

Kanglaite injection plus fluorouracil-based chemotherapy on the reduction of adverse effects and improvement of clinical effectiveness in patients with advanced malignant tumors of the digestive tract

A meta-analysis of 20 RCTs following the PRISMA guidelines

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Abstract

Background: The digestive tract malignancies are a series of malignant tumor with high morbidity and mortality. Traditional Chinese medicine (TCM) combined with chemotherapy drugs interventions have been applied for the treatment of malignant tumors in Asian countries for decades. This study aimed to assess the effectiveness and safety on the combination of Kanglaite injection and fluorouracil-based chemotherapy for treating digestive tract malignancies.

Purpose: To assess the effectiveness and safety on the combination of Kanglaite injection and fluorouracil-based chemotherapy for digestive tract malignancies.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed when conducting the meta-analysis. Randomized controlled trials (RCTs) of Kanglaite injection combined with fluorouracil-based chemotherapy in the treatment of digestive tract malignant tumors were selected and assessed for inclusion. RevMan 5.3 software (Cochrane Collaboration, Oxford, UK) was used for meta-analysis. The objective response rate (ORR) was defined as the primary endpoint, and the disease control rate (DCR), quality of life (QoL), and toxicities were the secondary outcomes.

Results: 20 RCTs enrolling 1339 patients with advanced digestive tract malignancies were included. The methodological quality of most included trials was low to moderate. Compared with fluorouracil-based chemotherapy alone, Kanglaite injection plus fluorouracil-based chemotherapy can improve DCR (risk ratio (RR)=1.18, 95% confidence interval (CI) 1.11–1.25, $P < .00001$), ORR (RR=1.35, 95% CI 1.18–1.54, $P < .00001$), QoL (RR=1.58, 95% CI 1.35–1.85, $P < .00001$), and can reduce adverse drug reactions (ADRs) such as myelosuppression (RR=0.33, 95% CI 0.25–0.43, $P < .00001$), leukopenia (RR=0.31, 95% CI 0.22–0.43, $P < .00001$), thrombocytopenia (RR=0.6, 95% CI 0.38–0.49, $P = .03$), neutropenia (RR=0.26, 95% CI 0.12–0.55, $P = .0005$), anemia (RR=0.41, 95% CI 0.23–0.75, $P = .004$), gastrointestinal reaction (RR=0.35, 95% CI 0.27–0.46, $P < .00001$), nausea/vomiting (RR=0.41, 95% CI 0.28–0.61, $P < .00001$), diarrhea (RR=0.34, 95% CI 0.18–0.62, $P = .0004$), hepatotoxicity (RR=0.28, 95% CI 0.17–0.47, $P < .00001$), neurotoxicity (RR=0.58, 95% CI 0.41–0.82, $P = .002$), mucositis (RR=0.59, 95% CI 0.29–1.21, $P = .15$).

Conclusion: Kanglaite injection combined with fluorouracil-based chemotherapy could remarkably improve the clinical effectiveness and reduce the adverse effects in patients with advanced malignant tumors of the digestive tract which may provide evidence to judge whether TCM is an effective and safe intervention for the digestive tract malignancies.

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Abbreviations: ADRs = adverse drug reactions, CHIs = Chinese herb injections, CI = confidence interval, CR = complete response, DCF = docetaxel, cisplatin plus 5-fluorouracil, DCR = disease control rate, DDP = cisplatin, DF = cisplatin plus 5-fluorouracil, FEM = fixed-effects model, FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin, GRADE = Grades of Recommendation Assessment, Development, and Evaluation, KPS = Karnofsky Performance Status, L-OHP = oxaliplatin, MD = mean difference, NMA = network meta-analysis, ORR = objective response rate, OS = overall survival, PCF = paclitaxel, cisplatin plus 5-fluorouracil, PD = progressive disease, PFS = progression-free survival, PR = partial response, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PROSPERO = International prospective register of systematic reviews, QoL = quality of life, RCTs = randomized controlled trials, RECIST = Response Evaluation Criteria In Solid Tumors, REM = random-effects model, RR = risk ratio, SD = stable disease, SOX = TS-1 plus oxaliplatin, Taxol = paclitaxel, Taxotere = docetaxel, TCM = traditional Chinese medicine, TS-1 = tegafur, gimeracil and oteracil potassium capsules, TSA = trial sequential analysis, WHO = World Health Organization.

Keywords: digestive tract malignancy, fluorouracil-based chemotherapy, Kanglaite injection, meta-analysis, randomized controlled trial (RCT)

1. Introduction

Given the intensification of urbanization, industrialization, and aging; ecological environment deterioration; and lifestyle changes, there has been a continuous increase in the malignant tumor incidence. Consequently, it has become a major public health issue that poses a threat to human life and social development. In 2018, the worldwide number of new cancer cases reached 18.1 million with nearly 9.6 million of them resulting in death, which made it the leading cause of death after cardiovascular disease. The leading 3 causes of cancer death were lung cancer (22.0%), liver cancer (10.2%), and stomach cancer (9.5%) in males and breast cancer (15%), lung cancer (13.8%), and colorectal cancer (9.5%) in females.^[1] World Health Organization (WHO) reported that there were 2.76 million worldwide cases of digestive tract malignancies in 2012 with an incidence rate of 35.2/100,000. Further, the number of deaths from malignant digestive tract tumors was 1.82 million with a case fatality rate of 22.3/100,000. In China, the annual number of cases and deaths from malignant digestive tract tumors is >2 million and 1.6 million, respectively, which makes it have the highest incidence and mortality among the malignant tumors in China with the 2 showing an annual increase.^[2]

Chemotherapy is among the main treatment methods for malignant digestive tract tumors. However, its drug toxicity in tumor treatment often causes many adverse reactions, including bone marrow suppression, immunosuppression, and gastrointestinal reactions, which seriously affect the quality of life (QoL) for individuals with malignant tumors. As a multi-target and multi-effect treatment method with fewer side effects, traditional Chinese medicine confers unique advantages against chemotherapy-induced adverse reactions.^[3]

Kanglaite injection (Z10970091, China Food and Drug Administration), which is extracted from Coix seed, is an effective anti-cancer treatment in traditional Chinese medicine. It has been shown to induce apoptosis and inhibit cancer cell proliferation by regulating PI3K/Akt/mTOR signaling pathway.^[4] Further, it has been reported to be clinically effective in the treatment of liver cancer, pancreatic cancer, lung cancer, and other malignant tumors.^[5–7] Malignant tumor treatment using Kanglaite injection combined with chemotherapy could improve clinical efficacy, reduce toxicity and side effects, and enhance immune function.^[8]

Fluorouracil (antineoplastic agent) is a cell-cycle-specific drug that exerts cytotoxic effects through DNA synthesis inhibition and RNA transcription interference.^[9] Fluorouracil (5-Fu) remains the first-line treatment for digestive tract tumors.^[10,11] Given its broad antineoplastic spectrum, it is also widely used in the treatment of breast cancer, ovarian cancer, bladder cancer,

etc.^[12–14] Fluorouracil agents include 5-Fu, tegafur, fluorouridine, capecitabine, and tigeo; among them, 5-Fu was the first to be clinically applied. Fluorouracil-based chemotherapy refers to the use of fluorouracil alone or in combination with cisplatin (DDP),^[15] oxaliplatin (L-OHP),^[16] paclitaxel (Taxol),^[17] or docetaxel (Taxotere),^[18] which are important therapeutic agents for gastrointestinal malignant tumors. There have been studies comparing the efficacy and safety of Kanglaite injection combined with chemotherapy vs chemotherapy alone in patients with advanced gastric cancer. However, these studies are limited by small sample sizes and low quality, which weakens the validity of their conclusions. A comprehensive evaluation of the efficacy of Kanglaite injection for advanced gastric cancer is difficult. In 2014, a meta-analysis by Wang et al^[19] reported that chemotherapy using a combination of Kanglaite and 5-fluorouracil, leucovorin plus oxaliplatin (FOLFOX), a typical fluorouracil-based regimen, significantly improved objective response rate (ORR) and QoL in patients with gastric cancer. Further, Kanglaite injection can significantly reduce the incidence of nausea, vomiting, and leukopenia (III–IV). This meta-analysis, which included 10 Chinese herb injections (CHIs) combined with FOLFOX, focused on horizontally comparing traditional Chinese medicine. A similar analysis^[20] reported that Kanglaite injection combined with FOLFOX had a more favorable clinical efficacy than that of the FOLFOX regimen alone. Several studies have compared the efficacy and safety of Kanglaite injection combined with chemotherapy vs chemotherapy alone in advanced digestive tract malignancies. However, they have several limitations including small sample sizes, as well as limited quality and reference values. Moreover, the clinical efficacy and effect of Kanglaite injection combined with fluorouracil-based chemotherapy on the QoL of patients with digestive tract malignancies remains unclear. Therefore, we aimed to conduct a comprehensive meta-analysis of the results of clinical randomized controlled trials (RCTs) on Kanglaite injection plus chemotherapy, as well as systematically evaluate the efficacy and safety of Kanglaite injection plus chemotherapy versus chemotherapy alone for advanced digestive tract malignancies.

2. Materials and methods

This meta-analysis was implemented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^[21] Given that we used data from published studies, there was no requirement for ethical approval. This meta-analysis has been registered at International prospective register of systematic reviews (PROSPERO) under the registration number CRD42019130508.

2.1. Searching strategies

Two investigators (Qi Song and Jie Zhang) independently retrieved related data from the databases using the following screening strategy: (“kang-lai-te” [Supplementary Concept] OR kanglaite OR kanglaite injection OR KLT) AND (Chemotherapy OR Chemotherapies OR “Fluorouracil”[Mesh] OR Fluorouracil OR 5-Fu OR Tegafur OR Capecitabine OR Carmofur OR Fluorouridine) AND (“Esophageal Neoplasms”[Mesh] OR “Stomach Neoplasms”[Mesh] OR “Gastrointestinal Neoplasms”[Mesh] OR “Colorectal Neoplasms”[Mesh] OR “Colonic Neoplasms”[Mesh] OR “Rectal Neoplasms”[Mesh] OR “Intestinal Neoplasms”[Mesh] OR Esophageal Cancer OR Gastric Cancer OR Intestinal Cancer OR Colorectal Cancer OR Colon Cancer OR Rectal Cancer). We searched the following Chinese databases: China Biological Medicine Database, China National Knowledge Infrastructure Database, Chinese Scientific Journals Full-Text Database, Wanfang Database, and Airiti Library. We searched the following English databases: Medline, Embase, Web of Science, and Cochrane Central Register of Controlled Trials. All retrievals were implemented using MeSH and free word. The retrieval period lasted from the established time to March 2019. After the evaluation of similar or related systematic reviews or meta-analysis, we selected the studies that met the inclusion criteria from related references.

2.2. Types of studies

We evaluated RCTs that assessed the beneficial effects and safety outcomes of Kanglaite injection combined with fluorouracil-based chemotherapy versus chemotherapy alone regardless of the language, publication status, or blinding. We excluded cluster randomization trials, cross-over design studies, before–after studies, cohort studies, non-randomized trials, case–control studies, cross-sectional studies, descriptive studies, reviews, case reports, and animal studies.

