Egger's regression asymmetry tests (Table 5), and PR and leucopenia were found with bias (PR, Begg, 0.038; Egger, 0.015; leucopenia, Begg, 0.003; Egger, <0.0001). To determine if the bias affects the pooled risk, we conducted a trim and fill analysis. The adjusted OR rate indicated the same trend with the result of the primary analysis (PR [before, $P<0.0001$; after, $P<0.0001$], leukopenia [before, $P=0.0002$; after. $P=0.0002$]), reflecting the

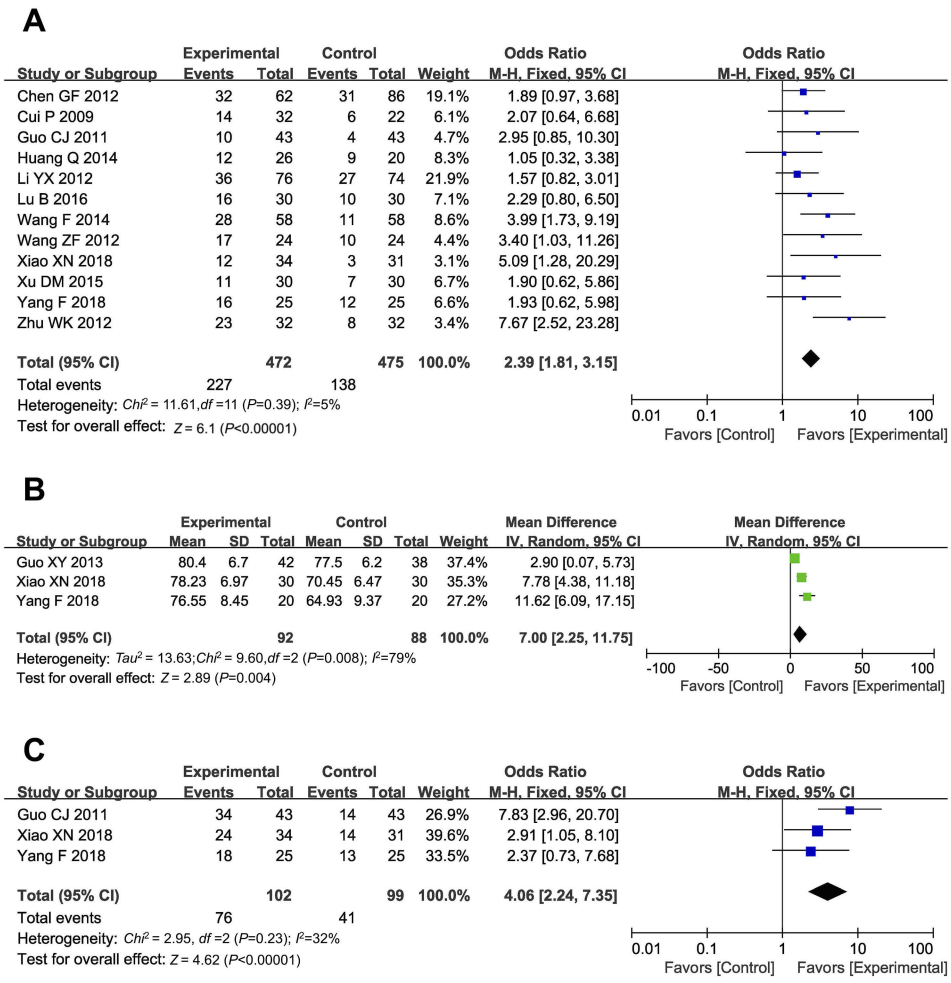

Figure 5 Forest plot of the comparison of quality of life improved rate (QIR, **A**), karnofsky performance score (KPS, **B**) and pain relief rate (PRR, **C**) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

reliability of our primary conclusions, except those based on a few number of trials.

Sensitivity analysis

We performed subgroup analysis to explore the source of heterogeneity in ORR and DCR with respect to therapeutic regimens, drug forms of cinobufotalin, sample sizes and research types. As shown in Table 6, our analysis results showed that no significant difference was found between different forms of cinobufotalin, sample sizes and research types. Moreover, cinobufotalin combined with FOLFOX/XELOX/capecitabine chemotherapy regimens was found to be more effective for GC treatment.

Discussion

In view of the limitations of the current chemotherapy for malignancies such as drug resistance and toxic side effects, clinicians have been exploring complementary and alternative medicine treatments to improve patients' survival time or QoL and reduce side effects caused by chemotherapy.[6,10,46,47] Traditional Chinese medicine, particularly cinobufotalin, has been clinically applied as an adjuvant therapy for decades.[7,10,11] Several studies have been reported that the addition of cinobufotalin could be beneficial to advanced GC patients.[16–42] Even though there was a statistical analysis of published clinical trials, the exact therapeutic effects were still not systematically evaluated because of small sample sizes and different applied protocols in different studies. Therefore, in this analysis, we conducted a wide range of online search according to strict inclusion and exclusion criteria to provide clear and systematical conclusion.

