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Oral Chinese Patent Medicine Combined With Oxaliplatin-Based Chemotherapy Regimen for the Treatment of Colorectal Cancer: A Network Meta-Analysis

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Abstract

Objective: To access the comparative effectiveness and safety of different oral Chinese patent medicine (OCPM) versus oxaliplatin-based chemotherapy regimen (C) alone for colorectal cancer (CRC) through network meta-analysis (NMA). **Methods:** Several electronic databases were searched for randomized controlled trials (RCTs) concentrated on the use of OCPM to treat CRC with C from the inception of the databases to January 10, 2021. We performed frequentist NMA and indirect comparison to compare study outcomes from the included RCTs. The risk of bias of each study was assessed using the Cochrane risk of bias tool. Confidence in evidence was assessed using Confidence in Network Meta-Analysis (CINeMA). **Results:** A total of 31 RCTs with 1985 participants comparing 10 OCPM, namely, Antike (ATK), Shenyi (SY), Huachansu (HCS), Boerning (BEN), Xiaoaiping (XAP), Jinlong (JL), Compound matrine (CC), Pingxiao (PX), Xihuang pill (XHW), Kangaiping (KAP) were identified. The methodological quality of included RCTs was not very high. The results of the NMA showed that the comparisons were all indirect. Among diverse OCPM, ATK + C had the highest objective response rate (ORR) with a *P*-score of .63 with risk ratio (RR) of 1.37 (95% CI 1.12-1.66); with a RR of 1.96 (1.26-3.05), SY + C had the highest performance status with a *P*-score of .73; KAP + C had the lowest nausea and vomiting with a *P*-score of .91 and with a RR of 0.29 (0.10-0.79); and JL + C had lowest leukopenia with a *P*-score of .95 with a RR of 0.47 (0.31-0.72). The results of pairwise comparison suggested no difference in outcomes among 10 kinds of OCPM + C. The comparison-adjusted funnel plots suggested that there might not be small-study effects for outcomes. According to the CINeMa approach, the confidence rating of this NMA ranged from "very low" to "low" for various comparisons. **Conclusion:** Based on the NMA, ATK + C, SY + C, KAP + C and JL + C were associated with more preferable and options for CRC patients when referring to ORR, performance status, nausea and vomiting, and leukopenia, respectively. However, owing to the limitations of this research, the above conclusions require further verification by more high-quality RCTs.

PROSPERO registration: CRD42020160658.

Keywords

oral Chinese patent medicines, oxaliplatin-based chemotherapy regimen, colorectal cancer, network meta-analysis

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Introduction

Colorectal cancer (CRC) is a common gastrointestinal malignant tumor worldwide, it ranks third in terms of incidence, but second in terms of mortality in 2020.[1] Chemotherapy is regarded as a standard treatment for CRC and plays a key role in improving prognosis Oxaliplatin is a third-generation platinum compound, which is the main drug of adjuvant and palliative chemotherapy for CRC. Studies have provided evidence that oxaliplatin can inhibit DNA replication and transcription of tumor cells.[2,3] The

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combination of 5-fluorouracil or capecitabine with oxaliplatin is a common chemotherapy regimen, which can further improve the survival rate of CRC patients in the clinic.[4,5] Thus, oxaliplatin-based chemotherapy regimens (C) were selected for analysis in this study.

However, the adverse reactions caused by chemotherapy often make patients suffer severe side effects. Traditional Chinese medicine (TCM) is deeply rooted in Chinese culture and covered by most Chinese health insurance. As an adjuvant therapy, it can improve the completion rate and efficiency of chemotherapy. There are various TCM treatments, which including Chinese herbal medicine, Chinese herbal injection, and oral Chinese patent medicine (OCPM). Compared with Chinese herbal medicine and Chinese herbal injection, OCPM has the advantages of convenient management and accurate dosage, which have been generally accepted and widely used in Chinese clinical practice.[6] Some studies have provided evidence that the combination of OCPM and chemotherapy can obtain a better clinical efficacy in the treatment of CRC.[7,8] However, there is a lack of head-to-head comparisons between different OCPM, and its relative advantages have not been well understood.

Network meta-analysis (NMA), which synthesizes evidence from direct and indirect comparisons, is therefore needed to determine the best available treatments.[9] Meta-analysis of Chinese herbal medicine[10] and Chinese herbal injections[11] as an adjuvant therapy for CRC have been reported. However, to the best of our knowledge, the NMA of OCPM combined with chemotherapy has not been involved. Thus, our study uses NMA to compare the efficacy and safety of multiple OCPM combined with C in the treatment of CRC, aiming to provide an evidence-based medicine basis for clinical decision-making.

Methods

We undertook this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental File 1).

Data Sources and Searches

PubMed, Cochrane Library, EMBASE Databases, China National Knowledge Infrastructure (CNKI), WanFang, and the Chinese Biomedical Literature Database (SinoMed) were searched for RCTs in any language from inception to January 10, 2021. The search terms were divided into 3 categories: CRC, OCPM, and RCTs. In the Chinese databases, the search strategy used a combination of subject words and free-text words. Search terms about CRC were "Colorectal cancer, Colon cancer, Colonic neoplasms, Rectal cancer, Rectal neoplasms, Colorectal cancer, Colorectal neoplasms" with a full text search for "random." In English databases, the search words in the CRC category were "Colorectal Neoplasm* Colorectal Tumor* Colorectal Carcinoma* Colorectal Cancer* Colonic Neoplasm* Rectal Neoplasm*" and English search terms for each OCPM. The specific Chinese and English search terms for each OCPM and the specific retrieval strategies are shown in Supplemental File 2.