2.3. Inclusion and exclusion criteria

We applied the following inclusion criteria:

- Studies enrolling histopathologically or cytologically confirmed patients with advanced (stage III–IV) digestive tract malignancies without surgical operations.
- Studies that employed an RCT study design.
- Experiment group with patients treated with the combination of Kanglaite injection and fluorouracil-based chemotherapy and a control group with patients treated with a corresponding routine fluorouracil-based chemotherapy alone.
- Patients not receiving any other adjuvant treatments, including other chemotherapies, radiotherapy, and additional traditional Chinese herbs prior to study enrollment.
- Main outcomes involving short-term clinical efficacy evaluated as tumor responses, QoL, and adverse drug reactions (ADRs).
- Additional outcomes involving the immune function index, including CD3⁺, CD4⁺, CD8⁺, CD4⁺/CD8⁺, and NK.

We did not employ restrictions regarding the times and types of follow-up.

We excluded the following studies: case report studies; meeting abstracts; reviews; cohort studies; non-RCT studies; in vitro and animal studies; duplicated studies; studies including patients that received surgery, radiotherapy, or other traditional Chinese medicine treatment during the intervention period; studies that lacked at least 1 outcome among those for clinical efficacy, QoL, and ADRs; studies with a drop out ratio >10%.

2.4. Definition of outcome measures

We assessed the treatment efficacy according to Response Evaluation Criteria in Solid Tumors (RECIST) developed by WHO and the curative effect evaluation criteria after the scheduled treatment and follow-up. We classified the patients into 4 categories; namely, complete response (CR), partial response (PR), stable disease (SD), and progressive disease. The ORR, which is also known as the clinical effective rate, was considered as (CR + PR) and as the primary endpoint. Moreover, we defined the disease control rate (DCR) as (CR + PR + SD) against the total number of patients in each group. Moreover, we employed the standardization of the diagnosis and curative effect from the Guiding Principles for Clinical Research of New Drugs for Syndromes of traditional Chinese medicine (TCM) (National Medical Products Administration. *Guiding Principles for Clinical Research of New Drugs for Syndromes of TCM*, 2018) as a reference for curative effect evaluation. According to this evaluation system, we considered a decrease of post-treatment scores by >70%, 30% to 70%, <30% as significant, partial, and non-improvement, respectively.

QoL was assessed according to the Karnofsky Performance Status (KPS) scale.^[22] We defined QoL improvement as a post-treatment KPS score increase of ≥ 10 points. A post-treatment KPS score of <10 points was considered as declined QoL. A stable QoL was considered when the post-treatment score increased or decreased by <10 points.

ADRs were assessed and graded as I through IV degrees according to Recommendations for Grading of Acute and Subacute Toxicity.^[23] Moreover, we employed the Common Terminology Criteria Adverse Events version 4.0 developed by the National Cancer Institute of U.S. as a reference for evaluating anticancer drug toxicity [<http://evs.nci.nih.gov/ftp1/CTCAE/About.html>].

We set immune function indexes as the additional outcomes defined as peripheral blood T lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ levels) and serum NK cell count.

2.5. Study selection

Two investigators (Qi Song and Jie Zhang) independently evaluated and screened the identified studies in strict accordance with the inclusion and exclusion criteria. Disagreements were resolved through discussion with a third investigator (Elaine Leung).

2.6. Data extraction

We applied the search strategy to retrieve titles and abstracts of the selected studies. Studies identified from additional sources were independently screened by 2 review authors (Qi Song and Jie Zhang) to identify studies that potentially met the inclusion criteria. The 2 review authors independently assessed full-text articles for eligibility. Disagreements over the eligibility of certain studies were resolved through discussion with the third reviewer. The 2 review authors independently extracted the following information from each trial: name of the first author; published year; demographic characteristics, for example, sample size, age, and gender; study design and methodology; Kanglaite injection and chemotherapy regimen usage; and evaluation criteria and main outcome indicators, including ORR, DCR, QoL, and ADRs. Study details were not only obtained through direct information extraction from the articles but also by contacting the original authors for further information if necessary; further, data in diagram form were extracted through calculation.

2.7. Risk of bias (quality) assessment

We evaluated the methodological quality of the included clinical trials based on the Cochrane evaluation handbook of RCTs (5.1.0) (Higgins J, Green S, editors) and the Cochrane handbook for systematic reviews of interventions (Wiley Online Library; 2008). Two investigators used a unified method to independently evaluate and cross-check the quality of the eligible articles through 6 domains: random sequence generation (selection bias), allocation concealment (selection bias), participant and personnel blinding (performance bias), outcome assessment blinding (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Disagreements were jointly resolved through discussions with the third investigator. We regarded trials with low-bias risk for some domains as high-quality research and were judged with “Yes”. Studies with a high-bias risk in any domain were defined as poor-quality research and were judged with “No”. Finally, the remaining studies were thought to have an unclear risk of bias and were judged with “Unclear”.

2.8. Strategy for data synthesis

Two reviewers performed the statistical analysis using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). We determined the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous variables and $P < .05$ as statistically significant. We determined the mean difference (MD) with 95% CI for continuous variables. We examined the heterogeneity of the studies using the χ^2 -based Q test. Between-study heterogeneity was described using the I^2 index. Significant heterogeneity was confirmed when $I^2 > 50\%$ while non-significant heterogeneity was considered when $P > .05$ and $I^2 \leq 50\%$. The fixed-effects model (FEM) was applied to estimate the summary RR (or OR) while the random-effects model was applied for the MD and 95% CI. Subgroup or sensitivity analyses were used to explore heterogeneity when necessary. In the case of an unclear heterogeneity source, the stochastic effect model was employed to analyze the source. The combined effect was tested using the Z test with $P < .05$ indicating a significant difference. Funnel plots were used to assess publication bias if more than 10 studies were included in 1 outcome index.

Two independent reviewers (Qi Song and Jie Zhang) independently assessed the outcome evidence quality for each study based on the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach.^[24] Disagreements were resolved through discussion between themselves or with a third investigator (Guoping Li). GRADE classifies the evidence quality in the evaluation of diagnostic test systems by examining 5 downgrading domains, that is, the risk of bias, indirectness, inconsistency, imprecision, and publication bias, as well as 2 upgrading factors, that is, dose–response gradient and plausible confounding. The recommendation strength was graded into 4 levels; namely, high, moderate, low, and very low.

3. Results

3.1. Types of studies

The initial database search identified 184 records based on the established search strategy. Among them, 108 records were excluded after title screening for duplicates. After abstract screening, 41 records were rejected for failing to meet inclusion

criteria. The full texts of the remaining 35 records were downloaded with the subsequent exclusion of 15 unqualified studies (single-arm, cohort, non-random, etc). Finally, 20 trials were included in the meta-analysis (Fig. 1).

3.2. Characteristics of the included trials

We enrolled 20 trials on 1339 patients with advanced (stage III–IV) digestive tract malignancies (Table 1). All the selected trials had been performed in China and had been published between 1999 and 2019 with no significant baseline differences. A total of 1339 cases were studied with 673 in the Kanglaite injection combined with fluorouracil-based chemotherapy group (treatment group) and 666 in the routine chemotherapy group (control group). The number of males and females was 848 and 500, respectively, and the age ranged from 27 to 89 years. Nineteen trials reported administering intravenous Kanglaite injections at 200 mL/time, 1 to 4 week/cycle, and 2 to 4 cycles. The control groups underwent the following sole fluorouracil-based chemotherapies: SOX (TS-1 plus oxaliplatin), FOLFOX, DCF (docetaxel, cisplatin plus 5-fluorouracil), PCF (paclitaxel, cisplatin plus 5-fluorouracil), DF (cisplatin plus 5-fluorouracil), and TS-1 (tegafur, gimeracil, and oteracil potassium capsules). None of the selected trials reported information regarding placebo in the control groups. Seventeen trials reported the short-term efficacy as tumor responses according to the RECIST. Fourteen trials reported the QoL based on the KPS evaluation. Seventeen trials eligibly reported the ADRs based on the WHO criteria. There was only 1 trial with a follow-up duration of 36 months reported the overall survival (OS).

3.3. The methodological bias of the included studies

Only 4 trials^[25–28] clearly described the random sequence generation. None of the studies provided specific information regarding random allocation methods. Selection bias could exist in these included studies. Only 1 trial^[29] reported the details of the participant and personnel blinding, which indicates performance bias in the included studies. All the included trials had unclear details regarding the blinding of the outcome assessment. The data were complete in all trials and there was no evidence of selective reporting. Three,^[28,30,31] 5,^[26,29,31–33] and 2 trials^[32,34] did not completely report the DCR, QoL, and ADRs, respectively. Other biases were unclear (Fig. 2).

We applied the trial sequential analysis (TSA) software, sensitivity analysis, and subgroup analysis to assess the results' robustness and calculate the required information size in the meta-analysis.^[35] TSA indicated that Kanglaite injection combined with fluorouracil-based chemotherapy was significantly superior to fluorouracil-based chemotherapy alone and that the cumulated sample size of all the RCTs reached the required information size required for a conclusive and reliable meta-analysis (Fig. 3). This suggests that the findings for the DCR in this meta-analysis are robust.

3.4. Clinical efficacy

Seventeen trials^[25–27,29,32–34,36–45] detailedly reported the short-term efficacy using tumor responses (Figs. 4 and 5). A total of 1227 patients were included in subgroup analyses based on different therapeutic evaluation criteria. We used the DCR and ORR to assess the short-term efficacy based on the RECIST