Our meta-analysis revealed that cinobufotalin and chemotherapy combined therapy for GC patients achieved

Table 4 Comparison of adverse events between the experimental and control group

Adverse events	Experimental group	Control group	Analysis method	Heterogeneity		Odds Ratio (OR)	95% CI	*P*-value
	No. of patients (n)	No. of patients (n)		I^2 (%)	*P*-value			
Nausea, vomiting	452	437	Fixed	37	0.09	0.55	0.41 to 0.74	<0.0001
Nausea, vomiting I+II	292	279	Fixed	0	0.50	0.83	0.59 to 1.16	0.27
Nausea, vomiting III+IV	292	279	Fixed	4	0.41	0.41	0.23 to 0.75	0.003
Diarrhea	395	379	Fixed	0	0.88	0.65	0.46 to 0.90	0.010
Diarrhea I+II	235	221	Fixed	0	0.69	0.84	0.56 to 1.27	0.41
Diarrhea III+IV	235	221	Fixed	0	1.00	0.27	0.10 to 0.75	0.01
Leucopenia	420	429	Fixed	34	0.13	0.62	0.47 to 0.82	0.0008
Leucopenia I+II	250	238	Fixed	0	0.86	0.57	0.39 to 0.83	0.003
Leucopenia III+IV	250	238	Fixed	0	0.77	0.36	0.17 to 0.75	0.007
Thrombocytopenia	178	178	Fixed	0	0.81	0.69	0.44 to 1.11	0.13
Thrombocytopenia I+II	178	178	Fixed	0	0.84	0.70	0.43 to 1.13	0.14
Thrombocytopenia III+IV	178	178	Fixed	0	0.83	0.91	0.39 to 2.14	0.83
Hepatotoxicity	193	193	Random	56	0.04	0.53	0.24 to 1.16	0.11
Hepatotoxicity I+II	193	193	Fixed	26	0.24	0.61	0.38 to 0.97	0.04
Hepatotoxicity III+IV	193	193	Fixed	0	0.70	0.14	0.02 to 0.81	0.03
Nephrotoxicity	117	107	Fixed	0	0.77	0.56	0.16 to 1.95	0.36
Nephrotoxicity I+II	117	107	Fixed	0	0.54	0.63	0.16 to 2.46	0.51
Nephrotoxicity III+IV	117	107	Fixed			0.32	0.01 to 8.24	0.49
Oral mucositis	235	233	Random	64	0.010	0.62	0.28 to 1.34	0.22
Oral mucositis I+II	179	178	Fixed	44	0.13	1.08	0.68 to 1.72	0.74
Oral mucositis III+IV	179	178	Fixed	0	0.58	0.54	0.15 to 1.96	0.35
Alopecia	133	130	Fixed	0	0.58	0.61	0.24 to 1.56	0.30
Alopecia I+II	133	130	Fixed	0	0.93	0.93	0.48 to 1.81	0.83
Alopecia III+IV	133	130	Fixed	0	0.97	0.72	0.30 to 1.75	0.47
Hand foot syndrome	334	356	Fixed	0	0.52	0.57	0.41 to 0.79	0.0007
Hand foot syndrome I+II	92	92	Fixed	12	0.32	0.64	0.33 to 1.24	0.18
Hand foot syndrome III+IV	92	92	Fixed			0.48	0.04 to 5.63	0.56
Anemia	292	291	Fixed	0	0.91	0.69	0.48 to 0.99	0.05
Anemia I+II	186	187	Fixed	0	0.65	0.92	0.60 to 1.42	0.71
Anemia III+IV	186	187	Fixed	0	0.87	0.34	0.12 to 0.96	0.04
Gastrointestinal adverse effects	277	295	Random	57	0.04	0.56	0.32 to 1.00	0.05
Gastrointestinal adverse effects I+II	71	72	Fixed	0	0.75	0.71	0.35 to 1.42	0.33
Gastrointestinal adverse effects III+IV	71	72	Fixed			0.39	0.09 to 1.60	0.19
Peripheral neurotoxicity	265	263	Fixed	0	0.59	0.32	0.20 to 0.50	<0.00001

(*Continued*)

Table 4 (Continued).

Adverse events	Experimental group	Control group	Analysis method	Heterogeneity		Odds Ratio (OR)	95% CI	P-value
	No. of patients (n)	No. of patients (n)		I^2 (%)	P-value			
Peripheral neurotoxicity I+II	103	104	Fixed	29	0.24	0.52	0.26 to 1.03	0.06
Peripheral neurotoxicity III+IV	103	104	Fixed	0	0.53	0.58	0.21 to 1.63	0.30
Neutropenia	55	55	Fixed	0	0.98	0.45	0.14 to 1.42	0.17
Neutropenia I+II	55	55	Fixed	0	0.35	0.93	0.44 to 1.96	0.85
Neutropenia III+IV	55	55	Fixed	0	0.40	0.73	0.34 to 1.59	0.43
Myelosuppression	94	90	Random	80	0.03	0.38	0.08 to 1.84	0.23
Myelosuppression I+II	58	58	Fixed			1.09	0.48 to 2.49	0.83
Myelosuppression III+IV	58	58	Fixed			0.24	0.03 to 2.19	0.20

Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.

more beneficial effects in comparison with those treated with chemotherapy alone. Combined therapy-treated patients broadly exhibited increased ORR and DCR ($P<0.05$) and also significantly improved their QoL. These results indicated that using cinobufotalin could improve the curative effects of chemotherapy.