Study Selection

We followed the methods of Zhang et al.[11] In this study, we identified all OCPM that were listed in the Chinese National Essential Drug list of 2018 and those included in the National Basic Medical Insurance Drugs List of China. Trials were selected based on the following inclusion criteria: (I) The included participants were diagnosed with CRC, and without limitations on gender, race, or nationality. (II) The OCPM group was treated by C plus OCPM. (III) The control group solely received chemotherapy. (IV) The primary outcomes of the NMA were the objective response rate (ORR). and the performance status, and the secondary outcomes were adverse reactions (ADRs), such as leukopenia, nausea, and vomiting. ORR was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).[12] $ORR = \left[Complete\ Response\left(CR\right) + Partial\ Response\left(PR\right) \right] / total\ cases \times 100\%$. The improvement of performance status was considered to be an increase in the Karnofsky performance score (KPS) of more than 10 points after completed treatment. The exclusion criteria included the following: (I) Other diseases and interventions, such as gastric cancer, radiotherapy, other TCM treatment; (II) The intervention measure of chemotherapy, oxaliplatin, was not included in the case; (III) other study types were excluded, such as reviews, duplicate publications, pharmacological experiments, case reports, editorials, and letters; and (IV) There were no outcome indicators in this study.

Data Extraction

For each eligible study, 2 researchers (TM, ZJW) independently extracted the following items from each study: study characteristics (lead author and publication year), patients' characteristics, intervention (the drug, dose and duration), and outcomes (ORR, performance status, and ADRs). Discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer (HB).

Risk of Bias and Quality of Evidence

Risk of bias was assessed using the Cochrane Collaboration's tool (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0)[13]: The quality evaluation items of each trial included random sequence generation and 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), and other bias. These 7 items were scored as low, high, or unclear risk of bias. The quality of evidence was evaluated by using the Confidence in Network Meta-Analysis (CINeMA),[14] which is broadly based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, with several conceptual, and semantic differences. This tool has been widely used in assessing the strength of the NMA.

Statistical Analysis

Data Analysis

We carried out a frequentist network meta-analysis.[15] Risk ratio (RR) with 95% confidence interval (CI) for outcomes with 95% CI were summarized. The ranking probabilities for all treatments of being at each possible rank for each intervention were estimated. Ranking is performed by *P*-score. *P*-score is based solely on the point estimates and standard errors of the network estimates. *P*-score is a percentage interpreted as the probability of a treatment that is the most effective without uncertainty on the outcome, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the worst.[16] To check the assumption of consistency in the entire analytical network, a design-by-treatment approach was used.[17] Global heterogeneity was assessed with the I^2-statistic which incorporates the extent of heterogeneity and was used to evaluate the extent of uncertainty in the estimated effect size locally. Comparison-adjusted funnel plots were performed to investigate whether the integrated results have differences between imprecise trials and precise trials.[18] All analyses were conducted using R 3.6.2 via the netmeta V.1.1-0 package (https://CRAN.R-project.org/package=netmeta).

Results

Study Characteristics

A total of 553 studies were retrieved based on the searching strategy of the literature databases. Overall, 31 studies[19-49] were available for NMA. These trials evaluated 10 different types of OCPM, namely, Antike (ATK), Shenyi (SY), Huachansu (HCS), Boerning (BEN), Xiaoaiping (XAP), Jinlong (JL), Compound matrine (CC), Pingxiao (PX), Xihuang pill (XHW), Kangaiping (KAP). All RCTs were published in Chinese, and the flow diagram is presented in Figure 1. The patented formulations of involved literature are listed in Supplemental File 3.Ultimately, the present NMA included 1985 patients with CRC from 31 RCTs. Among them, 1020 patients were allocated to C plus OCPM, and 965 patients received chemotherapy alone. Between different treatment arms, there was no major difference in patient characteristics. The basic characteristics of each trial are listed in Table 1. Figure 2 shows the network graph of diverse interventions for the outcomes.

Quality of Included Studies

We used the Cochrane risk of bias tool and critically evaluated the methodological quality of the included RCTs. A total of 11 RCTs[21,25-28,32,35,41,42,47,49] provided the details of randomized grouping method: 7 RCTs[26,28,32,35,41,42,47,49] used a random number table and 4 RCTs[21,25,27,32] applied an envelope method for randomization. Therefore, these trials were rated as low risk. The remaining 20 studies were assessed as "Unclear" because the relative information was not acceptable. Regarding allocation concealment, only 2 RCTs[26,41] using sealed opaque envelopes were judged as "low risk," The remaining 29 RCTs did not mention the methods of the implementation of allocation concealment that were judged as "Unclear." Most studies were assessed as "Unclear risk" for not mentioning the blinding, and only 2 RCTs[26,41] that mentioned blinding and evaluated outcomes blinding were "low risk." As for attrition bias and reporting bias, 2 RCTs[29,48] were assessed as "Unclear." One RCT[19] was assessed as "high risk" of reporting bias for one outcome, namely, ORR was not previously stated. The other RCTs had no missing data on outcomes and all the concerned outcomes were reported, that were evaluated as "Low risk." The other biases were all assessed as "Unclear" for the relative information that was not acceptable. In conclusion, the methodological quality of included RCTs was not very high, suggesting the possibility of bias in this study. A summary of the risk of bias for each included RCT is illustrated in Figure 3.

Outcomes

ORR. This NMA included 27 RCTs involving 9 kinds of OCPM with 1946 patients. We used C as reference. Quantifying heterogeneity/ inconsistency: $\tau^2=0$; $I^2=0\%$. Therefore, we chose a fixed effect model. Compared with C, there were significantly higher probabilities of ORR for 4 kinds of OCPM + C, except for XHW + C, BEN + C, XAP + C, CC + C, PX + C, with RRs of 1.37 (95% CI 1.12-1.66) for ATK + C; 1.36 (1.07-1.73), SY + C; 1.33 (1.12-1.58), HCS + C; 1.28 (1.02-1.59), JL + C (Figure 4). There were no differences in ORR among 9 kinds of OCPM combined with C, the results of pairwise comparisons are indicated by the RRs and 95% CIs in Figure 8.