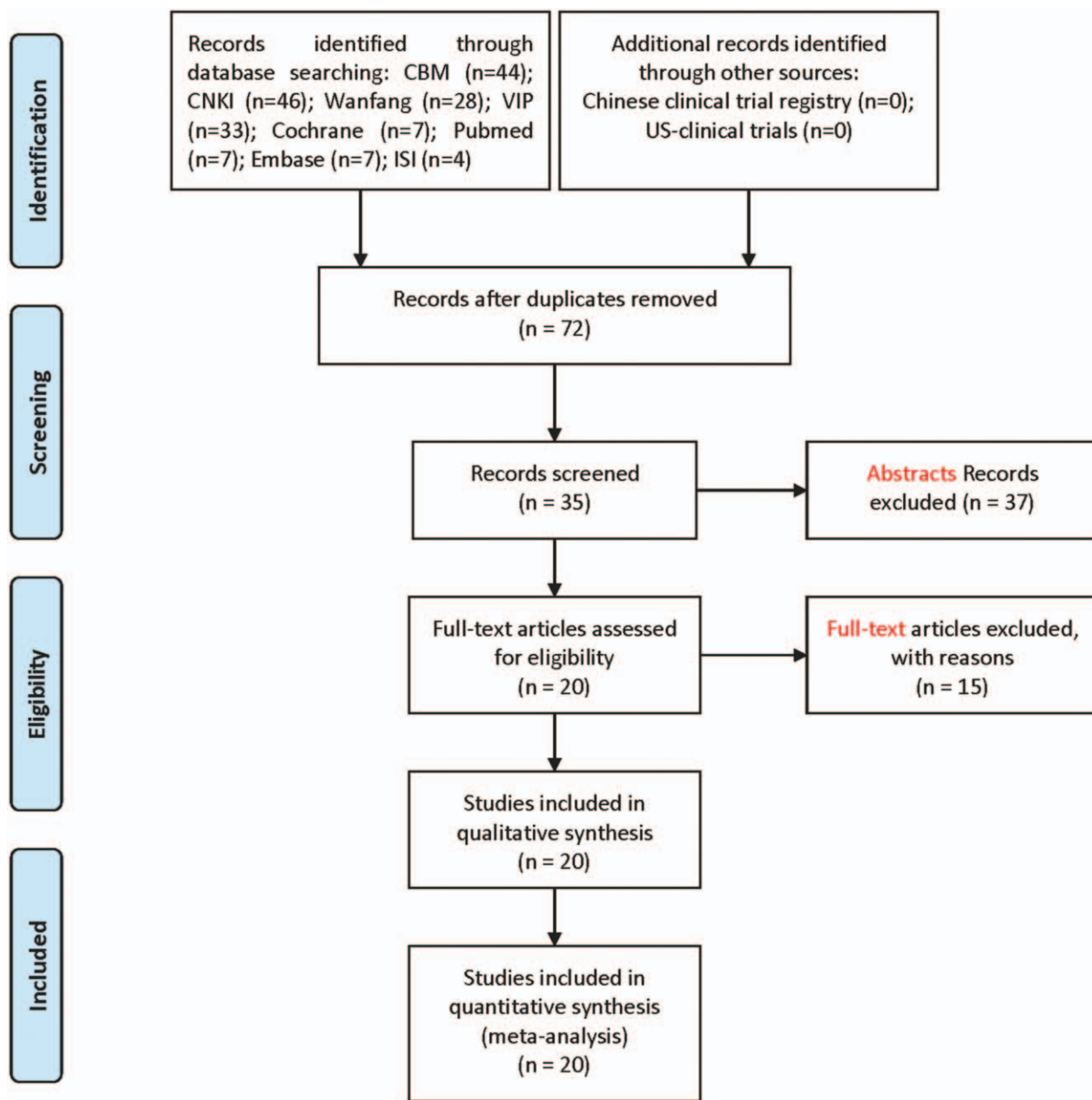


Figure 1. Articles retrieved and assessed for eligibility.

criteria. There was no statistical heterogeneity among the trials in the ORR ($P=.85$, $I^2=0\%$) and DCR ($P=.60$, $I^2=0\%$) after the I^2 test and Pearson’s chi-square test. Therefore, we used FEM to analyze the results. The short-term efficacy rate was significantly higher in the experiment group than that in the control group (RR=1.18, 95% CI 1.11–1.25, $P<.00001$). Compared with fluorouracil-based chemotherapy alone, the FEM indicated that fluorouracil-based chemotherapy combined with Kanglaite injection substantially improved the ORR (RR=1.35, 95% CI 1.18–1.54, $P<.00001$).

We divided the patients based on the different tumor sites into 3 subgroups; namely, gastric, colorectal, and esophageal cancer. The random-effects model showed that Kanglaite injection combined with fluorouracil-based chemotherapy for esophageal cancer (RR=1.14, 95% CI 0.99–1.31, $P=.07$), gastric cancer

(RR=1.15, 95% CI 1.06–1.24, $P=.0005$), and colorectal cancer (RR=1.26, 95% CI 1.11–1.42, $P=.0002$) were significantly superior to chemotherapy alone (Fig. 6). The ORR meta-analysis results similarly indicated that Kanglaite injection combined with fluorouracil-based chemotherapy for esophageal cancer (RR=2.37, 95% CI 1.21–4.65, $P=.01$), gastric cancer (RR=1.59, 95% CI 1.18–2.15, $P=.002$), and colorectal cancer (RR=1.79, 95% CI 1.11–2.88, $P=.02$) were significantly superior to chemotherapy alone (Fig. 7).

3.5. QoL evaluation

A total of 11 RCTs were included.^[27,30,34,36–40,42,44,45] I^2 test and Pearson’s chi-square test indicated that there was non-significant heterogeneity among the trials ($I^2=18\%$). FEM meta-analysis

Table 1
Characteristics of the included studies.

First author year	Patients with digestive tract malignancies			Interventions	Control	Outcomes
	E/C	M/F	Age	Kanglaite (D/T/C)	Chemotherapy	
Xu 2019	43/43	54/32	30–75	200 mL/1–10 d/2–8	SOX	ORR, DCR, QoL, ADRs
Liang 2018	36/36	45/27	40–85	200 mL/1–14 d/6	TS-1	ORR, DCR, ADRs
Gao 2018	24/24	31/17	39–70	200 mL/1–14 d/2	SOX	ORR, DCR, QoL, ADRs
Wang 2018	42/42	49/35	–	200 mL/1–21 d/3	DCF	ORR, DCR, ADRs
Shen 2017	54/50	69/35	31–75	200 mL/1–10 d/2	SOX	ORR, DCR, QoL, ADRs
Yu 2017	25/25	32/18	60	200 mL/1–21 d/2	TS-1	ORR, DCR, ADRs
Liu 2016	29/29	33/25	56–79	100 mL/1–21 d/1–3	DF	ORR, DCR, pain relief rate
Yao 2015	27/22	28/21	71–89	200 mL/1–14 d/–	SOX	ORR, DCR, QoL, ADRs
Wang 2015	44/44	62/26	70–91	200 mL/1–21 d/2	TS-1	ORR, DCR, QoL, ADRs, immune function index
Li 2015	24/24	23/25	42–69	100 mL/1–5 d/2	PCF	ORR, DCR, ADRs
Wang 2013	22/20	27/15	34–70	200 mL/1–15 d/2	TS-1	ORR, DCR, QoL, ADRs
Shen 2013	60/58	70/48	42–70	200 mL/1–10 d/2	DCF	ORR, DCR, QoL, ADRs
Lin 2013	48/48	60/36	30–76	200 mL/1–10 d/2	DCF	ORR, DCR, ADRs
Ma 2012	20/20	26/14	30–69	200 mL/1–28 d/2	FOLFOX	ADRs, TCM syndrome therapeutic effect ratio, immune function index
Zhou 2012	39/39	50/28	37–76	200 mL/1–10 d/2	FOLFOX4	ORR, DCR, QoL, ADRs, blood CEA, pain relief rate
Miao 2011	34/32	38/28	38–74	200 mL/1–10 d/2	FOLFOX4	ORR, DCR, QoL, ADRs, blood CEA, pain relief rate
Zhang 2010	22/23	27/17	32–75	200 mL/1–15 d/2	PCF	ORR, DCR, ADRs, immune function index
Luo 2001	21/21	32/20	27–73	200 mL/1–20 d/2	DF, PYM	QoL, pain relief rate
Liu 2000	15/15	17/13	41–70	200 mL/1–21 d/5	DF, VCR, MTX	ADRs, survival rate
Li 1999	44/51	75/20	27–72	200 mL/1–20 d/2	DF	ORR, DCR, QoL

E: experimental group (Kanglaite injection plus fluorouracil-based chemotherapy); C: control group (fluorouracil-based chemotherapy); M: male; F: female; Kanglaite: Kanglaite injection; D/T/C: dose/times/cycles. ADRs = adverse drug reactions; DCF = docetaxel, cisplatin plus 5-fluorouracil; DCR = disease control rate; DF = cisplatin plus 5-fluorouracil; FOLFOX = 5-fluorouracil, leucovorin plus oxaliplatin; ORR = objective response rate; PCF = paclitaxel, cisplatin plus 5-fluorouracil; SOX = TS-1 plus oxaliplatin; TCM = traditional Chinese medicine; TS-1 = tegafur, gimeracil and oteracil potassium capsules; QoL = quality of life.

showed that the QoL improvement rate after Kanglaite injection combined with chemotherapy was better than that after chemotherapy alone (RR = 1.58, 95% CI 1.35–1.85, $P < .00001$) (Fig. 8). Four trials^[25,28,41,43] reported the QoL as specific KPS scale scores with FEM meta-analysis showing that Kanglaite injection combined with chemotherapy was superior to chemotherapy alone (RR = 4.46, 95% CI 2.66–6.26, $P < .00001$) (Fig. 9).

3.6. ADRs evaluation

A total of 20 RCTs were included; among them, 3 RCTs^[30,32,34] did not report specific cases, and thus could not be used in this analysis. A meta-analysis of the remaining 17 RCTs^[25–29,31,33,36–45] showed that Kanglaite injection combined with chemotherapy for treating malignant digestive tract tumors (Table 2), including myelosuppression, leukopenia, gastrointestinal reaction, nausea/vomiting, diarrhea, hepatotoxicity, and neurotoxicity. Compared with the experiment group, the control group had a significantly lower incidence; however, there was no significant between-group difference in the incidence of mucositis. Although there were significant between-group differences in the incidence of thrombocytopenia, anemia, and neutropenia, there could be assessment bias due to sample size limitations.

3.7. Evaluation of immune function index

Only 3 RCTs^[28,33,40] reported the immune function index according to standards that allowed inclusion. There was no heterogeneity among the 3 studies using the CD3⁺ cell count as the immune indicator ($I^2 = 24\%$, $P = .27$); therefore, FEM meta-analysis was performed. The results indicated a significantly

higher CD3⁺ cell count in the experiment group than that in the control group (RR = 7.67, 95% CI 5.71–9.63, $P < .00001$) (Fig. 10). Moreover, we observed significant heterogeneity in the CD4⁺ cell count in the 3 studies ($I^2 = 68\%$ and $P = .04$); therefore, a CD3⁺ cell count meta-analysis was conducted. The results indicated a significantly higher post-treatment CD4⁺ cell count in the experiment group than that in the control group (RR = 5.51, 95% CI 1.99–9.02, $P = .002$) (Fig. 11).