Safety is the top priority of the clinical treatment. One trial[7] that was conducted at Fudan University Cancer Hospital showed that cinobufotalin is well tolerated by hepatocellular carcinoma, non-small-cell lung cancer and pancreatic cancer patients (only mild adverse events were observed in cancer patients who received cinobufotalin therapy; no grade III and IV toxicities were observed). Our analysis showed that most of the adverse events caused by chemotherapy, including nausea and vomiting, diarrhea, leucopenia, hand-foot syndrome, anemia, gastrointestinal side effects and peripheral neurotoxicity, were alleviated with cinobufotalin combination therapy ($P<0.05$). Therefore, cinobufotalin is a safe auxiliary antitumor medicine for GC and can effectively alleviate the adverse events associated with chemotherapy.

The analysis on therapeutic effects may be influenced by several factors. In our study, no difference was found between different drug forms of cinobufotalin, sample sizes and research types. Cinobufotalin combined with FOLFOX/XELOX/capecitabine chemotherapy regimens was more effective for GC treatment (Table 6). However, a comparative analysis of the above-mentioned individual chemotherapy regimens should be performed in the future to rule out the possibility that the therapeutic advantage of cinobufotalin combined with FOLFOX, XELOX or capecitabine is due to the better therapeutic effect of them alone compared to that of EOF. As a summary, recent studies on the impact of these factors on the curative effects of cinobufotalin adjuvant therapy remain insufficient, and hence, further investigations should be performed.

There are some limitations in our analysis. First, although traditional Chinese medicine has been exported to 185 countries and regions, its main markets still remained in Asia.[48] As a traditional medicine, cinobufotalin was mainly applied in China, which may bring the unavoidable regional bias and subsequently influence the clinical application of cinobufotalin worldwide. Second, according to the Cochrane Handbook for systematic reviews of interventions, the most appropriate way of summarizing survival outcomes is to use methods of survival analysis and express the intervention effect as a hazard ratio (HR) because this method takes into

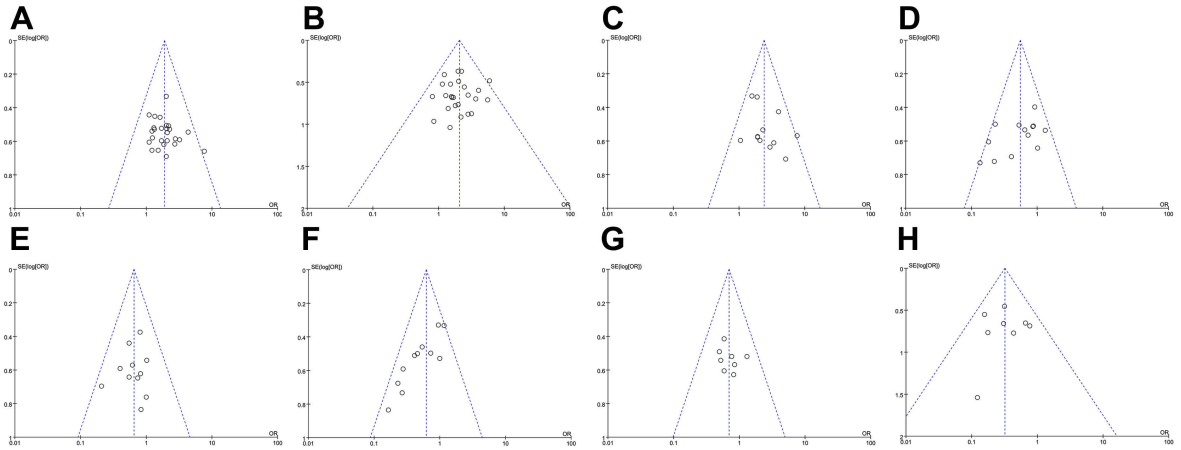

Figure 6 Funnel plot of overall response rate (ORR, **A**), disease control rate (DCR, **B**), quality of life improved rate (QIR, **C**), Nausea and vomiting (**D**), Diarrhea (**E**), Leukopenia (**F**), Anemia (**G**) and neurotoxicity (**H**).

Table 5 Publication bias on therapeutic efficacy indexes (CR, PR, SD, PD, ORR, DCR and QIR) and adverse events indexes (Nausea and vomiting, Diarrhea, Leucopenia, Anemia and Neurotoxicity)

Publication Bias	Therapeutic efficacy							Adverse events				
	CR	PR	SD	PD	ORR	DCR	QIR	Nausea and vomiting	Diarrhea	Leucopenia	Anemia	Neurotoxicity
Begg	0.742	0.038	0.513	0.870	0.280	0.870	0.304	0.161	0.755	0.003	0.454	1.000
Egger	0.833	0.015	0.721	0.905	0.331	0.905	0.235	0.069	0.623	<0.0001	0.528	0.894

Note: Parameters discussed in over 8 papers were conducted bias analyses.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; QIR, quality of life improved rate.