Performance status. This NMA included 23 RCTs involving 8 kinds of OCPM with 1701 patients. We used C as reference. Quantifying heterogeneity/inconsistency: $\tau^2=0$; $I^2=0\%$. Therefore, we chose a fixed effect model. There

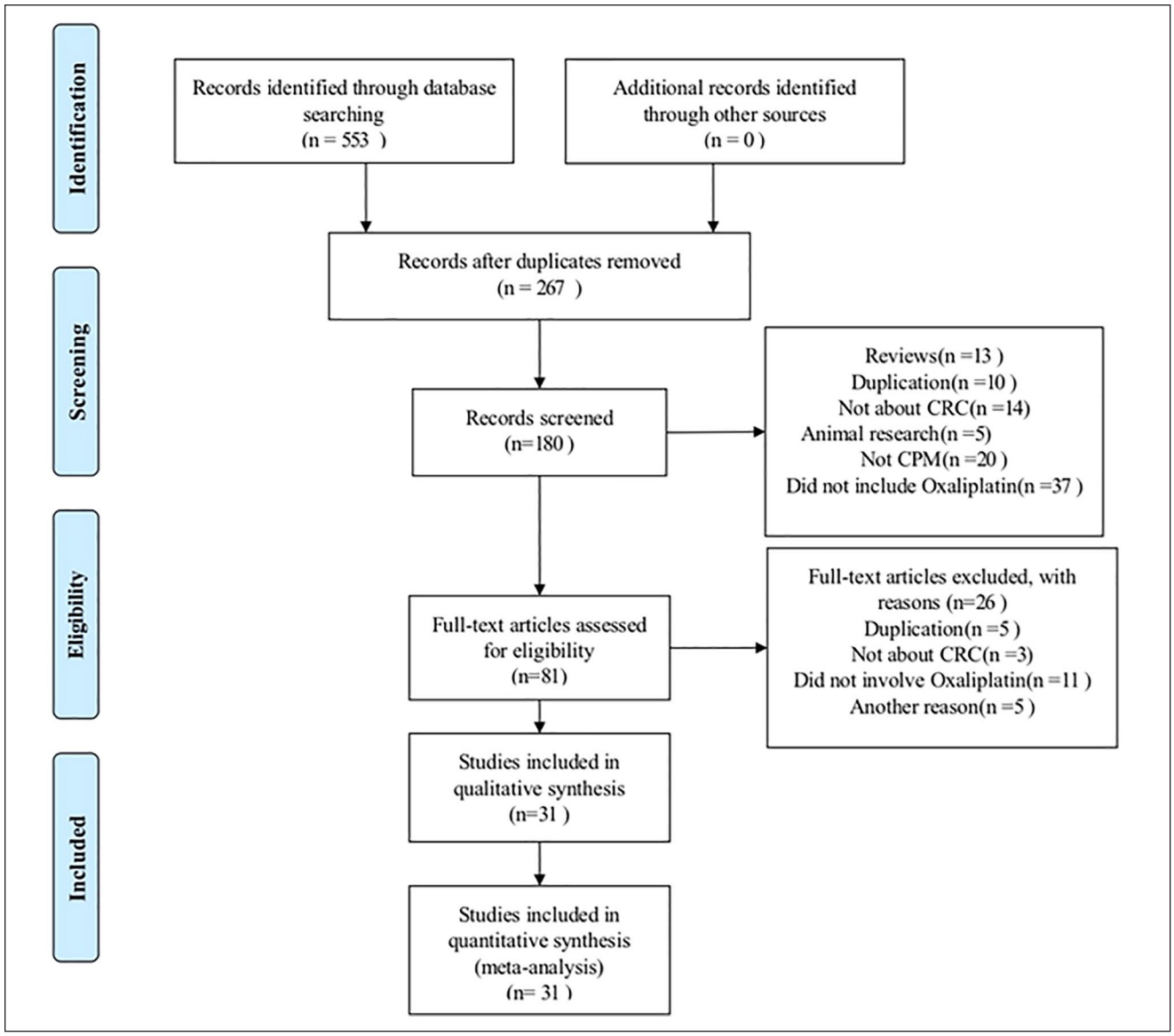

Figure 1. Flow chart of the search for eligible studies.

were significant differences in performance status between OCPM + C with C, except for XHW + C, and BEN+C. Six kinds of OCPM + C resulted in a significant improvement of performance status, with RRs of 1.96 (95% CI: 1.26-3.05) for SY + C; 1.78 (1.17-2.70) for PX + C; 1.67 (1.33-2.10) for CC + C; 1.64 (1.31-2.04) for HCS + C; 1.58 (1.11-2.26) for ATK + C; 1.44 (1.11-1.87) for JL + C (Figure 5). There were no differences in performance status among 8 kinds of OCPM combined with chemotherapy. The results of pairwise comparisons are indicated by the RRs and 95% CIs in Figure 8.

Nausea and vomiting. This NMA included 12 RCTs involving 6 kinds of OCPM with 951 patients. We used C as reference. Quantifying heterogeneity/inconsistency: $\tau^2=0$; $I^2=0\%$. Therefore, we also chose a fixed effect model. There were significant differences in nausea and vomiting between OCPM + C with C, except for ATK + C and SY + C. Compared with C, 4 kinds of OCPM + C resulted in a significant alleviation of nausea and vomiting, with RRs of 0.29 (95% CI: 0.10-0.79) for KAP + C; 0.52 (0.35-0.77) for JL + C; 0.57 (0.38-0.86) for CC + C; and 0.61 (0.51-0.74) for HCS + C (Figure 6). There were no differences in nausea and vomiting among 6 kinds of OCPM. The results of pairwise comparisons are indicated by the RRs and 95% CIs in Figure 8.

Leukopenia. This NMA included 16 RCTs involving 8 kinds of OCPM with 1139 patients. We used C as reference. Quantifying heterogeneity/inconsistency: $\tau^2=0$; $I^2=0\%$.

Table 1. The Basic Characteristics of the RCTs.