3.8. Subgroup analysis

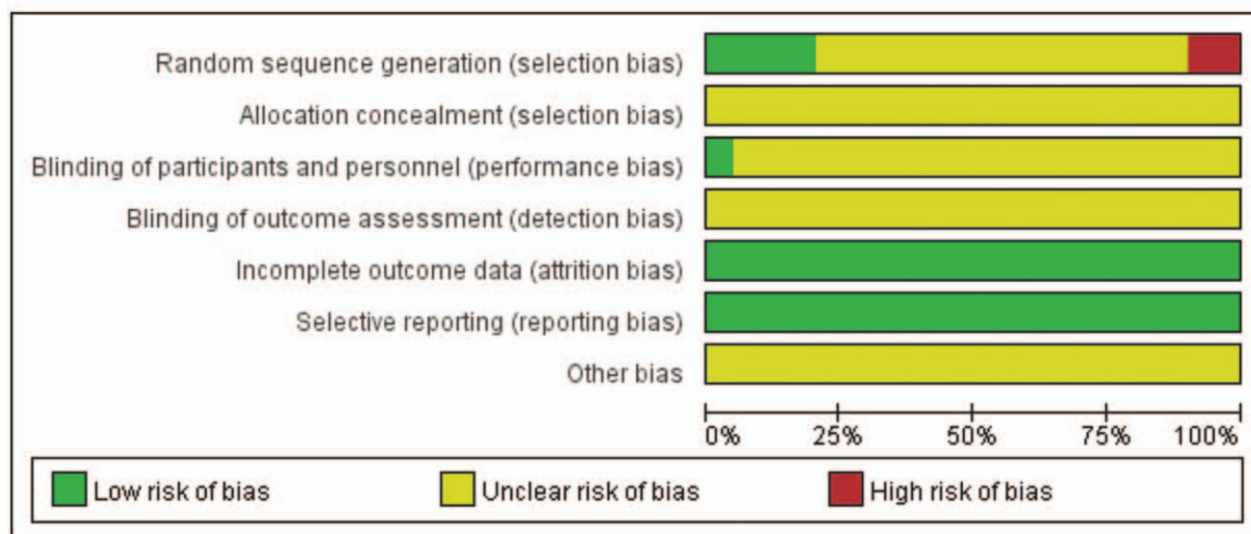
We conducted subgroup analyses to determine the influence of different Kanglaite injection scenarios and fluorouracil-based regimens on ORR and DCR. The dosages of Kanglaite injection were 200 mL/day in 18 trials. The treatment time and cycles were 10 days/2–8 cycles, 14–15 days/2–6 cycles, and 20–28 days/2–5 cycles, respectively. Subgroup analysis showed that Kanglaite injection at 200 mL/day doses could improve the ORR and DCR (Figs. 12 and 13). The fluorouracil-based chemotherapy regimens included SOX, FOLFOX, DCF, PCF, DF, and TS-1 (tegafur, gimeracil, and oteracil potassium capsules). Subgroup analyses indicated the effectiveness of SOX, DCF, and PCF, but not FOLFOX and DF, for the ORR and DCR (Figs. 14 and 15). Tumor responses were evaluated using the WHO criteria or RECIST. Subgroup analysis showed that Kanglaite injection combined with fluorouracil-based chemotherapy could increase the ORR and DCR based on the assessment of tumor responses.

3.9. Publication bias analysis

The funnel plots were symmetric for the ORR, DCR, myelosuppression, leukopenia, gastrointestinal reaction, nau-

Gao 2018	?	?	?	?	+	?
Li 1999	?	?	?	?	+	?
Li 2015	+	?	?	?	+	?
Liang 2018	+	?	?	?	+	?
Lin 2013	?	?	?	?	+	?
Liu 2000	?	?	?	?	+	?
Liu 2016	?	?	?	?	+	?
Luo 2001	+	?	?	?	+	?
Ma 2012	+	?	?	?	+	?
Miao 2011	?	?	?	?	+	?
Shen 2013	+	?	?	?	+	?
Shen 2017	?	?	?	?	+	?
Wang 2013	?	?	?	?	+	?
Wang 2015	?	?	?	?	+	?
Wang 2018	?	?	?	?	+	?
Xu 2019	?	?	?	?	+	?
Yao 2015	?	?	?	?	+	?
Yu 2017	?	?	?	?	+	?
Zhang 2010	?	?	?	?	+	?
Zhou 2012	?	?	?	?	+	?
	Random sequence generation (selection bias)					
	Allocation concealment (selection bias)					
	Blinding of participants and personnel (performance bias)					
	Blinding of outcome assessment (detection bias)					
	Incomplete outcome data (attrition bias)					
	Selective reporting (reporting bias)					
	Other bias					

A



B

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

sea/vomiting, diarrhea, hepatotoxicity, and neurotoxicity (Fig. 16). This indicated no publication bias and objective reporting by the included studies. Funnel plots were significantly asymmetric in QoL (Fig. 16C), which indicated publication bias. The QoL risk was over-estimated in 1 trial^[30] and underestimated in another.^[34] Therefore, we implemented meta-analysis by excluding the 2 aforementioned studies. In summary, except for QoL, all the results had good objectivity.

3.10. Sensitivity analysis

Two poor-quality trials^[30,34] showed a potential effect on the QoL with good consistency being acquired after their exclusion. Therefore, sensitivity assessment was performed after the exclusion of the inferior trials. The results had good stability before and after excluding the poor-quality trials.

There was no significant heterogeneity in the ORR, DCR, gastrointestinal reaction, myelosuppression, and leukopenia; however, they all had publication bias. The ORR, DCR,

gastrointestinal reaction, myelosuppression, and leukopenia had good consistency before and after excluding the trials with over- and under-estimated QoL. The results had good stability before and after excluding the over- and under-estimated studies. In conclusion, the results of this meta-analysis had good robustness.

3.11. Quality of evidence

A majority of the 20 included trials showed uncertainty in the risk of methodological bias. Only 4 trials reported using random number tables to generate random sequences. Eight trials had at least 1 domain with a high risk of bias. Sensitivity analysis showed that the results had good robustness before and after excluding the poor-quality trials. Thus, we rated down the outcomes by 1 level due to design limitations. There was heterogeneity in the ORR, DCR, myelosuppression, leukopenia, gastrointestinal reaction, nausea/vomiting, diarrhea, hepatotoxicity, neurotoxicity, and thrombocytopenia. Except for QoL, all

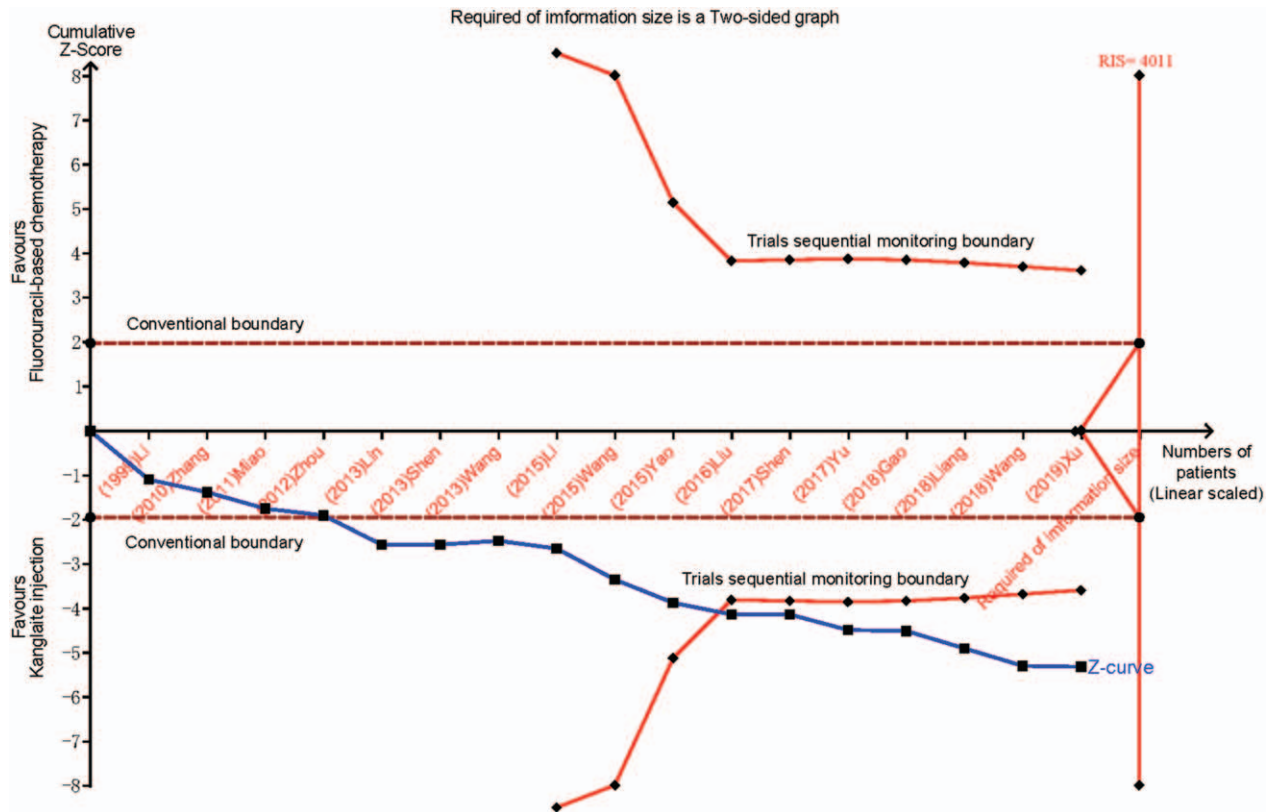


Figure 3. Trial sequential analysis. The Z curve is a measure of treatment effect, and the boundaries are thresholds for statistical significance that is adjusted for heterogeneity of multiple statistical testing and trial results. The treatment effect outside the statistical significance boundary (red line) indicates that there is a reliable evidence of treatment effect, and the treatment effect within the futility boundary (dotted line) indicates that there is no reliable evidence of treatment effect. The calculated optimum sample size is indicated by optimum size for statistical inference. RIS, required information size.

the other results showed good robustness. Consequently, only QoL was rated down by 1 level. The number of events for anemia, neutropenia, and mucositis were <300; therefore, we rated down these outcomes by 1 level. The QoL, which showed publication

bias, had been over- and under-estimated. The evidence was not rated down since the results showed good robustness. There were no outcomes that met the eligibility for an upgrade. In general, the quality of the evidence was moderate.

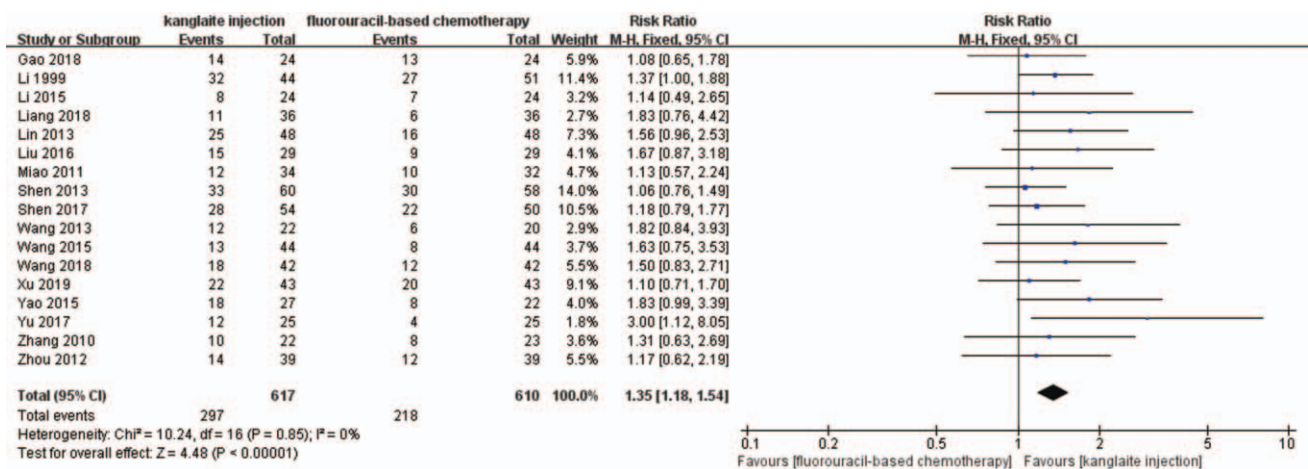


Figure 4. The analysis of objective response rate (ORR) between 2 groups. Forest plot of the comparison of ORR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