consideration the time factor and censored participants. However, the included articles that reported the OS rate only provided the survival number and the total number of patients at 6 months and 12 months, and none of them provided HR with 95% CI and Kaplan–Meier survival curves. Therefore, there were insufficient data to perform a statistical analysis using HR, which almost certainly will introduce bias. Third, treatment/medical history is very important in evaluating the efficacy of cinobufotalin-mediated therapy. However, our data were partly extracted from published papers rather than from the original patient records; therefore, analytical bias would possibly exist. Moreover, the therapeutic effects of the combined therapy may be influenced by numerous variables such as dosage of cinobufotalin, tumor stage and patient's age. However, based on currently available literature, there are insufficient data to perform more statistical analysis to evaluate the correlation. We will keep following up with upcoming clinical trials to obtain relevant data when available. Finally, the follow-up durations of the included studies were short, and the long-term efficacy of cinobufotalin for advanced GC remains to be further evaluated.

Conclusion

In summary, this meta-analysis indicated that cinobufotalin and chemotherapy combined therapy was effective in treating advanced GC. Clinical application of cinobufotalin not only evidently improved the therapeutic effects of chemotherapy but also effectively alleviated most of the side effects caused by chemotherapy. However, the long-term efficacy of cinobufotalin-mediated adjuvant therapy for advanced GC still needs methodologically rigorous trials to verify its efficacy.

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Table 6 Subgroup analyses of ORR and DCR between the experimental and control group

Parameter	Factors at study level	Experimental group No. of patients (n)	Control group No. of patients (n)	Analysis method	Heterogeneity		Odds Ratio (OR)	95% CI	*P*-value
					I^2 (%)	*P*-value			
ORR	**Therapeutic regimen**								
	Cinobufotalin +FOLFOX	215	200	Fixed	0	0.99	1.84	1.23 to 2.76	0.003
	Cinobufotalin +XELOX	92	86	Fixed	0	0.41	2.43	1.30 to 4.53	0.005
	Cinobufotalin+EOF	55	55	Fixed	22	0.26	1.93	0.91 to 4.10	0.09
	Cinobufotalin +Capecitabine	272	294	Fixed	0	0.85	1.98	1.29 to 3.04	0.002
	Drug form of cinobufotalin								
	Cinobufotalin capsule	186	185	Fixed	9	0.36	2.47	1.54 to 3.98	0.0002
	Cinobufotalin injection	724	723	Fixed	0	0.98	1.78	1.41 to 2.25	<0.00001
	Study sample size								
	>60	634	641	Fixed	0	0.67	2.05	1.58 to 2.65	<0.00001
	≤60	318	305	Fixed	0	0.99	1.64	1.18 to 2.28	0.003
	Type of control trials								
	RCT	833	829	Fixed	0	0.96	1.93	1.55 to 2.41	<0.00001
	Overall	952	946	Fixed	0	0.96	1.88	1.54 to 2.31	<0.00001
DCR	**Therapeutic regimen**								

(*Continued*)

Table 6 (Continued).

Parameter	Factors at study level	Experimental group No. of patients (n)	Control group No. of patients (n)	Analysis method	Heterogeneity		Odds Ratio (OR)	95% CI	*P*-value
					I^2 (%)	*P*-value			
	Cinobufotalin +FOLFOX	215	200	Fixed	0	0.97	2.26	1.26 to 4.04	0.006
	Cinobufotalin +XELOX	92	86	Fixed	0	0.39	2.55	1.24 to 5.23	0.01
	Cinobufotalin+EOF	55	55	Fixed	0	0.71	1.70	0.52 to 5.57	0.38
	Cinobufotalin +Capecitabine	272	294	Fixed	0	0.63	1.63	1.11 to 2.38	0.01
	Drug form of cinobufotalin								
	Cinobufotalin capsule	186	185	Fixed	0	0.49	2.78	1.69 to 4.58	<0.0001
	Cinobufotalin injection	696	694	Fixed	0	0.87	1.88	1.45 to 2.45	<0.00001
	Study sample size								
	>60	634	641	Fixed	0	0.53	2.21	1.68 to 2.90	<0.00001
	≤60	290	276	Fixed	0	0.94	1.73	1.13 to 2.64	0.01
	Type of control trials								
	RCT	805	800	Fixed	0	0.86	2.16	1.69 to 2.77	<0.00001
	Overall	924	917	Fixed	0	0.86	2.05	1.63 to 2.58	<0.00001

Notes: Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.

Abbreviations: ORR, overall response rate; DCR, disease control rate; FOLFOX, Oxaliplatin+Calcium folinate+5-Fluorouracil; XELOX, oxaliplatin+capecitabine; EOF, epirubicin+oxaliplatin+calcium folate+fluorouracil; RCT, randomized controlled trial.

