

Research Paper



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Effectiveness and Safety of Chinese Herbal Injections Combined with Fluoropyrimidine and Oxaliplatin-based Chemotherapy for Advanced Colorectal Cancer: A Systematic Review and Meta-analysis of 63 Randomized Controlled Trials

Shuo Wang^{1,2#}, Xueqian Wang^{1#}, Tong Zhou^{1#}, Shuaihang Hu^{1,2}, Peiyu Tian^{1,2}, Zheng Li¹, Yuxiao Li¹, Jun Dong¹, Yuerong Gui¹, Dandan Wang¹, Ying Zhang^{1⊠}, Wei Hou^{1⊠}

1. Department of Oncology, China Academy of Chinese Medical Sciences Guang'anmen Hospital, Beijing, China.

2. Beijing University of Chinese Medicine, Beijing, China.

#Co-first authors with equal contributions to this work.

🖂 Corresponding authors: Wei Hou (E-mail: houwei1964@163.com) and Ying Zhang (E-mail: zylzy501@163.com).

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Abstract

Purpose: To investigate effectiveness and safety of Chinese herbal injections (CHIs) in conjunction with fluoropyrimidine and oxaliplatin-based chemotherapy (FOBC) for advanced colorectal cancer (CRC).

Methods: A comprehensive search was conducted in 7 electronic databases for related randomized controlled trials (RCTs) from inception to April 30, 2021. The quality of each trial was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions, the differences in effectiveness and safety outcomes between two groups were evaluated, and the results were expressed as the risk ratios (RRs) and 95% confidence interval (Cl). Subgroup analyses were performed according to the types of CHIs, and Review Manager 5 was used to statistically analyze the outcomes.

Results: 63 studies involving 9 CHIs and 4733 patients were included in this review. The meta-analysis results suggested that compared with FOBC therapy, CHIs plus FOBC therapy showed significant improvements in objective response rate (ORR) (RR=1.34, 95% CI: 1.27-1.42, P<0.00001), disease control rate (DCR) (RR=1.09, 95%CI: 1.06-1.11, P<0.00001), 1-year survival rate (RR=2.27, 95% CI: 1.23-4.18, P=0.009) and quality of life (QoL) (RR=1.21, 95% CI: 1.14-1.28, P<0.00001), and decreases in the incidence of chemotherapy-induced leukopenia (RR=0.64, 95% CI: 0.50-0.82, P<0.0005), nausea and vomiting (RR=0.65, 95% CI: 0.51-0.83, P=0.0005) and diarrhea (RR=0.34, 95% CI: 0.20-0.58, P<0.0001).

Conclusion: From the evidence available, CHIs could increase ORR, DCR and 1-year survival rate, improve QoL and relieve chemotherapy-induced leukopenia, nausea and vomiting and diarrhea when combined with FOBC in advanced CRC treatment, Nevertheless, on account of the limitations, more rigorous RCTs with high-quality methodology were needed to further confirm the results.

Key words: advanced colorectal cancer, Chinese herbal injections, effectiveness, randomized controlled trial, systematic review

Introduction

Colorectal cancer (CRC), the third most common cancer worldwide, is a serious threat to people's health and life. CRC is the second leading cause of death among cancers, with an estimated 935,173 deaths, counting 9.4% of all cancer deaths [1]. Although surgery remains the primary treatment for CRC, 50% of patients recur or metastasize after radical resection. More than 25% of the patients confirmed in

its advanced stage [2], with the overall 5-year survival rate ranges from 10 to 18%. Fluoropyrimidines and oxaliplatin-based chemotherapy (FOBC) is the first-line treatment for patients with advanced CRC, some cases can benefit from FOBC to improve survival as well as locoregional control [3]. However, studies have demonstrated that it often accompanied by adverse reaction, further leading a reduced quality of life.

In Asia, Traditional Chinese Medicine (TCM) is a considerable adjuvant treatment for advanced CRC in combination with chemotherapy, and has been shown to increase effectiveness and reduce side effects. Chinese herbal injection (CHI), prepared by extracting and purifying effective ingredients from Chinese herbal medicines, is an important part of TCM [4]. It breaks the limitations of the traditional delivery way of Chinese herbal medicines via oral administration, but intravenous injection instead, thus has the advantages of high bioavailability, high blood concentration, rapid action and no digestive tract absorption process. Many researches indicated that it has obvious advantages in improving short-term effectiveness, enhancing life quality and reducing chemotherapy-related toxicity. However, previous studies commonly focused on an individual CHI, while the types of CHIs are various, and the effectiveness and safety of all potential CHIs still remains inconclusive [5]. Thus, a systematic review was designed to fill this knowledge gap by quantitatively synthesizing the evidence. The aim was to evaluate the effectiveness and safety of all potential CHIs for treating advanced CRC and to provide help for clinical medication in the future.

Materials and Methods

This systematic review and meta-analysis was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, and has been registered through International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) as INPLASY2020100050. The complete study protocol was previously published [6]. Ethical approval was not required as all the research materials were published studies.

Eligibility criteria

Only randomized controlled trials (RCTs) were selected and assessed for inclusion based on the following eligibility criteria: (1) Types of Participants: Patients were cytologically or pathologically confirmed cases of CRC and belong to Stage III or IV according to American Joint Committee on Cancer Staging System (8th edition) or mentioned

"advanced". (2) Types of Interventions: Control groups received FOBC that contained fluoropyrimidine and oxaliplatin, and the fluoropyrimidine drugs include 5-fluorouracil (5-FU) and Capecitabine. Treatment groups received CHIs plus FOBC therapy. In each trial, the FOBC regimen was eligible and the same in both treatment and control group. CHIs were given intravenously. (3) Types of Outcomes: The primary outcomes were objective response rate (ORR) and disease control rate (DCR). According to World Health Organization (WHO) [7] guidelines for solid tumor responses or Response Evaluation Criteria in Solid Tumors (RECIST) [8], the tumor responses were evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). ORR refers to the proportion of patients with CR plus PR. DCR calculated as the proportion of patients with CR plus PR plus SD. The secondary outcomes were progression-free survival (PFS), survival rate, quality of life (QoL) and safety outcomes. PFS defined as the time from study entry to relapse or death. Survival rate referred to the proportion of participants alive at the beginning of a time interval who survive to the end of the interval [6]. Improvement of QoL was considered when Karnofsky performance scale (KPS) score increased, or decreased no more than 10 scores after treatment.[14]. Safety outcomes covered the incidence of grade 2 or greater leukopenia, diarrhea, and nausea and vomiting, measured by Standard Classification of WHO or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). The included studies should reported at least one of the above outcomes of interest.

Information Sources

A comprehensive search was conducted from inception to April 30, 2021 in 7 electronic medical databases, including PubMed, EMBASE, Cochrane, China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Database for Chinese Technical Periodicals (VIP) and SinoMed.

Search Strategy

To identify all potential relevant publications, search terms were constructed for two domains: (1) colorectal cancer, (2) CHIs. The terms used for colorectal cancer contained: "Colorectal Neoplasms[MeSH]", "Colonic Neoplasms[MeSH]", "Rectal Neoplasms[MeSH]", "colorectal cancer", "colorectal neoplasm", "colorectal carcinoma", "colorectal tumor", etc. The following terms were used for CHIs: "Chinese herbal injection", "injection of TCM" and certain CHIs such as "Shenqifuzheng", "Kanglaite", "Fufangkushen", "Compound Kushen", "Xiaoaiping", "Cinobufacini", "Elemene",

"Lentinan", "javanica oil emulsio", "kangai", "Astragalus", "Shenfu", "Shenmai" and multiple synonyms for each term. More specific search strategies were showed on **File S1**.

Study Selection

2 independent reviewers (J Dong and YR Gui) screened all the relevant articles on the basis of titles and abstracts. The full texts were scanned for further elimination based on the eligibility criteria. All disagreements were resolved by consensus. All relevant articles were managed in NOTEEXPRESS software.

Data extraction

2 reviewers (T Zhou and SH Hu) completed the data extraction in Excel software independently, and the following items were extracted: general information including author, year, publication, sample size, detailed information of participants, intervention measures and outcomes. The disagreements between the 2 reviewers were settled by S Wang and Y Zhang.

Risk of bias and quality assessment

We evaluated methodological quality of the included articles according to "Risk of Bias Assessment Tool" of the Cochrane Handbook for Randomized Controlled Trials [9]. The risk of bias was evaluated in 7 items including random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other sources of bias, and finally evaluated as "low risk," "unclear risk," or "high risk" [10]. PY Tian and Z Li assessed the studies' quality independently, any differences were decided by XQ Wang and W Hou. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used to grade the quality of evidence [11].

Summary measures and data synthesis

Review Manager 5.3 was used to conduct statistical analyses. Risk ratios (RRs) were used to evaluate effectiveness and safety for dichotomous outcomes with 95% confidence intervals (CI). P values <0.05 were considered to indicate statistical significance. Subgroup analyses were performed according to the types of CHIs and presented with pooled data simultaneously. The heterogeneity was judged based on the I^2 value and P value. If the studies had non-significant heterogeneity within the studies or subgroups (I^2 <50%, P>0.1), we used a fixed effects model. If there was great heterogeneity within the studies or subgroups (I^2 >50%, P<0.1), we used the random effects model. If the data quantitative

synthesis was not possible, we analyzed the available data qualitatively.

Risk of Bias across trials

Funnel-plots were used to assess publication bias when the number of the included trials was more than 10.

Additional analyses

To determine the robustness of results, sensitivity analyses were conducted based on the quality of trials [12], participants' number, treatment duration of CHIs, stage of cancer and publication year. Trial sequential analysis (TSA) was used to calculate the required information size (RIS) in the meta-analysis.