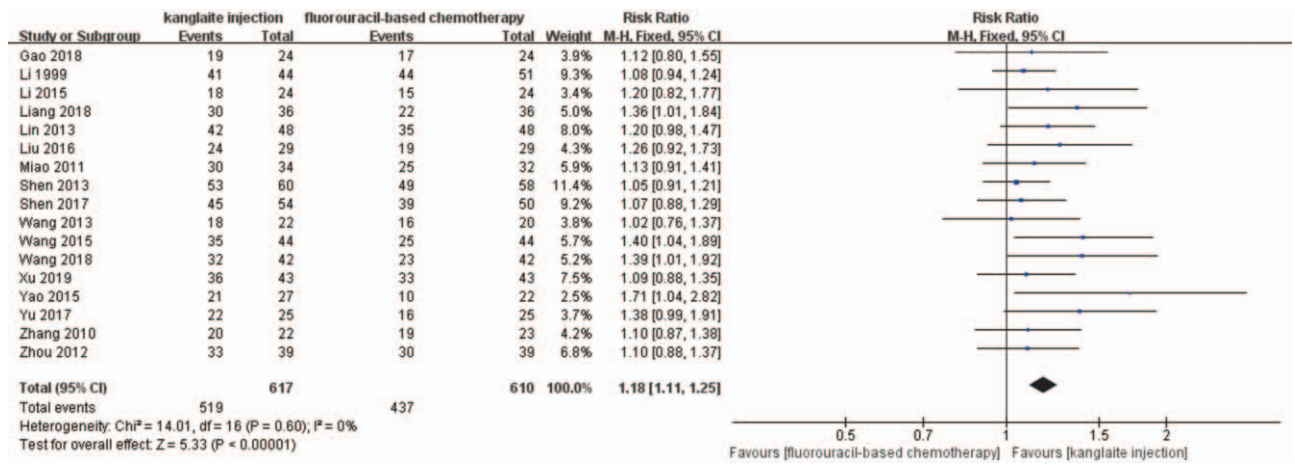


Figure 5. The analysis of disease control rate (DCR) between 2 groups. Forest plot of the comparison of DCR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

4. Discussion

In this meta-analysis, we included 20 trials involving 1339 patients with advanced (stage III–IV) digestive tract malignancies. There were 848 males and 500 females with an age range of 27 to 89 years. The interventions included intravenous Kanglaite injections administered at 200 mL/time for 5–10 days/2–8 cycles,

14–15 days/2–6 cycles, and 20–28 days/2–5 cycles, as well as at 100 mL/time for 21 days/1–3 cycles. This meta-analysis evaluated the tumor response, QoL, ADRs, and immune function indexes.

Kanglaite injection is a Coix seed extract prepared by modern pharmaceutical technology. The active components of Coix seed

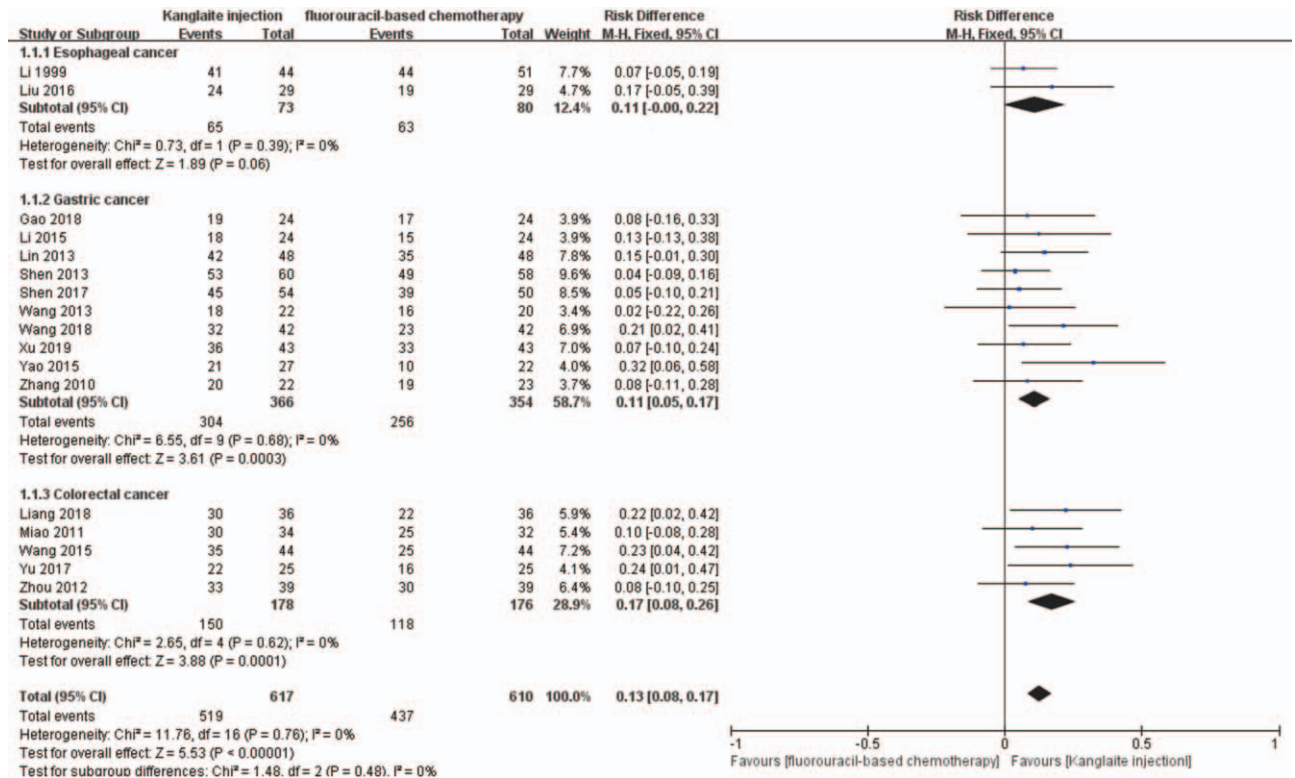


Figure 6. The analysis of disease control rate (DCR) between 2 groups based on tumor sites. Forest plot of the comparison of DCR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

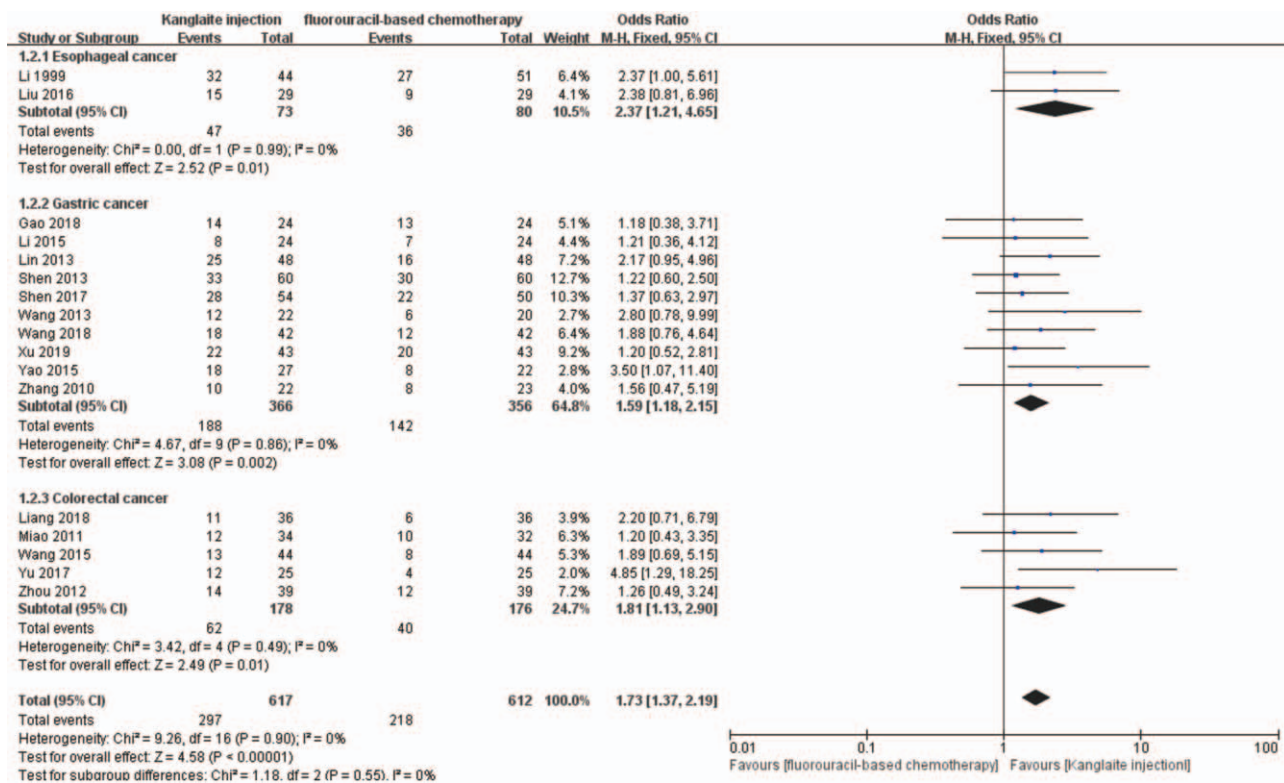


Figure 7. The analysis of objective response rate (ORR) between 2 groups based on tumor sites. Forest plot of the comparison of ORR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

oil have been shown to inhibit tumor cell proliferation and reduce tumor sizes, including lung cancer, pancreatic cancer, stomach cancer, and breast cancer.^[46,47] Kanglaite injection regulates human immune function; further, it promotes cancer cell apoptosis and inhibits cancer cell proliferation. In vivo, in vitro, and clinical trials have suggested that Kanglaite injection could directly promote tumor cell apoptosis,^[48] reverse chemotherapy resistance of tumor cells,^[49] regulate and enhance the immune system.^[50] Further, the prevention and reversal of cancer cachexia contribute to improving chemotherapy effectiveness and reducing side effects in patients with cancer.^[51]

Kanglaite injection combined with chemotherapy is widely used in China. It is unclear whether Kanglaite injection combined with chemotherapy could have improved clinical efficacy and survival rate in patients with digestive tract malignancies. Seventeen trials with 1227 patients evaluated the ORR and DCR based on solid tumor response guidelines. A meta-analysis of these trials showed that Kanglaite injection combined with chemotherapy significantly improved ORR and DCR in patients with digestive tract malignancies compared with chemotherapy alone. Further, we performed subgroup analyses based on different tumor sites, chemotherapy regimens, and treatment