Study ID	N (E/C)	Sex (M/F)	Average age	Early	Advanced	KPSs	Type of OCPM	Treatment		Outcomes
								Dose	Days	
Quan[19]	31/31	46/16	41-75		√	≥60	HCS	1.5 g	21 d × 2	1, 2, 4
Zhou et al[20]	18/17	21/14	42-47		√	≥60	HCS	2.7 g	21 d × 4	1, 2, 4
Chang[21]	24/24	29/19	36-75		√	≥60	HCS	1.5 g	14 d × 4	1, 2, 3, 4
Dong et al [22]	38/38	46/30	36-78		√	≥60	HCS	1.5 g	21 d × 4	1, 2, 4
Dong[23]	34/34	36/32	31-48		√	≥60	HCS	6 pills	21 d × 4	1, 2, 3, 4
Lu et al[24]	30/30	42/18	36-75		√	>70	HCS	1.5 g	14 d × 2	1, 2, 4
Shi et al[25]	34/34	33/35	31-49	NR		>60	HCS	1.2 g	21 d × 4	1, 2, 3, 4
Li and Li[26]	28/28	37/19	38-70		√	>60	HCS	1.5 g	14 d × 4	1, 2
Liu et al[27]	48/48	46/50	38-79		√	≥60	HCS	1.5 g	14 d × 2	1, 2, 3
Xing et al[28]	50/50	45/55	NR			NR	CC	1.5 g	14 d × 2	2
Hu et al[29]	60/60	68/52	40-70	NR		NR	CC	1.5 g	14 d × 8	2, 3
Bai and Hu[30]	44/43	49/38	NR		√	≥70	CC	1.5 g	14 d × 4	1, 2
Zhao and Cheng[31]	54/53	60/47	23-74		√	≥70	CC	1.5 g	14 d × 4	1, 2
Cao et al[32]	49/49	64/34	60-78		√	>60	CC	1.5 g	14 d × 3	1, 3, 4
Qin and Song[33]	30/30	39/21	32-80	NR		≥60	BEN	12 pills	14d × 4	1
Xie et al[34]	32/32	39/25	36-75	NR		≥60	BEN	1.8 g	21 d × 4	1, 2
Li[35]	32/32	44/20	41-75		√	≥60	XHW	6 g	21 × 2	1, 2, 4
Zeng et al[36]	35/32	46/21	50-70		√	≥70	SY	4 pills	14 d × 4	1, 2
Lou[37]	47/45	NR	41-75	NR		≥60	SY	40 mg	14 d × 4	3, 4
Gai et al[38]	25/24	28/21	35-75	NR		≥60	SY	40 mg	21 d × 3	1, 2, 3, 4
Wang and Wang[39]	35/33	47/21	≥65		√	≥60	SY	40 mg	30 d × 4	1
Cao et al[40]	29/28	30/27	46-69		√	NR	SY	40 mg	56 d	1
Ji and Zhang[41]	52/52	NR	NR		√	NR	SY	40 mg	14 d × 2	1
Xiang and Wei[42]	48/48	56/40	37-67	NR		>70	PX	6 g	21 d × 4	1, 2
Xu[43]	49/49	59/39	≤75		√	>60	XAP	7.2 g	21 d × 2	1
Yang et al[44]	40/40	46/34	31-74	NR		>60	JL	3 g	NR	1, 2, 3, 4
Zhu and Zhou[45]	34/34	55/23	23-73	NR		>60	JL	3 g	30 d × 2	1, 2, 3
Zhang and Pei[46]	32/32	39/25	32-73	NR		>60	JL	3 g	NR	1, 2
Tang and Zhao[47]	42/40	45/37	36-72		√	≥80	ATK	1.32 g	14 d × 6	1, 2, 4
Wang et al[48]	42/42	43/41	45-72		√	≥70	ATK	1.32 g	14 d × 9	1, 2, 3, 4
Fang et al[49]	39/39	54/24	NR	NR		NR	KAP	3 g	14 d × 2	3, 4

Abbreviations: √, confirmed; E, experimental group; C, control group; M, male; F, female; KPS, Karnofsky performance score; OCPM, oral Chinese patent medicine; NR, not report; 1, ORR; 2, performance status; 3, nausea and vomiting; 4, leukopenia.

Therefore, we chose a fixed effect model. There were significant differences in leukopenia between OCPM + C with C, except for CC + C, KAP + C, PX + C, and ATK + C. Compared with C, 4 kinds of OCPM + C resulted in a significantly improvement of leukopenia, with RRs of 0.47 (95% CI: 0.31-0.72) for JL + C; 0.57 (0.48-0.69) for HCS + C; 0.63 (0.41-0.95) for XHW + C; and 0.72 (0.58-0.90) for SY + C (Figure 7). There were no differences in leukopenia among 8 kinds of OCPM. The results of pairwise comparisons are indicated by the RRs and 95% CIs in Figure 8.

Ranking of Treatments

We used the calculated *P*-scores to rank the efficacy of 10 kinds of OCPM with C. A higher *P*-score indicates a higher effectiveness. Among diverse OCPM, the OCPM without statistical significance should be excluded. ATK + C had the highest ORR with a *P*-score of .63; SY + C had the highest performance status with a *P*-score of .73; KAP + C had lowest nausea and vomiting with a *P*-score of .91; and JL + C had lowest leukopenia with a *P*-score of .95 (Figure 9).

Small-Study Effects Analysis

As shown in the Figure 10, the comparison-adjusted funnel plots suggested that there might not be small-study effects for ORR, performance status, nausea and vomiting, and leukopenia (Egger test $P > .05$).