Results

Study Selection

The study selection process was described in **Figure 1.** A total of 8334 articles were identified from the initial literature search. After removing duplicates and irrelevant articles, 480 articles remained. Through reviewing the full texts of the remaining, a total of 63 papers [13-75] finally reached the criteria for entrance into the meta-analysis.

Study Characteristics

63 RCTs recruiting 4733 patients were included. The baseline characteristics of the included trials were summarized in Table 1. All trials were conducted in China. All participants enrolled were patients with advanced CRC. There were 2394 and 2339 patients in the experimental and control groups, respectively. The number of participants in each RCT varied from 36 to 250. The numbers of studies included for 9 different CHIs were as follows: Compound Kushen injection (26 trials) [14, 17, 19, 21, 23, 27, 33, 34, 39-41, 43, 46, 47, 48, 51, 54, 55, 59-61, 65, 67, 68, 70, 71]; Aidi injection (15 trials) [16, 18, 20, 22, 26, 28, 35, 37, 42, 44, 45, 53, 56, 64, 69]; Shenqifuzheng injection (11 trials) [24, 25, 30, 31, 36, 38, 52, 58, 66, 73, 75]; Kanglaite injection (3 trials) [57, 62, 63]; Cinobufacini injection (3 trials) [13, 29, 50]; Xiaoaiping injection (2 trials) [32, 72]; Javanica oil emulsion injection (1 trial) [49]; Astragalus injection (1 trial) [15]; Lentinan injection (1 trial) [74].

Quality evaluation

The results of the methodological evaluation were shown in **Figure 2.** With regard to random sequence generation, 22 studies [13, 17, 19, 22, 24, 26, 27, 32, 34, 36, 37, 47, 48, 50, 52, 56, 60, 62, 67, 69, 72, 73] were assessed as "low risk" because random number table and stratified randomization were adopted, the

other studies did not report any randomization procedure, and were evaluated as "unclear". Regarding allocation concealment, 1 trial [47] was evaluated as "low risk" because web-based central allocation was adopted, the risk of remaining RCTs were unclear.



Figure 1. Flow diagram of the search for eligible studies.

Table 1. Basic characteristics of the included St
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Study ID	N(T/C)	Age	TNM	Control group	Intervention group	CHIs dosage	CHIs Treatment	Interested
			stages					outcomes
Cai HF 2020	31/31	T: 70.37	NR	5-FU+L-OHP+LV	CI + 5-FU+L-OHP+LV	20 mL/day	21 days/course, 2-4	12
		C: 70.61					courses	
Cao ZY 2009	33/29	T: 53.6	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	15 mL/day	28 days/course, 2 courses	1256
		C: 54.7						
Chen F 2009	30/30	T: 53.8±14.4	IV	5-FU+L-OHP+LV	AS + 5-FU+L-OHP+LV	60 mL/day	21 days/course, 3 courses	12567
	,	C: 52.5±12.6				, ,	5	
Chen LF 2013	30/30	T: 53.6	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	80 mL/day	10 days/course, 4 courses	(1)(2)(5)(6)(7)
	,	C: 54.8				, ,	<i>,</i>	
Chen XY 2017	35/35	T: 49.36	NR	5-FU+L-OHP+LV	AD + 5-FU+L-OHP+LV	50 mL/dav	21 days/course, 2 courses	(1)(2)(7)
	/	C: 42.66				-,,	,.,	000
Ding X 2010	30/30	T: 64.5	NR	5-FU+L-OHP+LV	CKS + 5-FU+L-OHP+LV	20 mL/dav	14 days/course, 4 courses	(3)(6)(7)
8	,	C: 63						000
Fan S 2010	44/44	61	NR	5-FU+L-OHP+LV	AD+5-FU+L-OHP+LV	100 mL/dav	14 days/course, 4 courses	(1)
Fang XG 2012	36/36	T: 49 8+4 1	III-IV	5-FU+L-OHP+LV	CKS + 5-FU+L-OHP+LV	15 mL/day	14 days/course 2 courses	026
1 ung XO 2012	507 50	C: 48 6+3 9		STOPE OIL PEV	ele so rese ella sev	10 mill/ duy	11 duys/ course, 2 courses	
En H 2020	52/52	T: 60 39	NR	CAP+L-OHP	AD+ CAP+L-OHP	50-100	14 days / course 2 courses	10
1 u 11 2020	52/ 52	C: 60.08	T NIX	Chi (L-Ohi		mI /day	14 days/ course, 2 courses	
C W 2010	20/25	C. 00.00	117		CVC - F FULL OUD UV	20 mL / day	10 dame (annual 4 annual	
Gao w 2010	38/35	INK	1V	5-FU+L-OHF+LV	CKS+5-FU+L-OHF+LV	20 mL/day	10 days/course, 4 courses	125
Guo HM 2019	36/36	T: 53.03	NR	5-FU+L-OHP+LV	SQFZ+5-FU+L-OHP+LV	250 mL/day	14 days/course, 4 courses	(1)(2)

Study ID	N (T/C)	Age	TNM stages	Control group	Intervention group	CHIs dosage	CHIs Treatment	Interested outcomes
Gao X 2021	23/23	C: 52.61 T: 52.13±5.26 C: 51.07+4.89	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	15 ml/day	14 day/course,	12
Guo YR 2011	30/24	T: 65.4	III-IV	5-FU+L-OHP+LV	SQFZ+5-FU+L-OHP+LV	250 mL/day	14 days/course, 4 courses	12567
Hai YJ 2011	32/32	56.4	III-IV	5-FU+L-OHP+LV	AD + 5-FU+L-OHP+LV	50 mL/day	10 days/course, 4 courses	67
Hao LX 2019	34/34	76.26	NR	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	20 mL/day	$14~{\rm days}/{\rm course}, 4~{\rm courses}$	12
Huang J 2008	30/26	T: 65.4 C: 66 5	III-IV	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	50-100 mL (day	15 days/course, 2 courses	(1)(2)(5)(6)(7)
Huang JL 2012	21/20	T: 53.2 C: 52.6	IV	5-FU+L-OHP+LV	CI+ 5-FU+L-OHP+LV	15-20 mL/day	14 days/course, 2 courses	1256
Huo W 2008	22/14	51	III-IV	5-FU+L-OHP+LV	SQFZ+5-FU+L-OHP+LV	250 mL/day	14 days/course, 4 courses	12567
Jia CY 2016	43/43	T: 57.3 C:56.7	NR	5-FU+L-OHP+LV	SQFZ+5-FU+L-OHP+LV	250 mL/day	14 days/course, 4 courses	12
Kou WZ 2016	37/36	T: 56.8± 8.7 C: 56.2 ± 8.5	III-IV	CAP+L-OHP	XAP+ CAP+L-OHP	40 mL/day	10 days/course, 2 courses	125
Kuang YM 2007	30/30	NR	NR	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	15 mL/day	10 days/course, 4 courses	1267
Li D 2015	26/26	T: 54.46±8.47 C: 66 47±11 83	III-IV	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	15 mL/day	14 days/course, 4 courses	12
Li HJ 2007	65/52	T: 58 C: 59	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	60 mL/day	10 days/course, 4 courses	12567
Li RM 2018	32/32	T: 58 C: 57	III-IV	CAP+L-OHP	SQFZ+ CAP+L-OHP	250 mL/day	7 days/course, 3 courses	12567
Li SJ 2016	45/45	T: 54.82 C: 54.67	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	100 mL/day	21 days/course, 2 courses	12
Liang OL 2009	76 / 76	NR	NR	5-FU+L-OHP+LV	SOFZ+5-FU+L-OHP+LV	250 mL/day	10 days/course, 2 courses	(1)(2)(5)
Liao GQ 2009	125/125	T: 58.6 C:56 7	III-IV	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	20 mL/day	14 days/course	1256
Lei XB 2020	25/25	T: 57.21±1.64 C: 57.69±1.74	NR	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	15ml/day	7 days/course, 4 courses	12
Liu HX 2012	36/36	T: 59.25±13.65 C: 57.45±14.86	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	40 mL/day	15 days/course, 3	1256
Liu J 2017	36/35	T: 65.3±3.2 C: 64 8+3 1	NR	5-FU+L-OHP+LV	AD + 5-FU+L-OHP+LV	50 mL/day	21 days/course, 2 courses	12
Liu KH 2014	37/37	T: 61 C: 59	IIIb-IV	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	20 mL/day	14 days/course, 4 courses	1256
Liu T 2009	30/30	T: 63.2	NR	5-FU+L-OHP+LV	AD+5-FU+L-OHP+LV	50 mL/day	21 days/course, 2 courses	1267
Liu W 2012	56/52	T:58.5 C:60.2	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	50 mL/day	28 days/course, (2-6)	12567
Liu XG 2014	52/52	T: 59.5±3.6	NR	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	20 mL/day	14 days/course, 6 courses	12
Liu XY 2020	46/46	T: 53.81± 4.01 C: 54.09+3.93	IIIb-IV	CAP+L-OHP	CKS+CAP+L-OHP	15 mL/day	21 day/course, 4 courses	12
Ma X 2016	39/39	T: 48.27±5.31 C: 48.36±5.58	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	20 mL/day	7 days/course, 8 courses	124
Nie HX 2012	30/30	T: 50 C: 52	III-IV	5-FU+L-OHP+LV	JOE+ 5-FU+L-OHP+LV	30 mL/day	21 days/course, 4+	12
Pan J 2020	35/35	T: 60.2±2.3	III-IV	CAP+L-OHP	CI+ CAP+L-OHP	15-20	7 days/course, 3 courses	1267
Qi HW 2016	36/36	C: 59.8±2.5 T: 52.88±7.11	IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	15 mL/day	14 days/course, 3 courses	12
Shang CX	46/46	C. 64.82±7. 54 T: 57.31 C: 58.11	III-IV	5-FU +L-OHP	SQFZ+ 5-FU +L-OHP	250 mL/day	21 days/course, 4 courses	1267
Shi B 2009	18/18	52	NR	CAP+L-OHP	AD+ CAP+L-OHP	50-100	14 days/course, 2+	12567
Shui HF 2014	24 / 24	56	NR	CAP+L-OHP	CKS+ CAP+L-OHP	20 mL/day	10 days/course, (4-6)	125
Sun LQ 2013	40/40	T: 61	NR	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	20 mL/day	21-28 days/course,	125
Sun WR 2015	48/48	C: 50 T: 55.82	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	100 mL/day	21 days/course, 4 courses	12
Sun YY 2020	30/30	C: 55.67 T: 53.8±6.1	III-IV	5-FU+L-OHP+LV	KLT+5-FU+L-OHP+LV	200 mL/day	28 days	1267
Tan GG 2013	20/20	C. 33.313.8 64	III-IV	CAP+L-OHP	SQFZ+ CAP+L-OHP	250 mL/day	14 days/course, 2+	12
Tao CL 2013	36/38	T: 60.1±7.9	IV	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	15 mL/day	14 days/course, 3 courses	12567
Wang JX 2015	25/25	C. 60.418.9 T: 58	IIIb-IV	5-FU+L-OHP+LV	CKS + 5-FU+L-OHP+LV	12 mL/day	14 days/course, 4 courses	1256
Wang JY 2011	21/21	C: 60 T: 55.25	IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	12 mL/day	200 mL/course, 2-4	(5)
Wang RW	64/60	C: 54.80 T: 51.9±3.1	III-IV	5-FU+L-OHP+LV	KLT+ 5-FU+L-OHP+LV	100mg/day	NR	125
2015 Wang YH 2006	24/22	C: 50.5±3.3 T: 57.1 C: 58.2	IV	5-FU+L-OHP+LV	KLT+5-FU+L-OHP+LV	100 mL/day	21 days/course, 6 courses	(4)