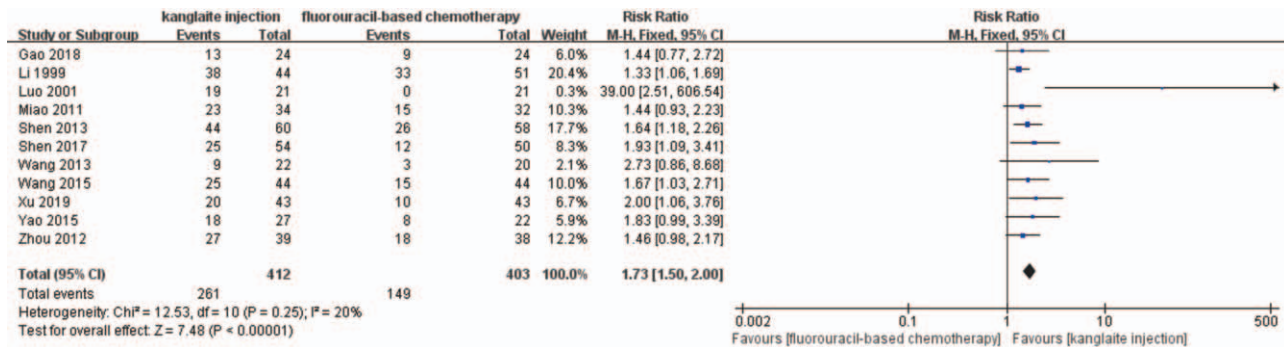


Figure 8. The analysis of quality of life (QoL) between 2 groups. Forest plot of the comparison of QoL between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

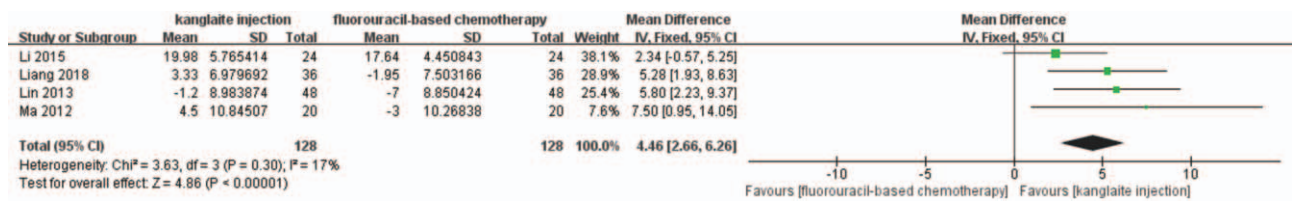


Figure 9. The analysis of Karnofsky Performance Status (KPS) scales between 2 groups. Forest plot of the comparison of ORR between the experimental and control group. Control group, chemotherapy alone group; Experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

Table 2
Meta analysis results of ADRs between 2 groups.

Toxicity	N	E	C	P%	Effect estimate RD (95% CI)	P value	SM	PB
Myelosuppression	17	216/579	335/526	0	0.33 (0.25, 0.43)	<.00001	FEM	No
Leukopenia	11	132/346	219/339	0	0.31 (0.22, 0.43)	<.00001	FEM	No
Thrombocytopenia	6	47/185	65/180	29	0.60 (0.38, 0.49)	=.03	FEM	No
Neutropenia	2	19/68	39/68	0	0.26 (0.12, 0.55)	=.0005	FEM	No
Anemia	4	22/115	42/116	0	0.41 (0.23, 0.75)	=.004	FEM	No
Gastrointestinal reaction	17	210/579	324/565	0	0.35 (0.27, 0.46)	<.00001	FEM	No
Nausea/vomiting	9	96/300	142/296	0	0.41 (0.28, 0.61)	<.00001	FEM	No
Diarrhea	5	19/161	44/161	0	0.34 (0.18, 0.62)	=.0004	FEM	No
Hepatotoxicity	8	23/252	63/244	0	0.28 (0.17, 0.47)	<.00001	FEM	No
Neurotoxicity	9	119/325	151/314	0	0.58 (0.41, 0.82)	=.002	FEM	No
Mucositis	4	15/135	23/135	0	0.59 (0.29, 1.21)	=.15	FEM	No

N: No. of trials; E: experiment group (Kanglaite injection plus fluorouracil-based chemotherapy); C: control group (fluorouracil-based chemotherapy); P% is the percentage of total variation across studies due to heterogeneity rather than chance, $P^2 = 100\% \times (Q - df) / Q$, where Q is Cochran's heterogeneity statistics and df is the degree of freedom.
 CI = confidence interval; FEM=fixed-effects model; PB=publication bias; SM=statistical method.

courses to assess the effects of Kanglaite injection on digestive tract malignancies. Subgroup analysis based on tumor sites showed that Kanglaite injection combined with chemotherapy increased the ORR and DCR in patients with esophageal cancer, gastric cancer, or colorectal cancer. Subgroup analysis based on different chemotherapy regimens showed that Kanglaite injection combined with all the different fluorouracil-based chemotherapy

regimens increased the ORR and DCR. Further subgroup analysis based on different Kanglaite injection treatment courses revealed that Kanglaite injection administration at 5–10 days/2–8 cycles, 14–15 days/2–6 cycles, and 21–28 days/2–5 cycles improved the DCR and ORR.

QoL is an indispensable indicator for evaluating chemotherapy effectiveness. We included 11 trials with 815 patients to assess the

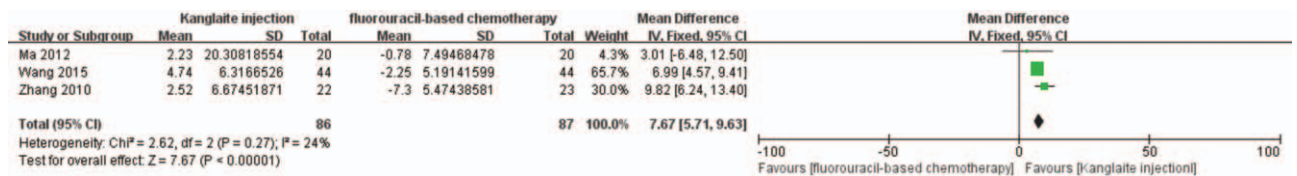


Figure 10. The analysis of CD3⁺ between 2 groups. Forest plot of the comparison of CD3⁺ levels between the experimental and control group. Control group, chemotherapy alone group; Experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

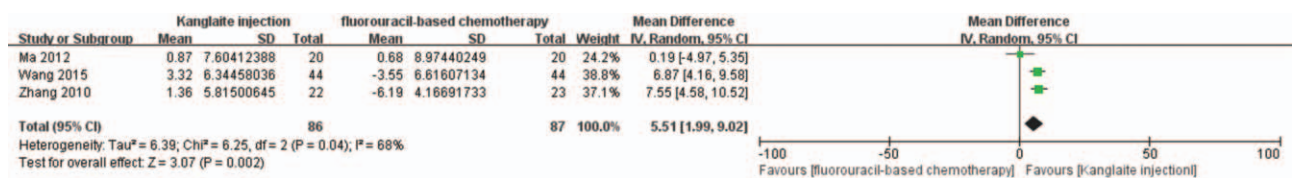


Figure 11. The analysis of CD4⁺ between 2 groups. Forest plot of the comparison of CD4⁺ levels between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The random-effects model was used.

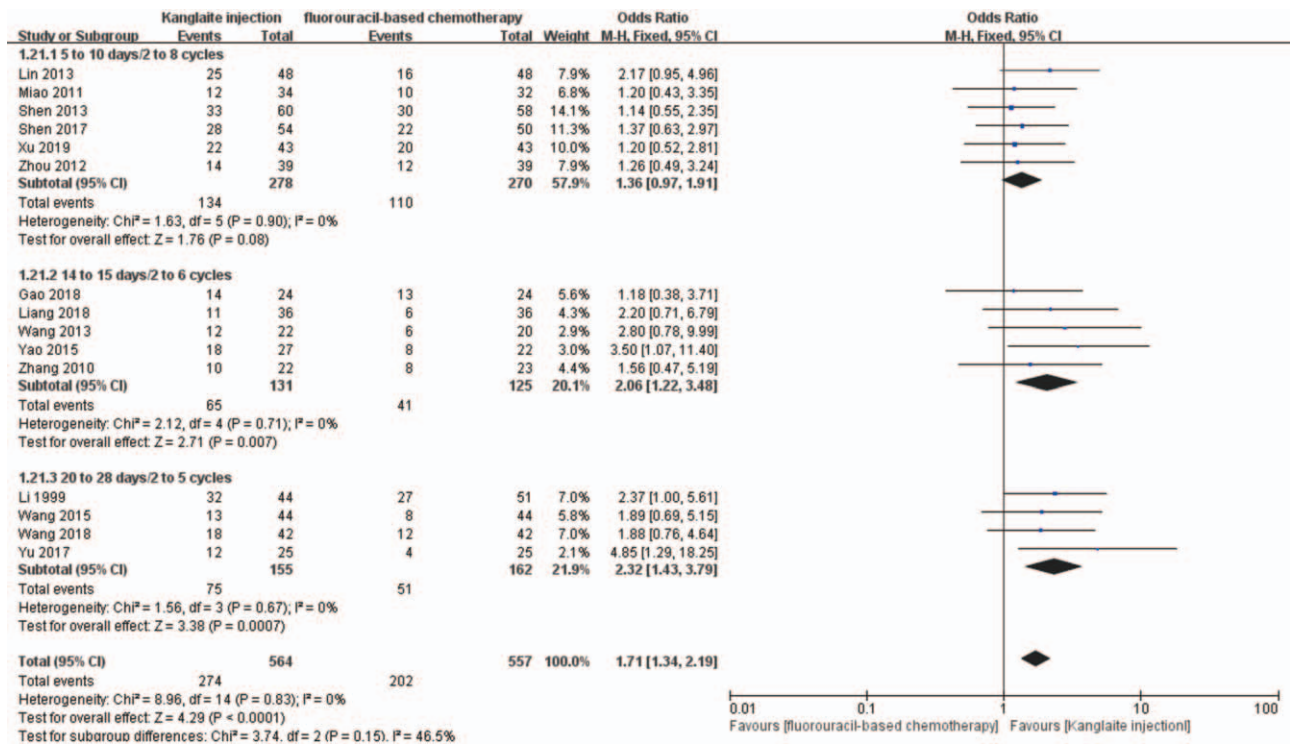


Figure 12. The subgroup analysis of objective response rate (ORR) between 2 groups based on usage of Kanglaite injection. Forest plot of the comparison of ORR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