Confidence in Evidence

The grading of the comparisons with CINeMA showed mainly "low" to "very low" confidence ratings. This was due to the network without closed loops of evidence

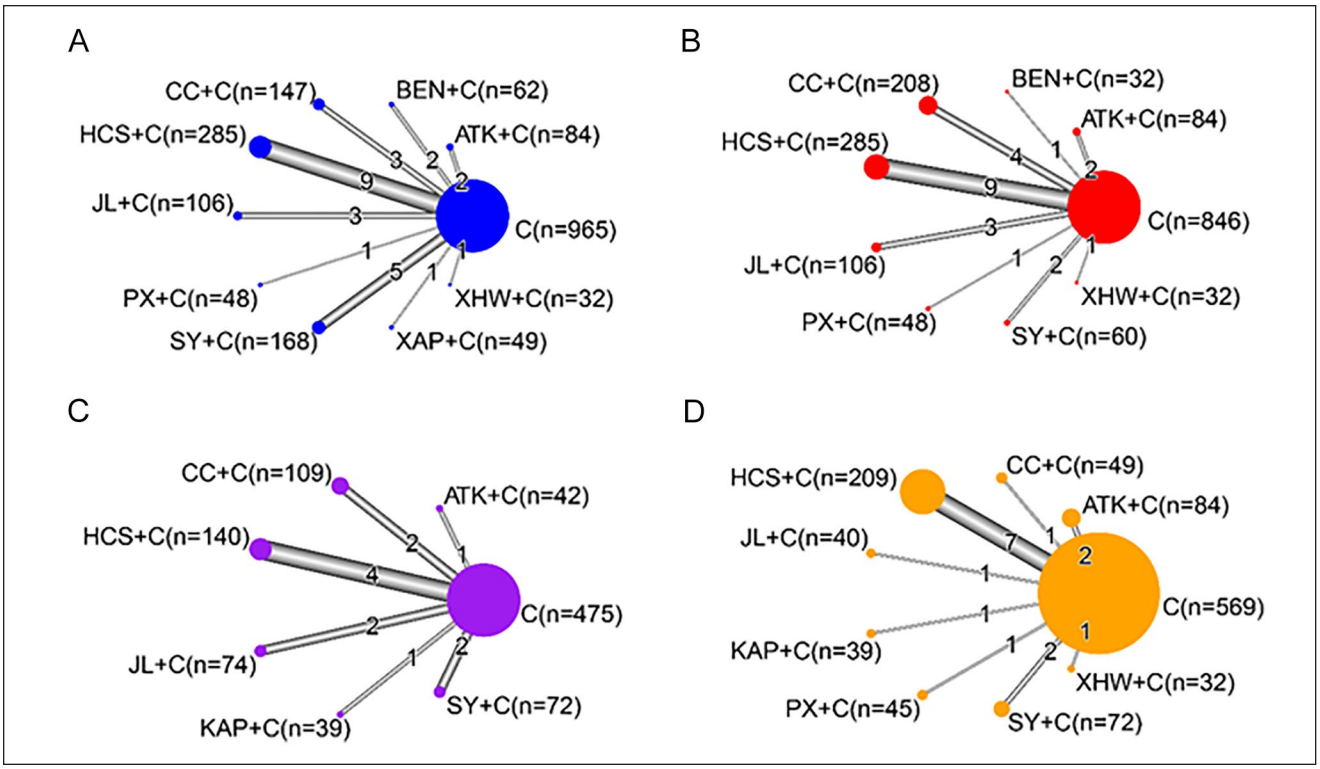

Figure 2. Network graphs of outcomes. Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of circles is proportional to the number of patients. (A) ORR. (B) Performance status. (C) Nausea and vomiting. (D) Leukopenia.

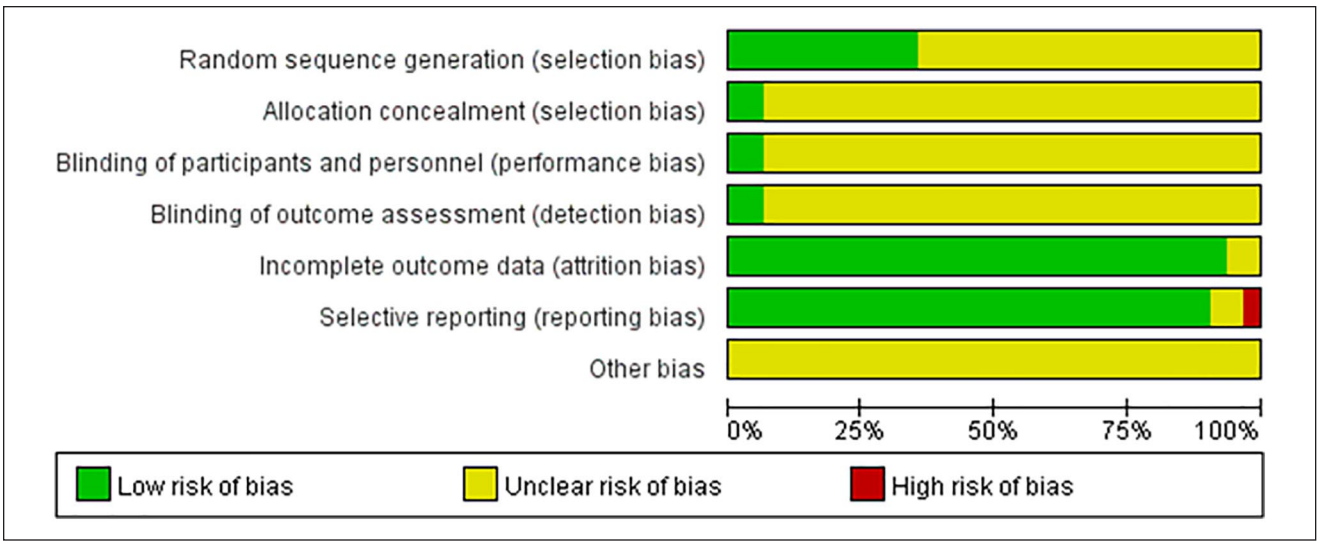

Figure 3. Risk of bias graph.

(without mixed evidence), so inconsistency cannot be assessed.[14] Thus, the "Incoherence" levels were all illustrated as "Major concerns." There were "Major concerns" about "Imprecision," usually related to the low numbers of trials available for some comparisons in this study. Details are provided in Supplemental File 4.