Author contributions

All authors contributed to study design, data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

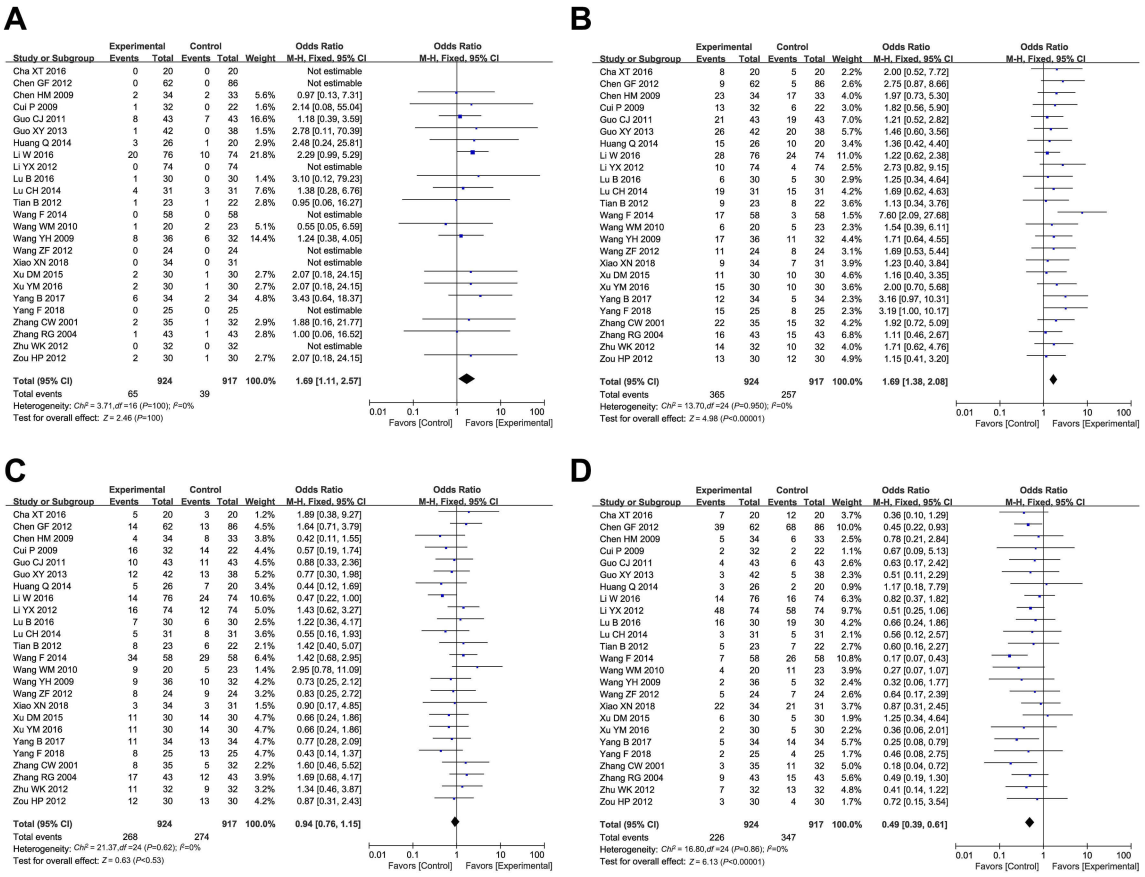


Figure S1 Forest plot of the comparison of complete response rates (CR, **A**), partial response rates (PR, **B**), stable disease rates (SD, **C**) and progressive disease rates (PD, **D**) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group. The fixed-effects meta-analysis model (Mantel–Haenszel method) was used.