Study ID	N (T/C)	Age	TNM	Control group	Intervention group	CHIs dosage	CHIs Treatment	Interested
			stages					outcomes
Wang YT 2012	38/36	52	NR	5-FU+L-OHP+LV	AD+ 5-FU+L-OHP+LV	80 mL/day	10 days/course, 4 courses	125
Weng ML 2020	45/45	T: 51.07±5.21 C: 50.11±4.25	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	20 mL/day	7 days/course, 4 courses	1256
Xing F 2015	30/30	T: 52 C: 53	III-IV	5-FU+L-OHP+LV	SQFZ+5-FU+L-OHP+LV	250 mL/day	10 days/course, 4 courses	125
Yan Q 2015	41/41	T: 55.1 C: 53.6	NR	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	20 mL/day	7 days/course, 4 courses	125
Yang J 2015	39/39	T: 55.1 C: 53.8	IV	CAP+L-OHP	CKS+ CAP+L-OHP	12 mL/day	7 days/course, 4 courses	125
Yu ZH 2016	43/43	T:54.59 C:4.85	NR	5-FU+L-OHP+LV	CKS+5-FU+L-OHP+LV	40 mL/day	15 days/course, 4 courses	12
Zan L 2015	40/40	T: 52 C: 51	III-IV	5-FU+L-OHP+LV	CKS+ 5-FU+L-OHP+LV	30 mL/day	7 days/course, 2 courses	125
Zhang L 2012	20/20	T: 59.24±20.37 C: 61.56±21.53	III-IV	5-FU+L-OHP+LV	XAP+ 5-FU+L-OHP+LV	1 mg/day	7 days/course, 2 courses	125
Zhang Q 2021	65/65	T: 59±10 C: 59±10	III-IV	5-FU+L-OHP+LV	AD+5-FU+L-OHP+LV	50ml/day	14 days/course, 4 courses	12
Zhang W 2015	43/43	64.3	III-IV	CAP+L-OHP	SQFZ+ CAP+L-OHP	250 mL/day	14 days/course, 2 courses	(1)(2)
Zhang ZH 2011	38/34	T: 58 C: 59	NR	5-FU+L-OHP+LV	LE+ 5-FU+L-OHP+LV	1 mg/day	14 days/course, 8 courses	127
Zhao T 2011	32/32	NR	NR	5-FU+L-OHP+LV	SOF7+5-FU+L-OHP+LV	250 mL/day	14 days / course 2 courses	12567

5-FU: 5-fluorouracil; AD: Aidi injection; AS: Astragalus injection; C: control group; CAP: Capecitabine; CI: Cinobufacini injection; CKS: Compound Kushen injection; JOE: Javanica oil emulsion injection; KA: Kangai injection; KLT: Kanglaite injection; LE: Lentinan injection; LV: leucovorin; NR: not reported, and the "NR" in the column of "TNM stages" means not reporting exact stages but mentioning "advanced"; SQFZ: Shenqifuzheng injection; T: treatment group; XAP: Xiaoaiping injection; ①: ORR; ②: DCR; ③: PFS; ④: survival rate; ⑤: quality of life; ⑥: leukopenia; ⑦: gastrointestinal side effects.



Regarding blinding, since placebos were not mentioned in any of the studies, blinding was considered not performed in any of them. However, when the outcomes were ORR and DCR, it was considered that clinical judgements would not be influenced by lack of blinding because outcomes measured based on imaging. Therefore, 19 studies [17, 20, 22, 27, 31, 34, 37, 40, 46, 47, 48, 51, 56, 58, 62, 69, 70, 72, 73] that only reported ORR and DCR with clearly diagnostic criteria were evaluated as "low risk". 40 studies [13-16, 18, 21, 23-25, 28-30, 32, 33, 35, 36, 38, 39, 41-45, 49, 50, 52-55, 57, 59, 61, 64-68, 71, 74, 75] in which subjective assessments were included in outcomes, making estimation of the influence of blinding on the study results difficult, were evaluated as "unclear". 4 studies [19, 26, 60, 63] that only performed subjective assessments were evaluated as "high risk", since blinding could have affected the study results.

The risk of incomplete outcome data was low as the reported data was consistence with the stated randomized numbers. The risk of selective reporting was low because the outcome results reported just as description in methods. Regarding other bias, 9 trials [13, 39, 45, 49, 53-55, 58, 62] took a range like "2-6" to limit the courses instead a definite figure or did not mention duration, which was a potential source of bias and were assessed as "high risk", the other studies were not clear [76].

The results of the GRADE evaluation of studies which evaluated effectiveness and safety were presented in **Table 2.** All the reasons for downgrading are labeled [77].

Effectiveness and safety

The findings of the meta-analyses were summarized in **Table 3**, and subgroup analyses conducted according to categories of CHIs were shown in **Table 4**.

Table 2. The results of GRADE evaluation

Quality assessment	Numbers of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	RR (95% CI)	Certainty of evidence
ORR	59	serious ^a	not serious (I2=0%, P=0.98)	not serious	not serious	strongly suspected ^d	1.34 (1.27-1.42)	LOW
DCR	58	serious ^a	not serious (I2=0%, P=0.71)	not serious	not serious	strongly suspected ^d	1.09 (1.06-1.11)	LOW
1-year survival rate	2	serious ^a	not serious (I2=0%, P=0.54)	not serious	very serious ^c	undetected	2.27 (1.23-4.18)	VERY LOW
Quality of life	30	very serious ^a	serious ^b (I2=32%, P=0.05)	not serious	not serious	strongly suspected ^d	1.21 (1.14-1.28)	VERY LOW
Leukopenia	20	serious ^a	serious ^b (I ² =53%, P=0.004)	not serious	not serious	strongly suspected ^d	0.64 (0.50-0.82)	VERY LOW
Nausea and vomiting	13	serious ^a	not serious (I2=0%, P=1.00)	not serious	serious	strongly suspected ^d	0.65 (0.51-0.83)	VERY LOW
Diarrhea	12	serious ^a	not serious (I2=0%, P=0.94)	not serious	Not serious	strongly suspected ^d	0.34 (0.20-0.58)	LOW

a Unclear description of the hidden methods of random sequence and random allocation.

b Point estimates vary widely from study to study.

c The number of studies was too small and the confidence interval was too wide to be accurate.

d The funnel plots were asymmetrical, which indicated that publication bias might influence the results of the analysis.

Table 3. Summary of the Meta-analysis

Outcomes	Studies	Participants	Statistical methods	Pooled RRs (95% CI)	Р	Heterogenei	ty
						I^2	P_h
ORR	59	4595	FEM	1.34 (1.27-1.42)	< 0.00001	0%	0.98
DCR	58	4507	REM	1.09 (1.06-1.11)	< 0.00001	0%	0.71
1-year survival rate	2	124	FEM	2.27 (1.23-4.18)	0.009	0%	0.54
QoL	30	2217	REM	1.21 (1.14-1.28)	< 0.00001	32%	0.05
Leukopenia	20	1504	REM	0.64 (0.50-0.82)	0.0005	53%	0.004
Nausea and vomiting	13	955	FEM	0.65 (0.51-0.83)	0.0005	0%	1.00
Diarrhea	12	785	FEM	0.34 (0.20-0.58)	< 0.0001	0%	0.94

FEM: fixed-effects model; CI: confidence interval; RRs: risk ratios; REM: random-effects model.