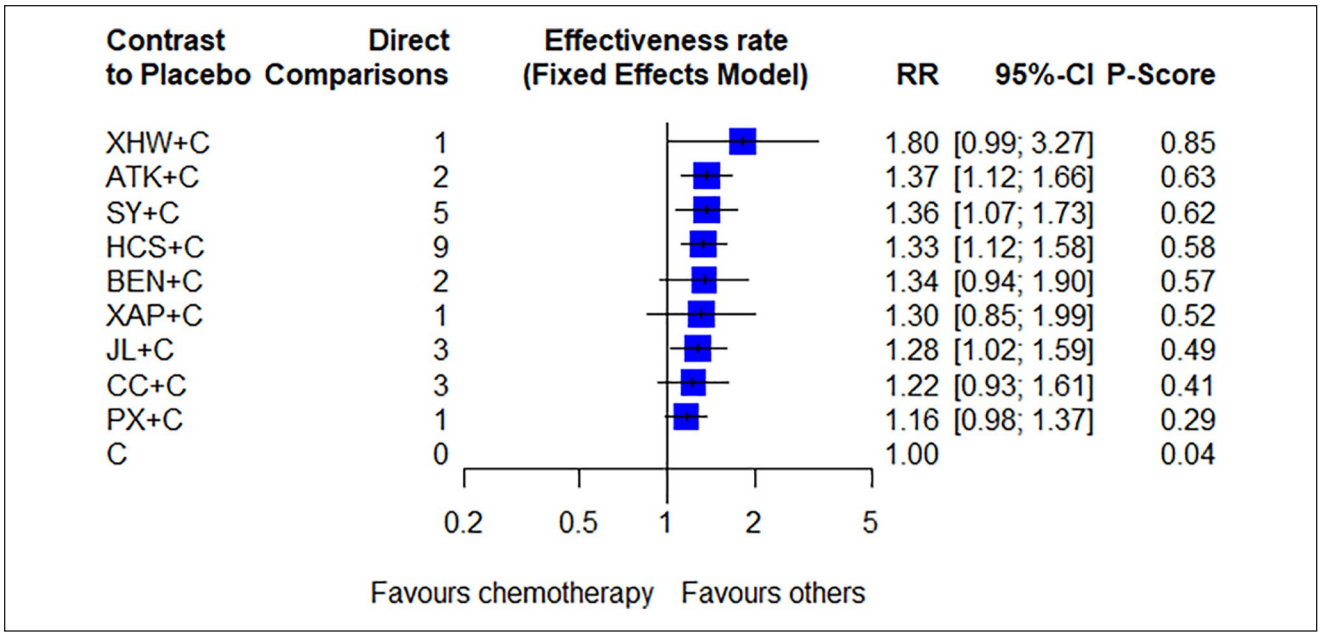

Figure 4. Forest plot of NMA for ORR.
Abbreviations: RR, risk ratio; CI, confidence interval.

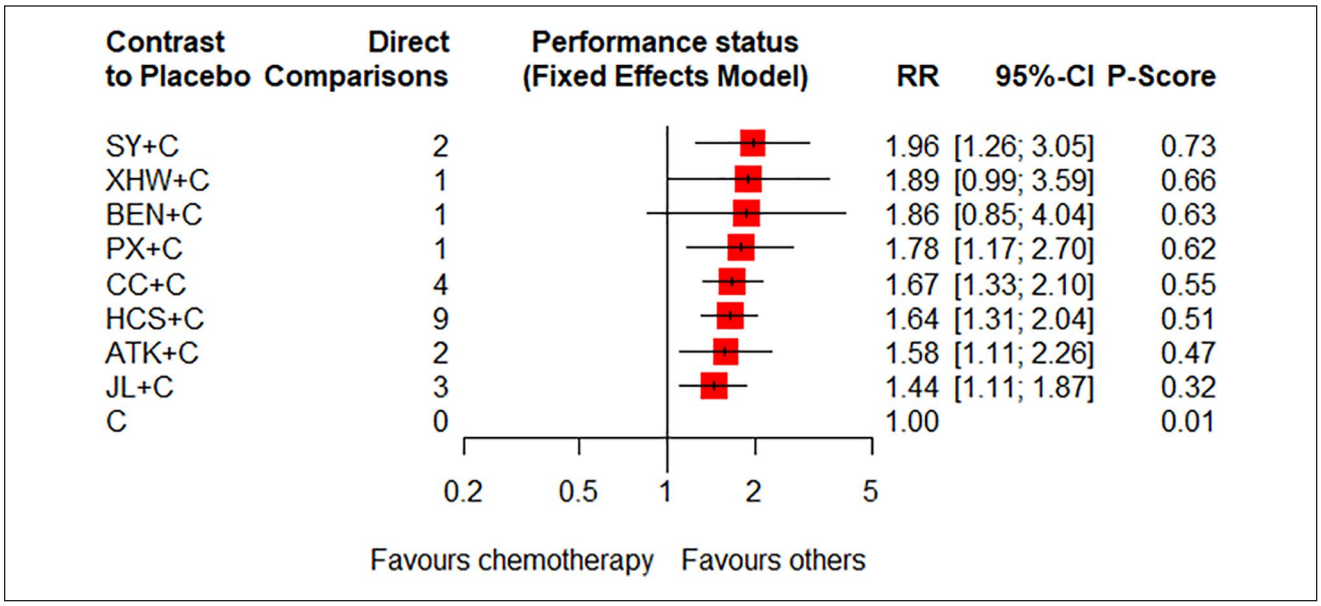

Figure 5. Forest plot of NMA for performance status.
Abbreviations: RR, risk ratio; CI, confidence interval.