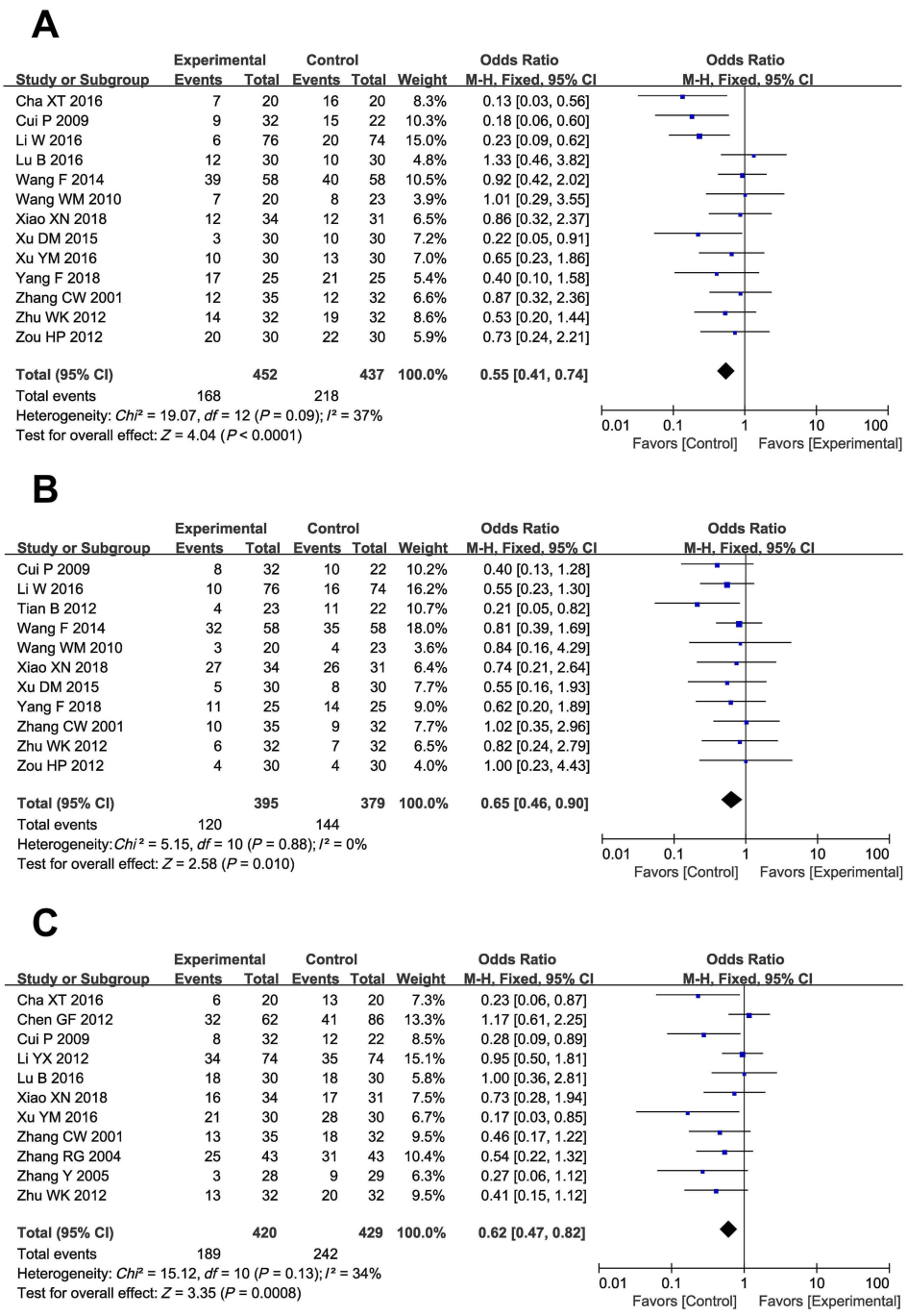
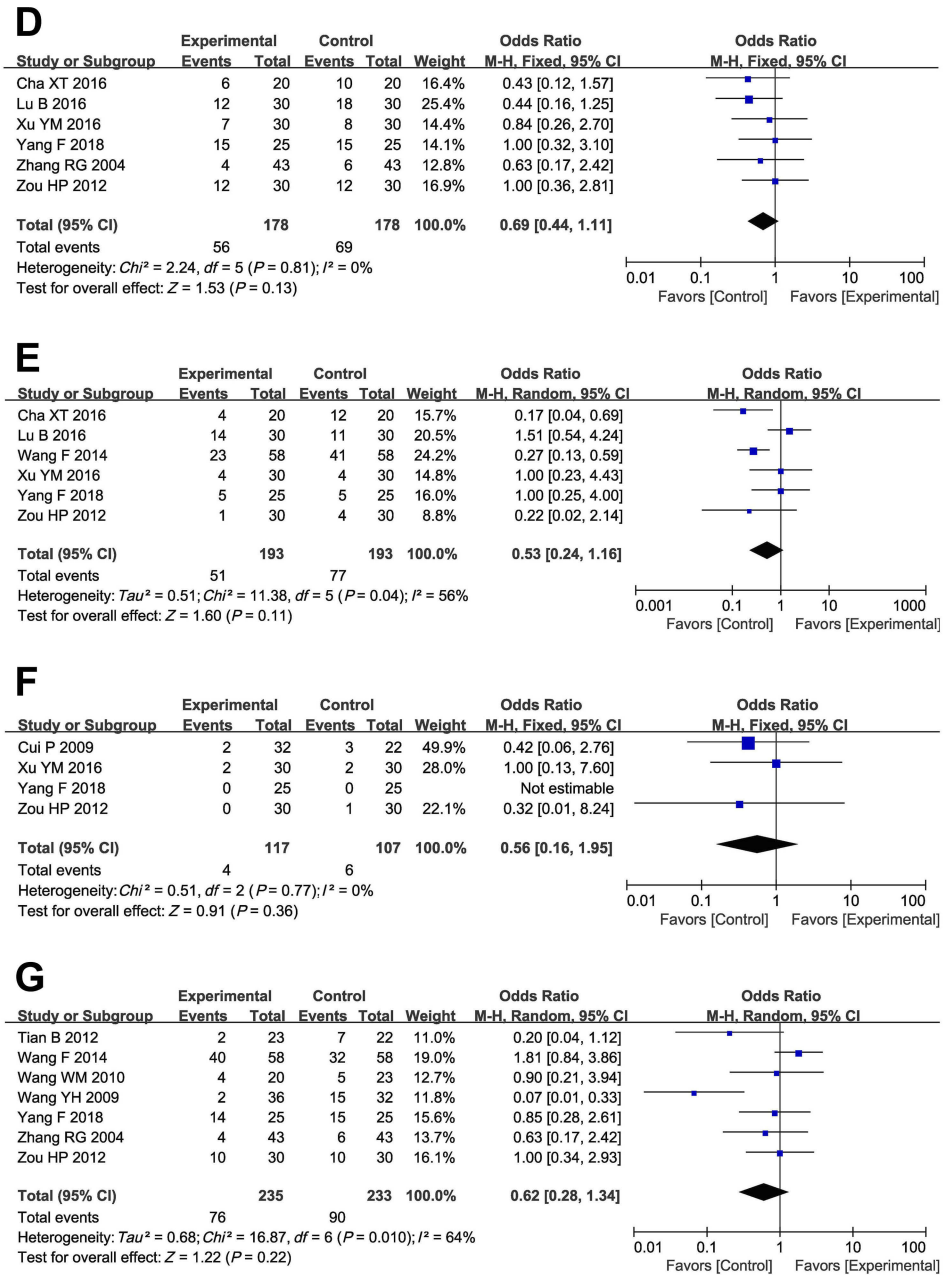