Table 4. Subgroup analyses of all outcomes

Subgroups	Number of studies	Pooled RRs	Z	Р	Heterogenei	ty
		(95% CI)			I ²	P_h
ORR						
Compound Kushen injection	24	1.41 (1.30, 1.54)	7.89	< 0.00001	0%	0.87
Aidi injection	14	1.19 (1.07, 1.31)	3.38	0.0007	0%	1.00
Shenqifuzheng injection	11	1.38 (1.20, 1.60)	4.37	< 0.0001	0%	0.94
Kanglaite injection	2	1.61 (1.18, 2.20)	3.02	0.003	0%	0.94
Cinobufacini injection	3	1.44 (1.17, 1.78)	3.43	0.0006	0%	0.72
Xiaoaiping injection	2	1.56 (0.97, 2.53)	1.82	0.07	0%	0.41
DCR						
Compound Kushen injection	24	1.10 (1.06, 1.13)	5.37	< 0.00001	0%	0.83
Aidi injection	13	1.07 (1.02, 1.12)	2.99	0.003	0%	0.71
Shenqifuzheng injection	11	1.11 (1.02, 1.21)	2.43	0.01	40%	0.08
Kanglaite injection	2	1.19 (0.93, 1.51)	1.36	0.17	55%	0.14
Cinobufacini injection	3	1.08 (1.00, 1.18)	1.91	0.06	0%	0.59
Xiaoaiping injection	2	1.20 (0.99, 1.44)	1.89	0.06	0%	0.59
QoL						
Compound Kushen injection	13	1.20 (1.08, 1.34)	3.48	0.0005	62%	0.002
Aidi injection	7	1.25 (1.13, 1.38)	4.30	< 0.0001	0%	0.85
Shenqifuzheng injection	6	1.21 (1.08, 1.35)	3.25	0.001	0%	0.56
Xiaoaiping injection	2	1.16 (0.94, 1.43)	1.37	0.17	0%	0.36
Leukopenia						
Compound Kushen injection	5	0.66 (0.40, 1.08)	1.67	0.10	75%	0.003
Aidi injection	6	0.62 (0.43, 0.89)	2.59	0.010	0%	0.95
Shenqifuzheng injection	5	0.72 (0.47, 1.12)	1.47	0.14	0%	0.89
Nausea and vomiting						
Compound Kushen injection	2	0.58 (0.35, 0.96)	2.11	0.03	0%	0.61
Aidi injection	5	0.65 (0.45, 0.94)	2.27	0.02	0%	0.94
Shenqifuzheng injection	4	0.63 (0.35, 1.15)	1.50	0.13	0%	0.88
Diarrhea						
Aidi injection	6	0.31 (0.16, 0.61)	3.41	0.0006	0%	0.86
Shenqifuzheng injection	3	0.24 (0.06, 0.97)	2.00	0.05	0%	0.72

CI: confidence interval; DCR: disease control rate; ORR: objective response rate; RRs: risk ratios; QoL: quality of life.

	Experime	intal	Contro	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total E	vents	Total	Weight	M-H. Fixed, 95% CI	M-H. Fixed, 95% Cl
1.3.1 FOBC VS FOBC	Shenqifu: 17	zheng inj 32	ection 15	32	1.5%	1.13 [0.69, 1.85]	
Zhang W 2015	13	43	9	43	0.9%	1.44 [0.69, 3.02]	
Xing F 2015	18	30	16	30	1.6%	1.13 [0.72, 1.75]	
Shang CX 2017	26	46	16	46	1.6%	1.63 [1.02, 2.60]	
Liang QL 2009	48	76	35	76	3.5%	1.37 [1.02, 1.85]	
Li RM 2018 Jia CY 2016	21	32	12 15	32	1.2%	1.75 [1.05, 2.92]	
Huo W 2008	8	22	5	14	0.6%	1.02 [0.42, 2.49]	
Guo YR 2011	11	30	8	24	0.9%	1.10 [0.53, 2.30]	
Guo HM 2019 Subtotal (95% CI)	30	36 410	22	36 396	2.2%	1.36 [1.01, 1.84] 1.38 [1.20, 1.60]	•
Total events	223		157				
Heterogeneity: Chi ² = 4	.17, df = 10	(P = 0.9)	4); ² = (0%			
Test for overall effect: 2	. = 4.37 (P	< 0.0001)					
1.3.2 FOBC VS FOBC	Compour	nd Kushe	n inject	tion			
Zan L 2015 Yu ZH 2016	21	40	17	40	1.7%	1.24 [0.78, 1.97]	
Yang J 2015	14	39	13	39	1.3%	1.08 [0.58, 1.98]	
Yan Q 2015	20	41	13	41	1.3%	1.54 [0.89, 2.66]	
Wang JX 2015	15	45	10	45	2.0%	1.55 [1.06, 2.27]	
Tao CL 2013	46	74	23	74	2.3%	2.00 [1.36, 2.93]	
Sun LQ 2013	17	40	15	40	1.5%	1.13 [0.66, 1.94]	
Qi HW 2016	22	36	10	36	1.0%	2.20 [1.22, 3.96]	
Ma X 2016	15	39	10	39	1.0%	1.50 [0.77, 2.92]	<u> </u>
Liu XY 2020 Liu XG 2014	33	46	25	46	2.5%	1.32 [0.96, 1.82]	Ŧ
Liu KH 2014	24	37	16	37	1.6%	1.50 [0.97, 2.33]	
Liu HX 2012	16	36	13	36	1.3%	1.23 [0.70, 2.17]	
Li D 2015	23	26	20	26	2.0%	1.15 [0.89. 1.48]	+-
Lei XB 2020	23	25	15	25	1.5%	1.53 [1.09, 2.15]	
Kuang YM 2007 Hao LX 2019	15	30	14	30	1.4%	1.07 [0.63, 1.81]	
Gao X 2021	20	23	14	23	1.4%	1.43 [0.99, 2.06]	
Gao W 2010	18	38	13	35	1.4%	1.28 [0.74, 2.20]	+
rang xG 2012 Cao ZY 2009	30 11	36 33	21	36 29	2.1%	1.43 [1.05, 1.95] 1.07 [0.52, 2.22]	
Subtotal (95% CI)		987	0	980	41.7%	1.41 [1.30, 1.54]	•
Total events	591	23 (P = 0.1	416	0%			
Test for overall effect: 2	= 7.89 (P	< 0.00001	1)	0.10			
1.3.3 FOBC VS FOBC	Cinobuta 32	35	24	35	2.4%	1.33 [1.04, 1.71]	-
Huang JL 2012	14	21	9	20	0.9%	1.48 [0.84, 2.62]	+
Cai HF 2020 Subtotal (95% CI)	24	31	15	31	1.5%	1.60 [1.06, 2.41]	
Total events	70	67	48	60	4.0%	1.44 [1.17, 1.70]	•
Heterogeneity: Chi ² = 0	.65, df = 2	(P = 0.72)	; I ² = 09	%			
Test for overall effect: 2	= 3.43 (P	= 0.0006)					
1.3.4 FOBC VS FOBC	Huangqi i	injection					
Chen F 2009	12	30	10	30	1.0%	1.20 [0.61, 2.34]	
Subtotal (95% CI)	12	30	10	30	1.0%	1.20 [0.61, 2.34]	
Heterogeneity: Not app	licable		10				
Test for overall effect: 2	= 0.53 (P	= 0.59)					
135 FORC VS FORC	Aidi iniec	tion					
Zhang Q 2021	61	65	50	65	5.0%	1.22 [1.05, 1.41]	-
Wang YT 2012	17	38	14	36	1.4%	1.15 [0.67, 1.98]	- <u>-</u> -
Sun WR 2015 Shi B 2009	34	48	27	48	2.7%	1.26 [0.92, 1.71]	
Liu W 2012	24	56	19	52	2.0%	1.17 [0.73, 1.87]	
Liu T 2009	12	30	11	30	1.1%	1.09 [0.57, 2.07]	
Liu J 2017	17	36	14	35	1.4%	1.18 [0.69, 2.01]	
Li HJ 2007	29	65	16	52	1.8%	1.45 [0.89, 2.37]	
Huang J 2008	11	30	9	26	1.0%	1.06 [0.52, 2.15]	
Fan S 2010	42	44	38	44	3.8%	1.11 [0.97, 1.26]	-
Chen XY 2017	16	35	14	35	1.4%	1.14 [0.66, 1.97]	<u> </u>
Chen LF 2013 Subtotal (95% CI)	13	30 592	12	30 568	1.2%	1.08 [0.59, 1.97]	•
Total events	348		285		_0.070	[]	
Heterogeneity: Chi ² = 2	.68, df = 13	B (P = 1.00	0); l ² = (0%			
rescior overall effect: 2	- 3.38 (P	- 0.0007)					
1.3.7 FOBC VS FOBC	Javanica	oil emuls	ion inje	ection			
Nie HX 2012 Subtotal (95% CI)	15	30 30	12	30 30	1.2%	1.25 [0.71, 2.20] 1.25 [0.71, 2.20]	-
Total events	15		12	50		[0	
Heterogeneity: Not app	licable	= 0.44					
rest for overall effect: 2	v.// (P	- 0.44)					
1.3.8 FOBC VS FOBC	Xiaoaipin	g injectio	n e	20	0.00	2 00 10 04 4 23	
Kou WZ 2016	12	37	11	20 36	1.1%	1.33 [0.71, 2.49]	
Subtotal (95% CI)		57		56	1.7%	1.56 [0.97, 2.53]	◆
Total events Heterogeneity: Chi2 = 0	27 67. df = 1	(P = 0.44)	17 : ² = 0 ⁴	%			
Test for overall effect: 2	= 1.82 (P	= 0.07)					
1 2 0 5000 40 5000	Kanclak	inio-ti-					
Wang RW 2015	45	64	26	60	2.7%	1.62 [1 17 2 26]	
Sun YY 2020	11	30	7	30	0.7%	1.57 [0.71, 3.50]	+
Subtotal (95% CI)		94		90	3.4%	1.61 [1.18, 2.20]	•
rotal events Heterogeneity: Chi ² = 0	56 .01. df = 1	(P = 0.94)	33 : ² = 0 ⁰	%			
Test for overall effect: 2	= 3.02 (P	= 0.003)					
1.3.10 FORC VE FOR	+l entine-	iniactic					
Zhang ZH 2011	15	38	13	34	1.4%	1.03 [0.58. 1.85]	<u> </u>
Subtotal (95% CI)		38		34	1.4%	1.03 [0.58, 1.85]	+
Total events Heterogeneity: Not and	15 licable		13				
Test for overall effect: 2	= 0.11 (P	= 0.91)					
Total (95% CI)		2325		2270	100.0%	1.34 [1.27, 1.42]	•
Total events Heterogeneity: Chi2 = 2	1357 8 33 df = f	58 (P = 0 4	991	0%			
Test for overall effect: 2	= 10.46 (F	> < 0.0000	01)	v 70			0.05 0.2 1 5 20
Test for subaroup differ	ences: Chi	² = 10.68.	df = 8 (P = 0.	22). I ² = 25	5.1%	avous control - avours (experimental)

Figure 3. Forest plot of ORR in FOBC versus FOBC plus CHIs.