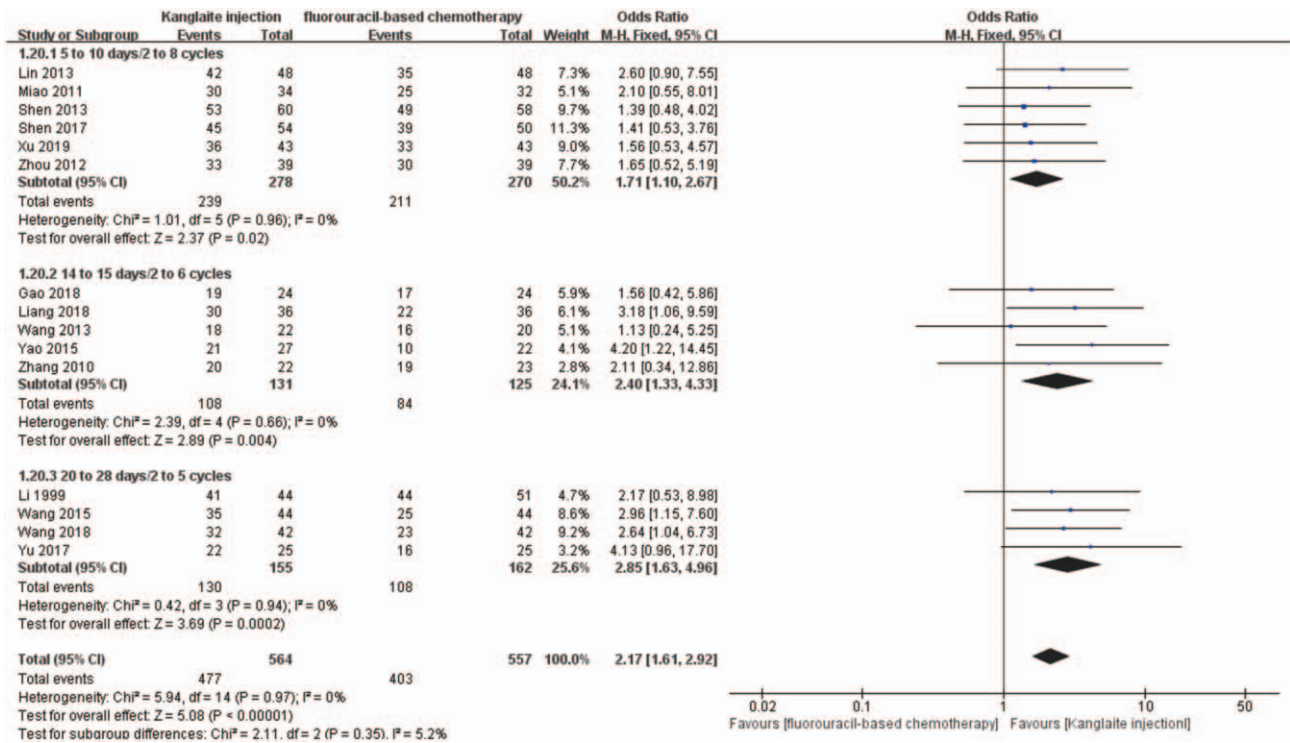


Figure 13. The subgroup analysis of disease control rate (DCR) between 2 groups based on usage of Kanglaite injection. Forest plot of the comparison of DCR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

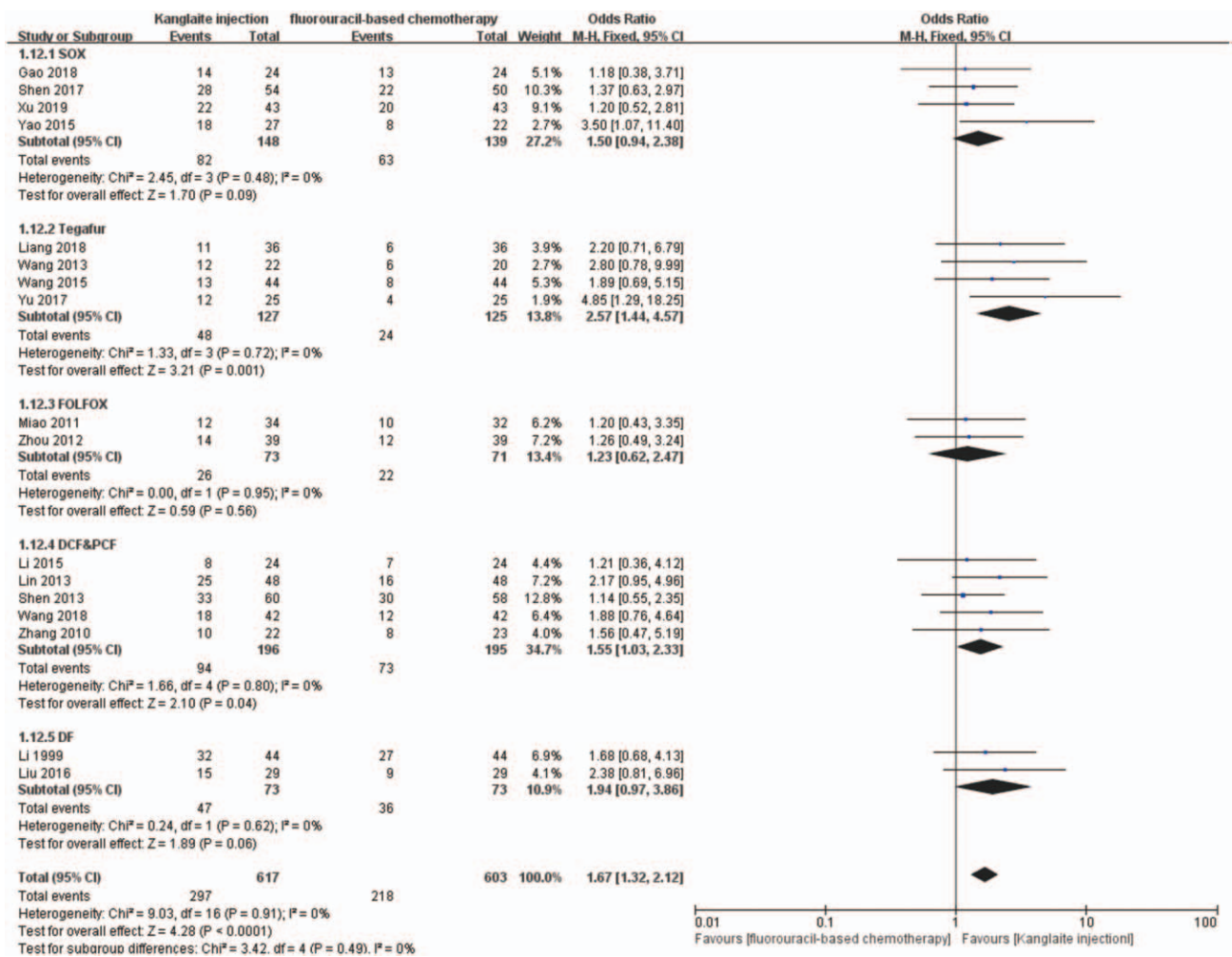


Figure 14. The subgroup analysis of objective response rate (ORR) between 2 groups based on regimen of chemotherapy. Forest plot of the comparison of ORR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

QoL in patients with advanced (stage III–IV) digestive tract malignancies. A meta-analysis of the QoL showed that Kanglaite injection combined with chemotherapy significantly improved the QoL in the patients. Moreover, a meta-analysis of 4 trials with 256 patients reported the QoL as specific KPS scale scores revealed similar results. The sufficient sample sizes of the included studies ensured accurate evaluation of the ORR, DCR, and QoL. Unfortunately, there was an unclear risk of bias in the majority of the included trials. The studies objectively reported the ORR and DCR; further, the good robustness of the results was confirmed by sensitivity analysis.

A previous network meta-analysis showed that among the CHIs, Kanglaite injection is the best for strengthening the ORR, improve QoL, and reducing nausea, vomiting, and leukopenia incidence in patients with gastric cancer. Further, Kanglaite injection combined with the FOLFOX regimen was better than other CHIs combined with the FOLFOX regimen and FOLFOX alone.^[19] A related meta-analysis showed that compared with the FOLFOX regimen alone, Kanglaite injection combined with the FOLFOX regimen could improve the clinical efficacy for colorectal cancer treatment.^[61] A similar strategy has been

adopted by Chinese meta-analysis reports,^[52–55] which indicated that Kanglaite injection might have a synergistic effect on chemotherapy for digestive tract malignancies. They all horizontally compared the efficacy of various traditional Chinese medicine injections combined with a similar chemotherapy regimen. In our meta-analysis, we performed a subgroup analysis of efficacy based on different chemotherapy regimens, including SOX, TS-1, FOLFOX, DCF and PCF, and DF. The subgroup analysis confirmed the effectiveness of SOX, DCF, and PCF, but not FOLFOX and DF, for ORR and DCR. The results regarding the FOLFOX and DF subgroups are inconsistent with those of previous studies, which could be attributed to small sample sizes. This study might be associated with statistical bias. The effect of different treatment courses of Kanglaite injection on patients with advanced digestive tract malignancies remains unclear. Therefore, in an attempt to clarify this, we selected 15 trials with 880 cases for further subgroup meta-analysis. We found significant differences in all the subgroups (10 days/2–8 cycles, 14–15 days/2–6 cycles, and 20–28 days/2–5 cycles). This indicated that Kanglaite injection improved the DCR and ORR in all the 3 subgroups of Kanglaite injection administration.