Figure S2 Forest plot of the comparison of adverse effects including nausea and vomiting (**A**), diarrhea (**B**), leukopenia (**C**), thrombocytopenia (**D**), hepatotoxicity (**E**), nephrotoxicity (**F**), oral mucositis (**G**), alopecia (**H**), hand-foot syndrome (**I**), anemia (**J**), gastrointestinal adverse effects (**K**), peripheral neurotoxicity (**L**), neutropenia (**M**) and myelosuppression (**N**) between the experimental and control group. Control group, chemotherapy alone group; Experimental group, chemotherapy and cinobufotalin combined group.



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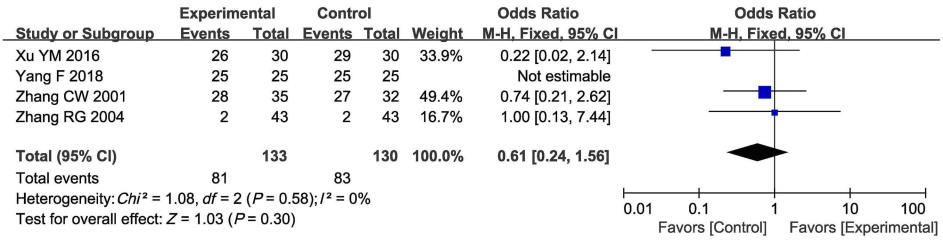

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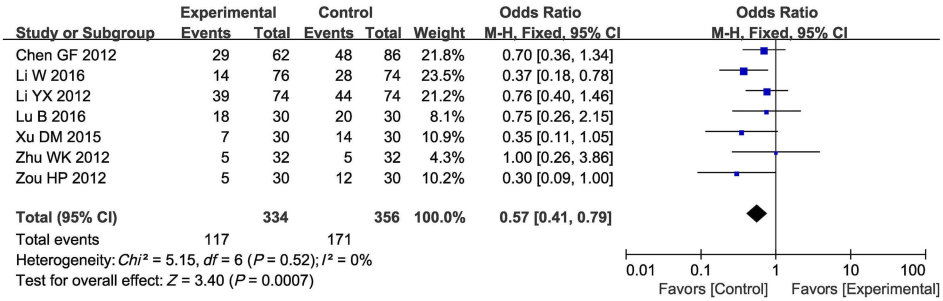

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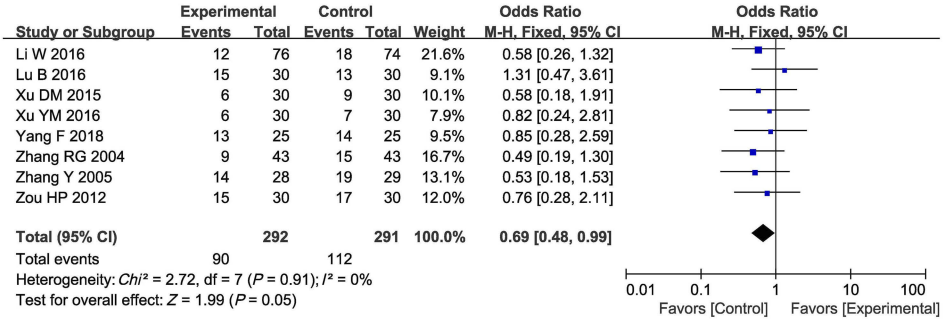

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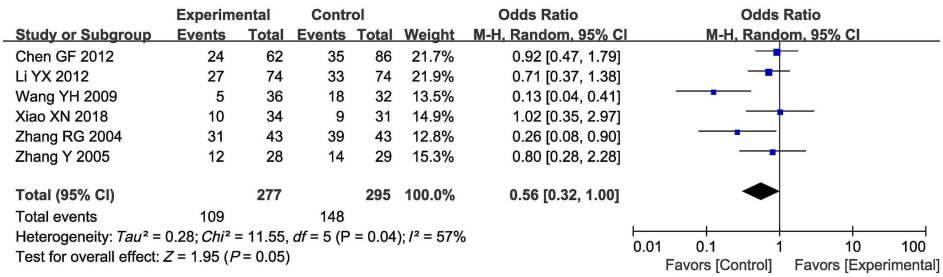