Discussion

According to the eligibility criteria, this NMA identified 30 RCTs involving 10 commonly used OCPM, namely, ATK, XHW, JL, SY, BER, PX, CC, KAP, XAP, and HCS. Based on the NMA, the results showed that ATK + C, SY + C, KAP + C, and JL + C illustrated the maximum probability of being the optimal choice for CRC patients when referring to ORR, performance status, nausea and vomiting, and leukopenia, respectively. ATK, a compound preparation extracting from toad skin and angelica *(Angelica sinensis)*, has been confirmed as an effective anti-tumor drug.[50] It obtained a new drug certificate in China in 1996 and has been widely used in clinical practice for many years. It can

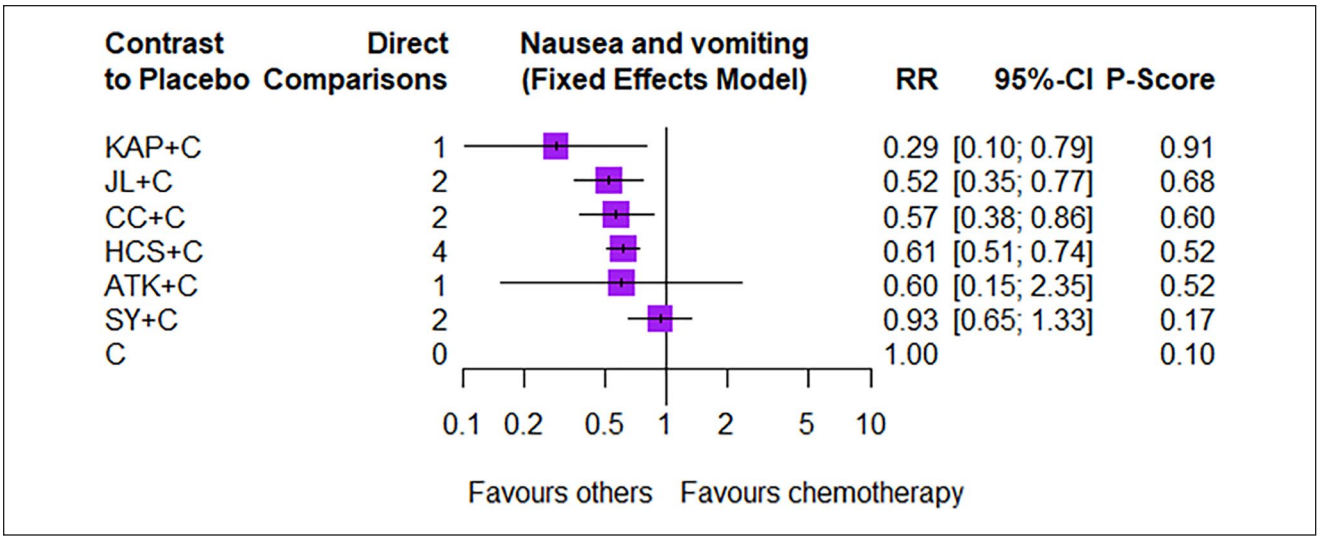

Figure 6. Forest plot of NMA for nausea and vomiting.

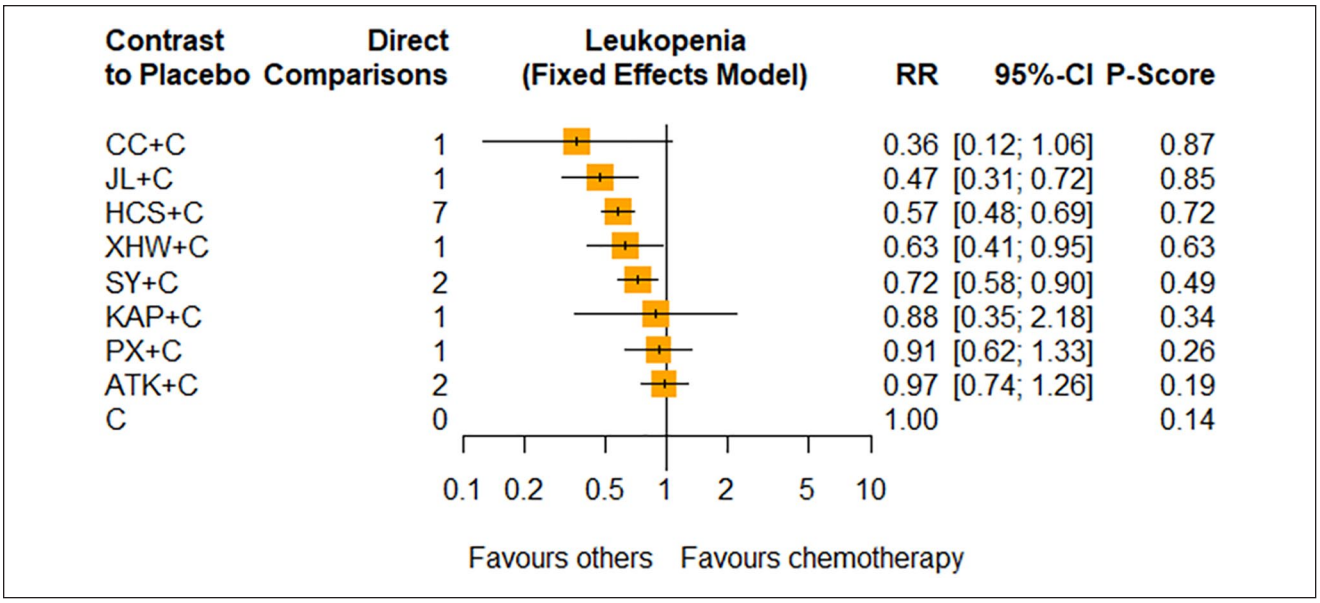

Figure 7. Forest plot of NMA for leukopenia.
Abbreviations: RR, risk ratio; CI, confidence interval.

soften hardness to dissipate stagnation and transport blood in the whole body. Studies show that the numerous monomeric compounds from ATK play important anti-tumor roles in vitro and in vivo. It can stimulate human body to release anti-tumor cell factors (like TNF, NKC, and IL-2).[51] SY is composed of the ginseng root extract component, ginsenoside Rg3. It can strengthen the immune system and promote blood and qi circulation.[52] Ginsenoside Rg3 inhibits tumor growth through suppressing angiogenesis and proliferation, infiltration and metastasis of tumor cells.[53] It has been shown that it can ameliorate the symptoms of qi deficiency and improve performance status. KAP is composed of Pearlescent, Scubela, Hedyotis, Snakeberry, Rattan pear root, Toad venom, Camellia sinensis, and Cypress.[54] It can clear heat and detoxify, and remove stagnation pain. KAP may be correlated with inhibiting tumor cell growth.[55] JL has the function of tonifying qi and blood, dredging collaterals, and detoxification, It is traditionally prepared from 3 animals with medicinal properties: Bungarus, Agkistrodon, and Gecko.[8] Studies have shown that JL can suppress