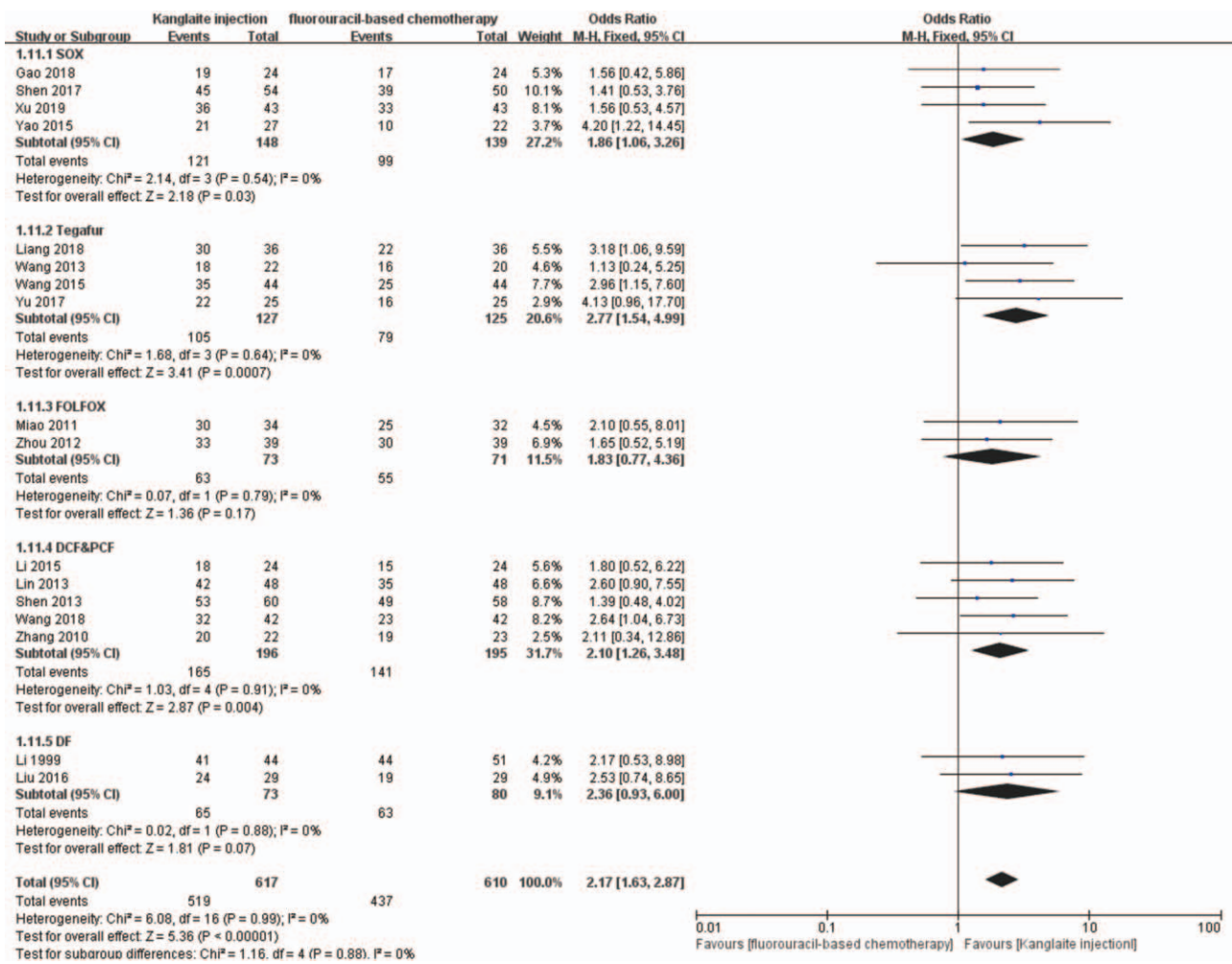


Figure 15. The subgroup analysis of disease control rate (DCR) between 2 groups based on regimen of chemotherapy. Forest plot of the comparison of DCR between the experimental and control group. Control group, chemotherapy alone group; experimental group, Kanglaite injection and fluorouracil-based chemotherapy combined group. The fixed-effects model was used.

There have been studies on whether Kanglaite injection combined with chemotherapy decreases the risk of ADRs. A previous meta-analysis^[56,57] reported that Kanglaite injection combined with routine chemotherapy had a lower risk of hepatotoxicity, leukopenia, and gastrointestinal reactions compared with chemotherapy alone. Another meta-analysis^[58] reported that Kanglaite injection had a low risk of hepatotoxicity and cachexia. Consistent with these previous findings, we found that Kanglaite injection combined with chemotherapy lowered the risk of hematological, gastrointestinal, and other chemotherapy-induced toxicities in patients with digestive tract malignancies. Our meta-analysis had a sufficient number of included RCTs and patients with sensitivity analysis of results showing good robustness.

The immune system function is an important prognosis indicator in patients with advanced malignancies undergoing systemic chemotherapy. The most direct index of immune function is the peripheral blood CD8⁺ and CD4⁺ T cell count. We found that Kanglaite injection could affect the immunity level in patients with advanced digestive tract malignancies. Three trials reported changes in immune function after assessing the population of T cell subsets in peripheral blood.^[28,33,40] They

all reported that Kanglaite injection effectively protected the immune function in patients after chemotherapy. Meta-analysis of CD3⁺, CD4⁺, CD8⁺, and CD4⁺/CD8⁺ levels indicated significant difference in CD3⁺ (RR = 7.67, 95% CI 5.71–9.63, *P* < .00001) and CD4⁺ (RR = 5.51, 95% CI 1.99–9.02, *P* = .002). Unfortunately, an insufficient number of trials and patients might have led to insufficient assessment; therefore, there is a need for new evidence to support these findings.

A majority of the included studies had an unclear risk of bias. The sample size of clinical trials ranged from 30 to 124 patients; further, none of the studies performed a priori calculation of the sample size, which might have resulted in selection bias. Although all the clinical trials randomly recruited patients, only 4 trials^[25–28] reported information generated by specific random sequences, which increases the risk of selection bias. None of the studies provided information regarding allocation concealment, which also increases the risk of selection bias. Only 1 clinical study^[29] provided details regarding participant and personnel blinding. None of the RCTs reported information regarding outcome assessment blinding, which increases the risk of reporting bias. Only 1 trial^[31] reported follow-up details with the remaining studies not reporting details regarding follow-up or withdrawal,

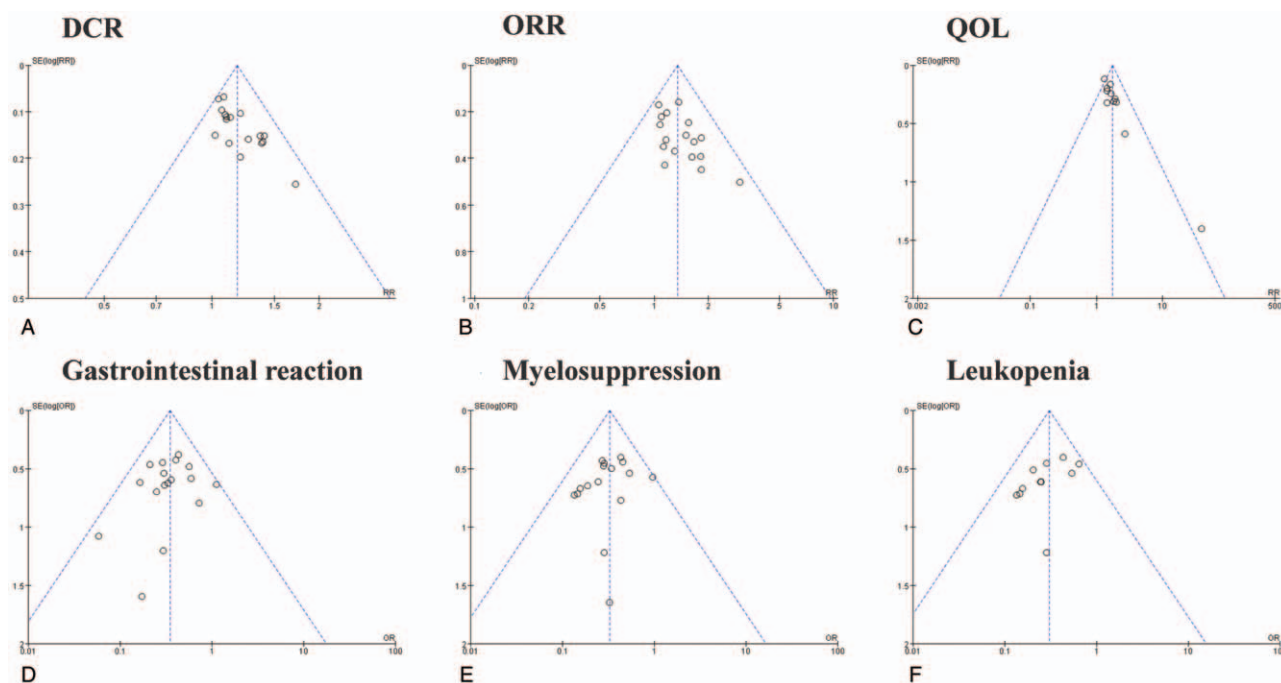


Figure 16. Publication bias analysis. Funnel plot of DCR (A), ORR (B), QoL (C), gastrointestinal reaction (D), myelosuppression (E), leukopenia (F).

which indicates a high withdrawal bias. Generally, 11 trials reported the QoL^[27,30,34,36–40,42,44,45] with the remaining studies adopting other evaluation methods, which further increases the risk of reporting bias. Although all the studies reported ADRs, there did not use a common standard in the degree confirmation. Among them, 7,^[27,28,33,40,42,43,45] 2,^[38,41] 1,^[39] and 1 trial^[37] used grade I–IV, III–IV, I–II, and II–IV ADRs, respectively, as the evaluation standard with the remaining not explicitly introducing an evaluation standard. Avoiding these biases requires a more in-depth analysis of the studies as well as supplements regarding the essential descriptions in the literature, including direct emails or phone calls to the researchers, to allow a more precise and detailed literature review. Further, subgroup analysis could be performed to rule out heterogeneity in case of different evaluation criteria. Finally, more comprehensive design, implementation, and addressing of statistical irregularities in clinical studies might increase the reliability of the evaluation.

A recent meta-analysis^[59] on the effectiveness of Kanglaite injection in patients with advanced pancreatic cancer recommended collection of information regarding patients' smoking history and past medical history for enhanced rationality. Contrastingly, since malignant digestive tract tumors involve a high genetic correlation with family heritability, it is better to evaluate the curative effect with the inclusion of information regarding family history. Another Chinese meta-analysis^[60] evaluated the QoL in patients with advanced non-small-cell lung cancer undergoing Kanglaite injection combined with chemotherapy. It included cancer pain in the evaluation system and concluded that Kanglaite injection could effectively alleviate cancer pain. Future studies on chemotherapy for malignant digestive tract tumors should consider digestive tract obstruction and constipation in addition to common gastrointestinal toxicity, including nausea, vomiting, and anorexia. A network meta-analysis^[61] attempted to explore the comparative effectiveness

and safety of different CHIs combined with the FOLFOX regimen versus FOLFOX alone for colorectal cancer. Similarly to our study, this previous meta-analysis included RCTs on patients of Asian descent; therefore, the conclusions might not be suitable for other populations.

This study has several limitations. First, there were few RCTs on the use of Kanglaite injection in the treatment of advanced digestive tract malignancies, which might contribute to sample size bias. Second, a majority of the included clinical trials lacked detailed descriptions of random sequence generation, allocation concealment, and blinding methods. Further, they did not provide sufficient information to allow determination of the study quality, which might have led to over- or under-estimation of efficacy. Third, the use of different chemotherapy regimens and administration modes might have affected efficacy and safety evaluation. Fourth, the treatment course of the included studies was insufficient for evaluating long-term efficacy, for example, OS and progression-free survival. Therefore, there is a need for well-designed, strictly implemented, high-quality, and double-blinded RCTs with large sample sizes for further evaluation.

5. Conclusion

We found that Kanglaite injection combined with fluorouracil-based chemotherapy, including TS-1, could remarkably improve the clinical effectiveness and QoL and reduce the risk of hematotoxicity, gastrointestinal reactions, neurotoxicity, and hepatotoxicity in patients with advanced digestive tract malignancies. The subgroup analysis indicated that the optimal regime for Kanglaite injection treatment could be 200 mL/day, 20 to 28 days, and 2 to 5 cycles. Kanglaite injection shows synergistic effects on fluorouracil-based chemotherapy.

However, given the intrinsic limitations of the enrolled RCTs, there is a need for well-designed, strictly implemented, and high-

quality studies with longer follow-ups and important survival outcomes for further evaluation.

Author contributions

Conceptualization: Qi Song.

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Formal analysis: Qi Song, Jie Zhang.

Investigation: Qi Song, Jie Zhang.

Methodology: Qibiao Wu.

Project administration: Qi Song, Qibiao Wu.

Resources: Qi Song.

Software: Qi Song.

Supervision: Guoping Li, Elaine Lai-Han Leung.

Writing – original draft: Qi Song.

Writing – review & editing: Qibiao Wu, Guoping Li, Elaine Lai-Han Leung.

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