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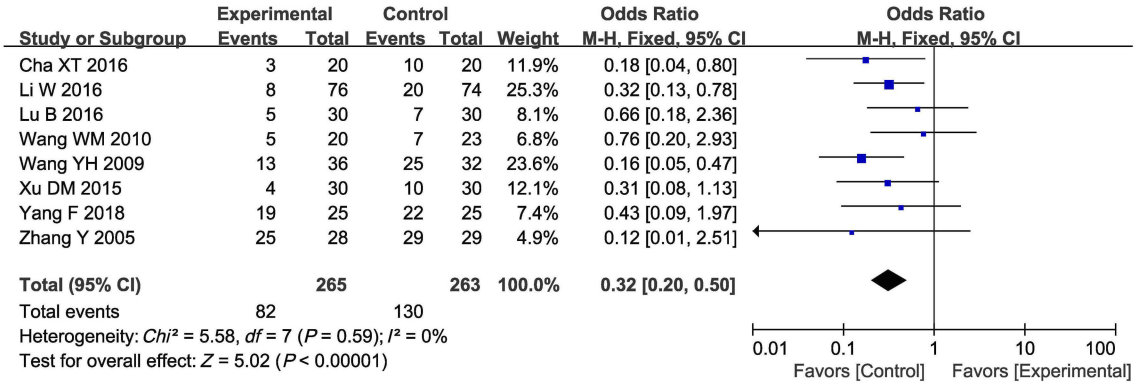
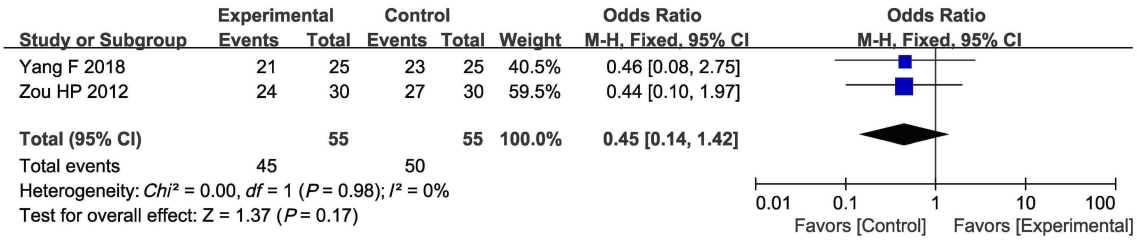


M



N

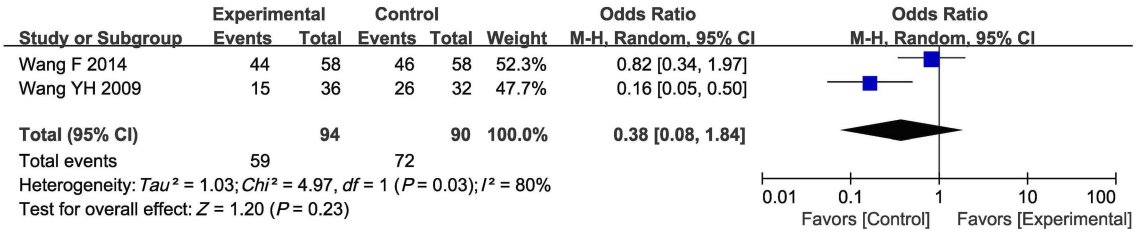


Figure S2 (Continued).

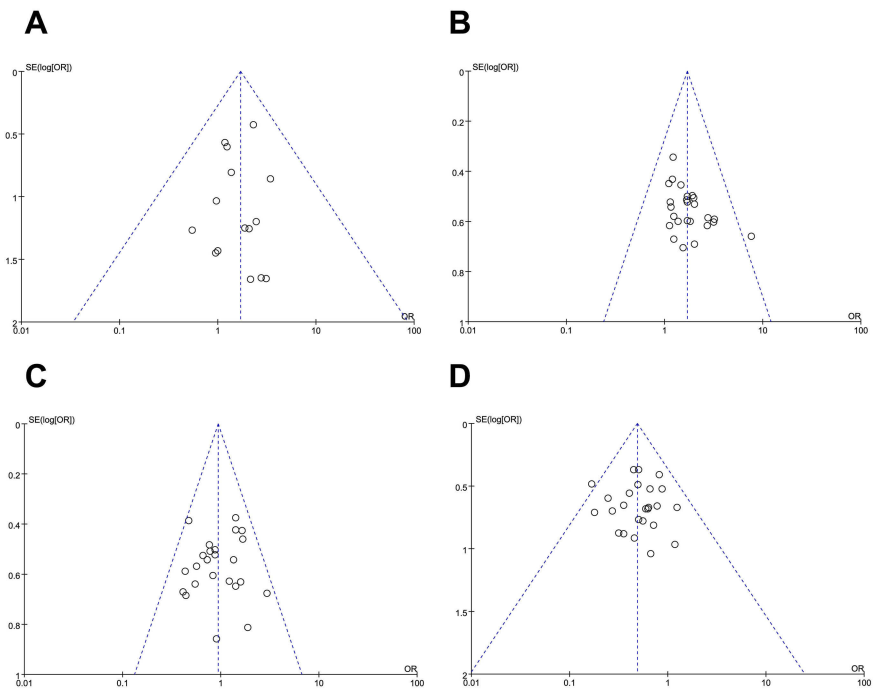


Figure S3 Funnel plot of percentage of complete response rates (CR, **A**), partial response rates (PR, **B**), stable disease rates (SD, **C**) and progressive disease rates (PD, **D**).