Objective response rate (ORR)

Data from 59 RCTs [13-18, 20-25, 27-48, 49-59, 61, 62, 64-75] with 9 types of CHIs contributed to the evidence for ORR. No statistical significant heterogeneity (I²=0%, P=0.98) was found and a fixed effect model was adopted. The results showed that the ORR was significantly enhanced in CHIs plus FOBC group when compared with FOBC group. (RR=1.34, 95%CI: 1.27-1.42, P<0.00001) (Figure 3). Subgroup analysis stratified by types of CHIs showed that the ORR was significantly enhanced in Compound Kushen injection subgroup (RR=1.41, 95% CI: 1.30-1.54, P<0.00001; I²=0%), Aidi injection subgroup (RR=1.19, 95% CI: 1.07-1.31, P= 0.0007; I²=0%), Shenqifuzheng injection subgroup (RR=1.38, 95% CI: 1.20-1.60, P<0.0001; I²=0%), Cinobufacini injection subgroup (RR=1.44, 95% CI: 1.17-1.78, P=0.0006; $I^2=0\%$), and Kanglaite injection subgroup (RR=1.61, 95% CI: 1.18-2.20, P=0.003; I²=0%), while showed no advantage in Xiaoaiping injection subgroup (RR=1.56, 95% CI: 0.97-2.53, P=0.07; I²=0%).

Disease control rate (DCR)

In total, 58 RCTs [13-18, 21-25, 27-48, 49-59, 61, 62, 64-75] with 9 CHIs contributed to the analysis of DCR with no significant heterogeneity $(I^2=0\%)$ P=0.71). The results showed that the DCR was significantly enhanced in CHIs plus FOBC group than that in FOBC group. (RR=1.09, 95%CI: 1.06-1.11, P <0.00001) (Figure 4). Subgroup analysis indicated that DCR was enhanced in Compound Kushen injection subgroup (RR=1.10, 95% CI:1.06-1.13, P<0.00001; I²=0%), Shenqifuzheng injection subgroup (RR=1.11, 95% CI: 1.02-1.21, P=0.01; I²=40%), Aidi injection subgroup (RR=1.07, 95% CI: 1.02-1.12, P=0.003; *I*²=0%), while showed no advantage in Cinobufacini injection subgroup (RR=1.08, 95% CI: 1.00-1.18, $P=0.06; I^2=0\%),$ Kanglaite injection subgroup (RR=1.19, 95% CI:0.93-1.51, P=0.17; I²=55%) and Xiaoaiping injection subgroup (RR=1.20, 95% CI: 0.99-1.44, *P*= 0.06; *I*²=0%).

Survival rate and Progression-free Survival (PFS)

There were 2 trials [47, 63] reported 1-year survival rate. The results indicated that the 1-year survival rate in CHIs plus FOBC group was higher than that in FOBC group (RR=2.27, 95% CI: 1.23–4.18, P=0.009) with low heterogeneity (I^2 =0%, P=0.54) (**Figure 5**).

2 RCTs [19, 69] reported progression-free survival (PFS), while because of the unextractable data and/or the diversity of survival outcomes in the included RCTs, meta-analysis was not possible for it

[78].

Quality of life (QoL)

The data on the QoL was available for 30 trials [14, 16, 21, 23, 25, 26, 28-30, 32, 35, 36, 38, 39, 41, 43, 45, 49, 53-55, 60, 61, 64, 66-68, 71, 72, 75] involving 6 types of CHIs. The results showed that the QoL in CHIs plus FOBC group was significantly higher than that in FOBC group (RR=1.21, 95% CI: 1.14-1.28, P<0.00001) with low heterogeneity (I²=32%, P=0.05). Subgroup analysis indicated that QoL was significantly improved in Compound Kushen injection subgroup (RR=1.20, 95% CI: 1.08-1.34, P=0.0005; I²=62%), Aidi injection subgroup (RR=1.25, 95% CI: 1.13-1.38, $P < 0.0001; I^2 = 0\%$) and Shengifuzheng injection subgroup (RR=1.21, 95% CI: 1.08-1.35, P=0.001; $I^2=0\%$), while showed no advantage in Xiaoaiping injection subgroup (RR=1.16, 95% CI: 0.94-1.43, *P*=0.17; *I*²=0%) (Figure 6).

Leukopenia

19 studies [15, 19, 25, 26, 28-30, 33, 35, 36, 39, 43-45, 49, 52, 53, 59, 75] with 6 types of CHIs reported the incidence of chemotherapy-induced leukopenia. Figure 7 showed that the incidence of leukopenia in CHIs combined with FOBC group was lower than that in FOBC group (RR=0.64, 95% CI: 0.50-0.82, P=0.0005) with obvious heterogeneity ($I^2=53\%$, P=0.004). Subgroup analysis showed that the incidence of leukopenia was decreased in Aidi injection subgroup (RR=0.62, 95%CI: 0.43-0.89, P=0.01; I2=0%), but showed no advantage in Compound Kushen injection subgroup (RR=0.66, 95% CI: 0.40-1.08, $P=0.10; I^2=75\%$) and Shenqifuzheng injection subgroup (RR=0.72, 95% CI: 0.47-1.12, $P=0.14; I^2=0\%).$

Nausea and Vomiting

A total of 13 studies [15, 19, 25, 26, 28, 30, 35, 36, 45, 49, 52, 53, 59] with 5 types of CHIs reported the data of nausea and vomiting, **Figure 8** exhibited that the incidence of nausea and vomiting in CHIs plus FOBC group was lower than that in FOBC alone group (RR=0.65, 95% CI: 0.51-0.83, *P*=0.0005. heterogeneity: I^2 =0%, *P*=1.00). Subgroup analysis showed that the incidence of nausea and vomiting was decreased in Aidi injection subgroup (RR=0.65, 95% CI: 0.45-0.94, *P*=0.02; I^2 =0%) and Compound Kushen injection subgroup (RR=0.58, 95% CI: 0.35-0.96, *P*=0.03; I^2 =0%), but showed no advantage in Shenqifuzheng injection subgroup (RR=0.63, 95% CI: 0.35-1.15, *P*=0.13; I^2 =0%).

Study or Subgroup	Experime Events	ntal Total	Contro	ol Total	Weight	Risk Ratio M-H. Random, 95% CI	Risk Ratio M-H. Random, 95% Cl
1.4.1 FOBC VS FOBC	Compoun	d Kush	en inject	ion	a and	0.0010 50 1 101	
Fang XG 2012	34	36	29	36	1.5%	1.17 [0.98, 1.40]	
Gao W 2010 Gao X 2021	29 22	38 23	25 19	35 23	0.6%	1.07 [0.81, 1.41] 1.16 [0.94, 1.42]	
Hao LX 2019 Kuang YM 2007	33 28	34 30	31	34	3.3%	1.06 [0.94, 1.20]	+
Lei XB 2020	24	25	20	25	1.1%	1.20 [0.97, 1.48]	
Liao GQ 2009	111	125	108	125	5.5%	1.03 [0.94, 1.13]	+
Liu HX 2012 Liu KH 2014	31 35	36 37	28 32	36 37	1.0%	1.11 [0.89, 1.38] 1.09 [0.94, 1.27]	
Liu XG 2014	51	52	48	52	6.3%	1.06 [0.97, 1.16]	<u> </u>
Ma X 2016	26	39	18	39	0.3%	1.44 [0.96, 2.17]	
Qi HW 2016 Shui HF 2014	32	36 24	25 21	36 24	0.8%	1.28 [1.00, 1.64] 1.05 [0.86, 1.27]	
Sun LQ 2013 Tao CL 2013	32 67	40 74	27 56	40 74	0.7%	1.19 [0.91, 1.54] 1.20 [1.03, 1.39]	
Wang JX 2015	24	25	21	25	1.3%	1.14 [0.95, 1.38]	<u></u>
Yan Q 2015	40	45	39	45	4.9%	1.05 [0.95, 1.16]	+-
Yang J 2015 Yu ZH 2016	30 27	39 43	30 18	39 43	0.8%	1.00 [0.78, 1.28] 1.50 [0.98, 2.28]	
Zan L 2015 Subtotal (95% CI)	33	40	31	40	1.0%	1.06 [0.85, 1.33]	
Total events	857	501	761	500	40.078	1.10 [1.00, 1.10]	
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.00; Chi ² = = 5.37 (P	16.58, c < 0.0000	f = 23 (P 01)	9 = 0.8	3); I ² = 0%		
1.4.2 FOBC VS FOBC	Shengifuz	theng in	iection				
Guo HM 2019	33	36	28	36	1.2%	1.18 [0.96, 1.44]	
Huo W 2008	17	30	18	24 14	0.4%	0.93 [0.67, 1.30] 1.08 [0.72, 1.62]	
Jia CY 2016 Li RM 2018	39 29	43 32	28 26	43 32	0.8%	1.39 [1.10, 1.77]	
Liang QL 2009	73	76	72	76	9.7%	1.01 [0.95, 1.09]	+
Tan GG 2013	17	20	13	20	0.8%	1.31 [0.90, 1.89]	
Xing F 2015 Zhang W 2015	24 37	30 43	23 27	30 43	0.7%	1.04 [0.80, 1.36] 1.37 [1.06, 1.78]	
Zhao T 2011 Subtotal (95% CI)	28	32	27	32	1.2%	1.04 [0.85, 1.26]	
Total events	352	410	305	390	17.470	1.11[1.02, 1.21]	ŀ
Heterogeneity: Tau ² = 0 Test for overall effect: 2	.01; Chi ² = = 2.43 (P	16.55, c = 0.01)	if = 10 (P	9 = 0.00	3); I ² = 40%	Ka	
1.4.3 FOBC VS FOBC	Aidi inject	tion					
Chen LF 2013 Chen XY 2017	23	30	16 24	30	0.3%	1.44 [0.97, 2.12]	
Fu H 2020	48	52	46	52	3.0%	1.04 [0.92, 1.18]	
Li HJ 2007	57	30 65	20 45	26 52	0.5%	0.91 [0.66, 1.25] 1.01 [0.88, 1.17]	
Li SJ 2016 Liu J 2017	41 30	45 36	39 28	45 35	2.2%	1.05 [0.91, 1.22] 1.04 [0.84, 1.30]	
Liu T 2009	26	30	21	30	0.6%	1.24 [0.94, 1.63]	<u>+</u>
Shi B 2009	40	18	40	18	0.4%	1.00 [0.71, 1.42]	
Sun WR 2015 Wang YT 2012	44 30	48 38	42	48 36	2.5%	1.05 [0.91, 1.20] 1.42 [1.02, 1.99]	
Zhang Q 2021	65	65	60	65	8.3%	1.08 [1.00, 1.17]	•
Total events	472	540	415	524	23.0%	1.07 [1.02, 1.12]	·
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.00; Chi ² = = 2.99 (P =	8.95, df = 0.003)	= 12 (P :	= 0.71)	; I ^z = 0%		
1.4.4 FOBC VS FOBC	Kang'ai in	jection					
Subtotal (95% CI) Total events	0	0	0	0		Not estimable	
Heterogeneity: Not appl Test for overall effect: N	icable lot applicab	ale					
	Huangal	nicetion					
Chen F 2009	25	30	21	30	0.6%	1.19 [0.90, 1.58]	
Subtotal (95% CI) Total events	25	30	21	30	0.6%	1.19 [0.90, 1.58]	
Heterogeneity: Not appl	icable = 1 20 (P :	= 0.23)					
	- nao (r	- 0.20)	eles inis	ation			
Nie HX 2012	28	30	27	30	2.0%	1.04 [0.89, 1.21]	+
Subtotal (95% CI) Total events	28	30	27	30	2.0%	1.04 [0.89, 1.21]	-
Heterogeneity: Not appl	icable	- 0.64)					
	- 0.47 (F	- 0.04)					
Cai HF 2020	30	31	28	31	2.7%	1.07 [0.94, 1.22]	+
Huang JL 2012 Pap. J 2020	20	21	15	20	0.7%	1.27 [0.97, 1.66]	
Subtotal (95% CI)		87	-	86	6.9%	1.08 [1.00, 1.18]	•
Heterogeneity: Tau ² = 0	84 .00; Chi ² =	1.73, df	= 2 (P =	0.42);	l ² = 0%		
Test for overall effect: 2	:= 1.91 (P	= 0.06)					
1.4.8 FOBC VS FOBC+ Kou WZ 2016	Xiaoaiping	g injecti 37	on 27	36	0.9%	1.15 [0.92, 1.45]	<u> </u>
Zhang L 2012	18	20	14	20	0.5%	1.29 [0.93, 1.77]	
Total events	50	57	41	50	1.470	1.20 [0.00, 1.44]	
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.00; Chi ² = = 1.89 (P =	0.29, df = 0.06)	= 1 (P =	0.59);	$I^2 = 0\%$		
1.4.9 FOBC VS FOBC+	Kanglaite	injectio	n				
Sun YY 2020 Wang RW 2015	25	30	18	30	0.4%	1.39 [1.00, 1.94]	
Subtotal (95% CI)		94		90	4.1%	1.19 [0.93, 1.51]	•
Heterogeneity: Tau ² = 0	86 .02; Chi ² =	2.22, df	70 = 1 (P =	0.14);	l² = 55%		
Test for overall effect: Z	= 1.36 (P	= 0.17)					
1.4.10 FOBC VS FOBC Zhang ZH 2011	+Lentinan 32	injectio 38	23	34	0.7%	1.24 [0.95, 1.63]	<u> </u>
Subtotal (95% CI)	22	38	20	34	0.7%	1.24 [0.95, 1.63]	•
Heterogeneity: Not appl	32 licable		23				
Test for overall effect: Z	= 1.59 (P	= 0.11)					
Total (95% CI)		2281		2226	100.0%	1.09 [1.06, 1.11]	•
Total events Heterogeneity: Tau ² = 0	1986 .00; Chi ² =	50.53, 0	1738 If = 57 (P	= 0.7	1); I² = 0%		
Test for overall effect: Z Test for subgroup differ	= 7.46 (P ences: Chi ²	< 0.0000)1) df = 8 (P	= 0.8	5). I ² = 0%		Favours [control] Favours [experimental]

Figure 4. Forest plot of DCR in FOBC versus FOBC plus CHIs.



Figure 5. Forest plot of 1-year survival rate in FOBC versus FOBC plus CHIs.

	Experimer	ntal	Contro	ы		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total E	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.3.1 FOBC VS FOBC	+Compound	d kushe	n inject	ion			
Cao ZY 2009	29	33	18	29	2.7%	1.42 [1.04, 1.93]	
Fang XG 2012	27	36	14	36	1.4%	1.93 [1.23, 3.03]	
Gao W 2010	30	38	25	30	4.2%	0.95 [0.75, 1.19]	-
Liao GQ 2009	106	125	91	125	7.5%	1.16 [1.02, 1.33]	-
Liu HX 2012	34	36	26	36	4.4%	1.31 [1.05, 1.63]	
Liu KH 2014	34	37	32	37	6.3%	1.06 [0.91, 1.25]	T
Shui HF 2014	23	24	22	24	6.8%	1.05 [0.90, 1.21]	+
Sun LQ 2013	17	40	13	40	0.9%	1.31 [0.74, 2.32]	
Wang JX 2015	17	25	9	25	0.9%	1.89 [1.05, 3.40]	
Wang JY 2011	17	21	11	21	1.4%	1.55 [0.98, 2.44]	· · ·
Yan Q 2015	39	41	36	41	7.3%	1.08 [0.95, 1.24]	-
Yang J 2015	34	39	32	39	5.2%	1.06 [0.88, 1.28]	+
Zan L 2015	34	40	20	40	2.4%	1.70 [1.21, 2.38]	
Subtotal (95% CI)		535		523	51.4%	1.20 [1.08, 1.34]	◆
Total events	441		349				
Heterogeneity: Tau ² =	0.02: Chi ² =	31.41. d	f = 12 (F	P = 0.0	02): $ ^2 = 62$	%	
est for overall effect:	7 = 3.48 (P =	= 0.0005)(0.0	02,,. 02		
	2 0.40 (1	0.0000	,				
.3.2 FOBC VS FOBC	+Shenaifuz	hena ini	jection				
Suo YR 2011	25	30	14	24	2 0%	1 43 [0 98 2 09]	
Juo W/ 2008	20	22	2	14	0.2%	1.40 [0.80, 2.00]	
i PM 2018	9	32	22	22	3 40/	1.31 [0.02, 0.00]	+
Ling OL 2000	21	32	23	32	5.4%	1.17 [0.90, 1.53]	L
Liang QL 2009	64	76	54	76	5.8%	1.19[1.00, 1.41]	
Ving F 2015	24	30	23	30	3.4%	1.04 [0.80, 1.36]	
nao 1 2011	26	32	18	32	2.2%	1.44 [1.02, 2.05]	
subtotal (95% CI)		222		208	17.1%	1.21 [1.08, 1.35]	
otal events	175		135				
Heterogeneity: Tau ² =	0.00; Chi ² =	3.90, df	= 5 (P =	0.56);	$I^2 = 0\%$		
Test for overall effect:	Z = 3.25 (P =	= 0.001)					
.3.3 FOBC VS FOBC	+Aidi inject	ion					
chen LF 2013	24	30	19	30	2.5%	1.26 [0.91, 1.75]	
lai YJ 2011	24	32	17	32	1.9%	1.41 [0.96, 2.07]	
luang J 2008	25	30	16	26	2.3%	1.35 [0.96, 1.91]	
i HJ 2007	58	65	41	52	6.1%	1.13 [0.96, 1.33]	-
iu W 2012	44	56	30	52	3 3%	1 36 [1 04 1 78]	
Shi B 2000	17	18	13	18	2 7%	1 31 [0 06 1 78]	
Mana XT 2012	21	20	22	26	2.1 /0	1.01 [0.00, 1.70]	
Subtotal (95% CI)	31	260	23	246	3.0%	1.20 [0.90, 1.70]	•
	222	209	150	240	21.0 /0	1.25 [1.15, 1.56]	·
lotal events	223	36 00 0	159	0.05)	12 - 00/		
leterogeneity: 1 au- =	0.00; Chi+ =	2.68, 01	= 6 (P =	0.85);	1- = 0%		
est for overall effect:	Z = 4.30 (P <	< 0.0001)				
2 4 EORO VO EORO	Cinker	allalast	lan				
	+Cinputacir	ni injecti	ion				
luang JL 2012	18	21	11	20	1.5%	1.56 [1.01, 2.40]	
ubtotal (95% CI)		21		20	1.5%	1.56 [1.01, 2.40]	
Total events	18		11				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 2.01 (P =	= 0.04)					
2.3.6 FOBC VS FOBC	+Javanica d	oil emul	sion inje	ection			
Nie HX 2012	24	30	19	30	2.5%	1.26 [0.91, 1.75]	+
Subtotal (95% CI)		30	1008000	30	2.5%	1.26 [0.91, 1.75]	◆
Total events	24		19				
Heterogeneity: Not and	plicable						
Test for overall effect	Z = 1.41 (P =	= 0.16)					
set for oronal ondot.		00)					
2.3.8 FOBC VS FOBC	+Xiaoaiping	g injectio	on				
Kou WZ 2016	29	37	22	36	2.7%	1.28 [0.94, 1.75]	+
Zhang L 2012	17	20	16	20	3.0%	1.06 [0.80, 1.41]	+-
Subtotal (95% CI)		57		56	5.7%	1.16 [0.94, 1.43]	◆
Total events	46		38				[-
Heterogeneity: Tau ² =	0.00: Chi ² =	0.83 df	= 1 (P =	0.36)	$l^2 = 0\%$		
Test for overall offect:	7 = 1 27 /D -	= 0 17)	(5.50),	- 0 /0		
reation overall effect; a	2 - 1.37 (P =	- 0.17)					
Total (05% CI)		1124		1082	100 09/	1 21 14 44 4 203	▲
Total (95% CI)	0.07	1134		1083	100.0%	1.21 [1.14, 1.28]	▼
i otal events	927	10.15	/11				
Heterogeneity: Tau ² =	0.01; Chi ² =	42.43, d	t = 29 (F	² = 0.0	5); l ² = 32%	0	0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 6.43 (P <	< 0.0000	1)				Favours [control] Favours [experimental]
Test for subaroup diffe	erences: Chi ²	= 1.78.	df = 5 (F	P = 0.8	8). $I^2 = 0\%$		for the second s

Figure 6. Forest plot of QoL in FOBC versus FOBC plus CHIs.

	Experime	ntal	Contro	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% Cl
4.4.1 FOBC VS FOBC	+Compoun	d kush	nen inject	ion			
Ding X 2010	3	30	7	30	3.1%	0.43 [0.12, 1.50]	
Kuang YM 2007	5	30	7	30	4.2%	0.71 [0.25, 2.00]	
Liao GQ 2009	106	125	109	125	13.9%	0.97 [0.88, 1.07]	t
Liu KH 2014	15	37	25	37	9.7%	0.60 [0.38, 0.94]	
Tao CL 2013	10	74	21	74	6.9%	0.48 [0.24, 0.94]	
Subtotal (95% CI)		296		296	37.8%	0.66 [0.40, 1.08]	•
Total events	139		169				
Heterogeneity: Tau ² = Test for overall effect:	0.19; Chi² = Z = 1.67 (P =	16.24, = 0.10)	df = 4 (P	= 0.00	3); l² = 75%	0	
4.4.2 FOBC VS FOBC	+Shengifuz	heng i	njection				
Guo YR 2011	3	30	4	24	2.6%	0.60 [0.15, 2.43]	
Huo W 2008	6	22	7	14	5.3%	0.55 [0.23, 1.29]	
Li RM 2018	8	32	10	32	5.9%	0.80 [0.36, 1.76]	
Shang CX 2017	8	46	8	46	5.1%	1.00 [0.41, 2.44]	
Zhao T 2011	3	32	5	32	2.8%	0.60 [0.16, 2.30]	
Subtotal (95% CI)		162		148	21.6%	0.72 [0.47, 1.12]	•
Total events	28		34				
Heterogeneity: Tau ² =	0.00; Chi ² =	1.13, c	if = 4 (P =	0.89);	$ ^2 = 0\%$		
Test for overall effect:	Z = 1.47 (P =	= 0.14)					
4.4.3 FOBC VS FOBC	+Aidi inject	tion					
Hai YJ 2011	0	32	1	32	0.6%	0.33 [0.01, 7.89]	
Huang J 2008	3	30	4	26	2.6%	0.65 [0.16, 2.64]	
Li HJ 2007	8	65	13	52	5.8%	0.49 [0.22, 1.10]	
Liu T 2009	6	30	12	30	5.5%	0.50 [0.22, 1.16]	
Liu W 2012	16	56	20	52	8.6%	0.74 [0.43, 1.27]	
Shi B 2009	2	18	3	18	1.9%	0.67 [0.13, 3.53]	
Subtotal (95% CI)		231		210	24.9%	0.62 [0.43, 0.89]	\bullet
Total events	35		53				
Heterogeneity: Tau ² =	0.00; Chi ² =	1.17, c	if = 5 (P =	0.95);	$ ^2 = 0\%$		
Test for overall effect:	Z = 2.59 (P =	= 0.010))	,.			
	+Huanggi ii	niactio					
4.4.5 FOBC V3 FOBC	Tuangqi ii	20	6	20	2 00/	0 50 10 14 1 921	
Subtotal (95% CI)	3	30	0	30	3.0%	0.50 [0.14, 1.82]	
Total overts	3	50	6	50	5.0 %	0.50 [0.14, 1.02]	
Heterogeneity: Not apr	Jicable		0				
Test for overall effect:	7 = 1.05 / P	- 0 20)					
rescior overall effect.	2 - 1.05 (F -	- 0.29)					
4.4.6 FOBC VS FOBC	+Javanica	oil emu	ulsion inj	ection			
Nie HX 2012	7	30	10	30	5.6%	0.70 [0.31, 1.59]	
Subtotal (95% CI)		30		30	5.6%	0.70 [0.31, 1.59]	-
Total events	7		10				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.85 (P =	= 0.40)					
4.4.7 FOBC VS FOBC	+Cinobufac	cini inio	ection				
Huang JL 2012	7	21	15	20	7.2%	0.44 [0.23, 0.86]	
Subtotal (95% CI)		21		20	7.2%	0.44 [0.23, 0.86]	•
Total events	7		15				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 2.42 (P =	= 0.02)					
Total (95% CI)		770		734	100.0%	0.64 [0.50, 0.82]	•
Total evente	210	110	297	1 34	100.070	0.04 [0.00, 0.02]	•
Heterogeneity: Tau ² -	2 19 0 11: Chi2 -	38 04	20/ df = 19 /	= 0.0	04)· 12 - F2	0/_	++
Test for overall offect:	7 = 3.50 / D	= 0.000	01 - 10 (F	- 0.0	0+), 1° = 33	70	0.005 0.1 1 10 200
Test for subgroup diffe	rences: Chi2	= 0.000	df = 5/F	2 = 0.8	9) $I^2 = 0.0\%$		Favours [experimental] Favours [control]
, sacior auburoub dille	onoca. oni	- 1.70	. ui = 0 (r	- 0.0	0.1 - 0 /0		

Figure 7. Forest plot of leukopenia in FOBC versus FOBC plus CHIs.

Diarrhea

A total of 12 RCTs [15, 18, 25, 26, 28, 30, 33, 35, 36, 45, 49, 53] with 5 types of CHIs reported diarrhea, **Figure 9** showed that the incidence of diarrhea in CHIs plus FOBC group was lower than that in FOBC alone group (RR=0.34, 95% CI: 0.20–0.58, P<0.0001. heterogeneity: I^2 =0%, P=0.94). In subgroup analysis, the incidence of diarrhea was decreased in Shenqifuzheng injection subgroup (RR=0.24, 95% CI: 0.06-0.97, P=0.05; I^2 =0%) and Aidi injection subgroup (RR=0.31, 95% CI: 0.16-0.61, P=0.0006; I^2 =0%).

Publication bias

Figure 10A-F showed the funnel plots based on the data of the ORR, DCR, QoL, leukopenia, nausea and vomiting and diarrhea were asymmetrical, which indicated that publication bias might influence the results of the analysis.

Additional analyses

Regarding ORR, the primary outcome, the pooled data showed that CHIs plus FOBC increased ORR significantly (RR=1.34, 95%CI: 1.27-1.42, P<0.00001). Similar increases were observed when the sensitivity analyses were performed based on the

results of Cochrane Risk of Bias Tool (excluded 9 RCTs [13, 39, 45, 49, 53-55, 58, 62] of poor quality with at least one "high risk" domain in risk of bias assessment) (RR=1.33, 95% CI: 1.26-1.42, *P*<0.00001), participants number (only included 8 RCTs with \geq 50 participants in each group) (RR=1.35, 95% CI: 1.22-1.49, *P*<0.00001), treatment duration of CHIs (only included 30 RCTs with \geq 4 courses) (RR=1.30, 95% CI: 1.21-1.40, *P*<0.00001), publication year (only included 21 studies published within 5 years) (RR=1.40, 95% CI: 1.29-1.53, P<0.00001) or stage (only included 6 studies enrolled patients with stage IV) (RR=1.59, 95% CI: 1.28-1.97, P<0.0001). It showed that the results of the primary outcome were robust before and after removing related trials (**Table 5**).

Table 5. Sensitivity analysis of objective response rate (ORR)

Types	Excluded trials	Remaining	Statistical	RRs	Р	I^2
	(references)	trials	methods	(95%CI)		
Quality of	9 [13, 39, 45, 49,	50	FEM	1.33 (1.26,	<	0%
trials	53-55, 58, 62]			1.42)	0.00001	
Participants	51 [13-18, 20, 21,	8	FEM	1.35(1.22,	<	0%
number	23-25, 27-34, 36, 37,			1.49)	0.00001	
	40-44, 47-59, 61,					
	64-68, 70-75]					
Treatment	29[13-15, 18, 21, 22,	30	FEM	1.30 (1.21,	<	0%
duration of	28, 29, 32, 36-39, 41,			1.40)	0.00001	
CHIs	42, 44, 45, 50, 51, 53,					
	55, 57-59, 62, 71-73,					
	75]					
Publication	38 [14-16, 20, 21, 23,	21	FEM	1.40 (1.29,	<	0%
year	25, 28-30, 33-35, 38,			1.53)	0.00001	
	39, 41, 43-46, 49,					
	53-56, 58,59, 61, 62,					
	64, 66-68, 71-75]					
Stage	53 [13, 14, 16-18,	6	FEM	1.59 (1.28,	<	9%
	20-22, 24, 25, 27, 28,			1.97)	0.0001	
	30-50, 52-58, 61, 62,					
	64-67, 69-75]					

FEM: fixed-effects model; RRs: risk ratios; CI: confidence interval.



Figure 8. Forest plot of nausea and vomiting in FOBC versus FOBC plus CHIs.

Chudu an Outanaur	Experime	ental	Contro	ol Tatal	Mainh4	Risk Ratio	Risk Ratio
Study of Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI							
5.6.1 FOR VS FOR TOBUTO RUSHEN INJECTION							
Kuang YM 2007	0	30	0	30		Not estimable	
Subtotal (95% CI)	0	30	0	30		Not estimable	
lotal events	U		0				
Text for survey of applicable							
Test for overall effect. Not applicable							
5.8.2 FOBC VS FOBC	+Huangqi	injection					
Chen F 2009	2	30	4	30	8.4%	0.50 [0.10, 2.53]	
Subtotal (95% CI)		30		30	8.4%	0.50 [0.10, 2.53]	
Total events	2		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.84 (P = 0.40)							
5.8.3 FOBC VS FOBC	+Aidi injec	tion			10.00/		
Chen XY 2017	0	35	6	35	13.6%	0.08 [0.00, 1.32]	
Hai YJ 2011	3	32	9	32	18.9%	0.33 [0.10, 1.12]	
Huang J 2008	1	30	4	26	9.0%	0.22 [0.03, 1.82]	
LI HJ 2007	2	65	5	52	11.6%	0.32 [0.06, 1.58]	
LIU W 2012	3	50	5	52	10.9%	0.56 [0.14, 2.22]	
Shi B 2009 Subtotal (05% CI)	1	18	2	18	4.2%	0.50 [0.05, 5.04]	
Subtotal (95% CI)	10	230	21	215	00.270	0.31 [0.16, 0.61]	•
10 = 10 = 10							
Test for overall effect: $7 = 3.41$ ($P = 0.006$)							
Test for overall effect. $2 = 3.41$ (F = 0.0000)							
5.8.4 FOBC VS FOBC+Shenaifuzhena injection							
Guo YR 2011	1	30	4	24	9.3%	0.20 [0.02, 1.67]	
Huo W 2008	1	22	1	14	2.6%	0.64 [0.04, 9.37]	
Li RM 2018	0	32	3	32	7.3%	0.14 [0.01, 2.66]	
Subtotal (95% CI)		84		70	19.2%	0.24 [0.06, 0.97]	
Total events	2		8				
Heterogeneity: Chi ² = 0.66, df = 2 (P = 0.72); l ² = 0%							
Test for overall effect: $Z = 2.00 (P = 0.05)$							
5.8.5 FOBC VS FOBC+Javanica oil emulsion injection							
Nie HX 2012	2	30	2	30	4.2%	1.00 [0.15, 6.64]	
Subtotal (95% CI)		30		30	4.2%	1.00 [0.15, 6.64]	
Total events	2		2				
Heterogeneity: Not app	olicable						
Test for overall effect: Z = 0.00 (P = 1.00)							
Total (95% CI)		410		375	100.0%	0.34 [0.20, 0.58]	◆
Total events	16		45				
Heterogeneity: Chi ² = 4.07, df = 10 (P = 0.94); l ² = 0%							
Test for overall effect:	Z = 3.93 (P	< 0.0001)					0.002 0.1 1 10 500
Test for subgroup differences: $Chi^2 = 1.78$, $df = 3 / P = 0.62$, $l^2 = 0.96$ Favours [experimental] Favours [control]							





Figure 10. Funnel plots of outcomes: A. ORR; B. DCR; C. QoL; D. leukopenia; E. nausea and vomiting; F. diarrhea.



TSA was implemented to evaluate the required information size (RIS). As it showed in **Figure 11**, although the RIS has not been reached, the positive conclusion was obtained in advance as Z-curve had crossed the traditional boundary and TSA boundary. Therefore, it could be thought that CHIs combined with FOBC was significantly superior to FOBC alone in improving ORR, and the evidence was reliable [79].

Discussion

To explore the effectiveness and safety of CHIs combined with FOBC in advanced CRC treatment, we conducted this meta-analysis to analyze the evidence in published RCTs. In general, the results of our study indicated that CHIs in conjunction with FOBC showed significant improvements in ORR, DCR, 1-year survival rate and QoL; and decreases in incidence of leukopenia, diarrhea and nausea and vomiting, while because of the unextractable data, whether PFS was improved remained unknown. In terms of methodology, the overall quality of the included studies could be considered moderate. GRADE assessments showed a low-quality of evidence. Most results showed low heterogeneity and good robustness.

Although FOBC regimen has been shown to prolong survival and reduce the advent of major complications in patients with advanced CRC [3], due to the lack of anti-tumor selective effects, it also has damaging effects on normal cells while suppressing tumor growth. Thus enhancing therapeutic effects and reducing adverse reactions became an urgent problem in current advanced CRC treatment [80], and CHIs proven to have those effects according to our results. As the products of the combination of TCM and modern science and technology, CHIs not only retain the characteristics of Chinese medicines under the guidance of Chinese medicine theory, but also obtain the advantages of modern chemical medicine like stable composition and fast onset. Compound Kushen injection is extracted from Kushen (Radix sophorae flavescentis) and Baituling (Rhizoma smilacis glabrae), it is extensively used for the treatment of malignant tumor such as liver cancer, lung cancer, and gastrointestinal cancer, and has been found to has the potiential to induce tumor cell differentiation and apoptosis and to inhibit tumor angiogenesis [81]. The main active compounds of Aidi injection include cantharidin, astragalosides, ginsenosides, isofraxidin and syringin that are derived from Chinese herbs, various studies have shown that Aidi injection in relation to anti-tumor activity, immune regulatory action and adverse events relieving [82]. Shenqifuzheng injection is composed of extracts from astragalus membranaceus and codonopsis pilosula, and was clinically indicated to improve body immunity and suppress tumor growth [83]. Regarding effectiveness and safety of CHIs, our review indicated that some CHIs showed great beneficial impact on enhancing short-term effectiveness, improving 1-year survival rate and QoL, and reliving adverse effects.

To identify certain effective CHIs, we conducted subgroup analyses for all outcomes according to different types of CHIs as predefined. For the primary outcomes – ORR and DCR, 3 CHIs showed great advantages including Compound Kushen injection, Shenqifuzheng injection and Aidi injection. We also concerned that Xiaoaiping injection that extracted from Marsdenia tenacissima revealed no advantage in ORR, DCR, QoL and adverse reaction improvement, which suggested it might not recommended in the treatment of advanced CRC considering insufficient evidence.

There were some limitations in this study. First, all trials were conducted in China, which might lead to an unavoidable regional bias. Second, publication bias might exist on account of the asymmetrical funnel plots. Third, some studies lacked methodological details in randomization, allocation concealment and blinding, which might result in the emergence of bias and overestimation of effectiveness [84]. Last, the study periods were generally short, and majority of the included trials did not report long-term endpoint outcomes such as overall survival (OS) and PFS that played a vital role in judging the therapeutic effects among patients with tumors. Given the limited quality and quantity of the included studies, more rigorous RCTs with high-quality methodology and long-term endpoint outcomes were needed to verify the beneficial role of CHIs combined with first-line chemotherapy in patients with advanced CRC.

Conclusion

In conclusion, from the available evidence, CHIs could increase ORR and DCR, improve 1-year survival rate and QoL, and relieve leukopenia, nausea and vomiting and diarrhea when combined with FOBC in advanced CRC treatment. Meanwhile, considering the limitations, clinicians should choose carefully when applying the conclusions of this study.

Abbreviations

CHIs: Chinese herbal injections; CI: Confidence CNKI: China National Knowledge Interval; Infrastructure; CR: complete response rates; CRC: colorectal cancer; DCR: disease control rate; FOBC: fluoropyrimidines and oxaliplatin-based chemotherapy; FUs: Fluoropyrimidines; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IARC: International Agency for Research on Cancer; INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols; KPS: Karnofsky performance scale; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NIH:

National Cancer Institute; RR: risk ratio; ORR: objective response rate; OS: overall survival; PD: progressive disease; PR: partial response; PFS: progression-free survival; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QoL: quality of life; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; TCM: Traditional Chinese Medicine; TSA: Trial sequential analysis; WHO: World Health Organization; 5-FU: 5-fluorouracil.

Supplementary Material

Supplementary search strategies. https://www.jcancer.org/v12p7237s1.pdf

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Author contributions

- Shuo Wang, Xueqian Wang, Tong Zhou: collecting data, statistical analysis, writing the article, final approval of the article;
- Tong Zhou, Shuaihang Hu: data extraction, statistical analysis;
- Peiyu Tian, Zheng Li: quality evaluation, final approval of the article;
- Yuxiao Li, Dandan Wang: developing search strategy, critical revision;
- Jun Dong, Yuerong Gui: developing criteria, study selection;
- Wei Hou, Ying Zhang: design, supervising the whole process, critical revision of the article, final approval of the article.

Competing Interests

The authors have declared that no competing interest exists.

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