Effectiveness rate		Treatments	Performance status					
ATK+C	0.85 [0.36; 2.00]	0.95 [0.62; 1.45]	0.97 [0.64; 1.47]	1.10 [0.71; 1.71]	0.89 [0.51; 1.54]	0.81 [0.46; 1.42]	0.84 [0.40; 1.74]	-	1.58 [1.11; 2.26]
1.02 [0.68; 1.53]	BEN+C	1.11 [0.49; 2.50]	1.14 [0.51; 2.55]	1.29 [0.57; 2.93]	1.04 [0.43; 2.52]	0.95 [0.39; 2.32]	0.98 [0.36; 2.70]	-	1.86 [0.85; 4.04]
1.12 [0.80; 1.56]	1.09 [0.70; 1.71]	CC+C	1.02 [0.74; 1.40]	1.16 [0.82; 1.64]	0.94 [0.58; 1.51]	0.85 [0.52; 1.40]	0.88 [0.45; 1.75]	-	1.67 [1.33; 2.10]
1.03 [0.79; 1.33]	1.00 [0.68; 1.49]	0.92 [0.66; 1.27]	HCS+C	1.14 [0.81; 1.60]	0.92 [0.57; 1.47]	0.84 [0.51; 1.37]	0.87 [0.44; 1.71]	-	1.64 [1.31; 2.04]
1.07 [0.80; 1.44]	1.05 [0.69; 1.58]	0.96 [0.68; 1.36]	1.04 [0.79; 1.38]	JL+C	0.81 [0.49; 1.32]	0.73 [0.44; 1.23]	0.76 [0.38; 1.52]	-	1.44 [1.11; 1.87]
1.18 [0.91; 1.53]	1.15 [0.78; 1.70]	1.06 [0.77; 1.46]	1.15 [0.90; 1.46]	1.10 [0.84; 1.45]	PX+C	0.91 [0.49; 1.67]	0.94 [0.44; 2.02]	-	1.78 [1.17; 2.70]
1.00 [0.73; 1.37]	0.98 [0.64; 1.50]	0.90 [0.62; 1.30]	0.98 [0.73; 1.32]	0.94 [0.68; 1.30]	0.85 [0.63; 1.14]	SY+C	1.04 [0.47; 2.26]	-	1.96 [1.26; 3.05]
1.05 [0.66; 1.68]	1.03 [0.59; 1.79]	0.94 [0.57; 1.57]	1.02 [0.65; 1.62]	0.98 [0.61; 1.59]	0.89 [0.56; 1.41]	1.05 [0.64; 1.71]	XAP+C	-	1.30 [0.85; 1.99]
0.76 [0.40; 1.42]	0.74 [0.37; 1.48]	0.68 [0.35; 1.31]	0.74 [0.40; 1.38]	0.71 [0.37; 1.34]	0.64 [0.35; 1.20]	0.76 [0.40; 1.44]	0.72 [0.35; 1.51]	XHW+C	1.89 [0.99; 3.59]
1.37 [1.12; 1.66]	1.34 [0.94; 1.90]	1.22 [0.93; 1.61]	1.33 [1.12; 1.58]	1.28 [1.02; 1.59]	1.16 [0.98; 1.37]	1.36 [1.07; 1.73]	1.30 [0.85; 1.99]	1.80 [0.99; 3.27]	C

Leukopenia		Treatments	Nausea and vomiting						
ATK+C	1.06 [0.25; 4.40]	0.98 [0.25; 3.89]	1.15 [0.28; 4.77]	2.10 [0.38; 11.54]	-	0.65 [0.16; 2.66]	-	0.60 [0.15; 2.35]	-
2.66 [0.88; 8.04]	CC+C	0.93 [0.59; 1.46]	1.09 [0.62; 1.92]	1.99 [0.66; 5.97]	-	0.61 [0.35; 1.06]	-	0.57 [0.38; 0.86]	-
1.68 [1.22; 2.32]	0.63 [0.21; 1.88]	HCS+C	1.18 [0.76; 1.81]	2.15 [0.76; 6.05]	-	0.66 [0.44; 0.99]	-	0.61 [0.51; 0.74]	-
2.06 [1.25; 3.42]	0.78 [0.24; 2.47]	1.23 [0.77; 1.95]	JL+C	1.82 [0.61; 5.43]	-	0.56 [0.33; 0.95]	-	0.52 [0.35; 0.77]	-
1.11 [0.43; 2.86]	0.42 [0.10; 1.70]	0.66 [0.26; 1.66]	0.54 [0.20; 1.47]	KAP+C	-	0.31 [0.10; 0.91]	-	0.29 [0.10; 0.79]	-
1.06 [0.67; 1.69]	0.40 [0.13; 1.25]	0.63 [0.42; 0.96]	0.52 [0.29; 0.91]	0.96 [0.36; 2.59]	PX+C	-	-	-	-
1.34 [0.95; 1.90]	0.51 [0.17; 1.51]	0.80 [0.60; 1.06]	0.65 [0.40; 1.06]	1.22 [0.48; 3.11]	1.26 [0.81; 1.96]	SY+C	-	0.93 [0.65; 1.33]	-
1.55 [0.94; 2.54]	0.58 [0.18; 1.84]	0.92 [0.58; 1.45]	0.75 [0.41; 1.37]	1.40 [0.51; 3.82]	1.45 [0.83; 2.56]	1.15 [0.72; 1.85]	XHW+C	-	-
0.97 [0.74; 1.26]	0.36 [0.12; 1.06]	0.57 [0.48; 0.69]	0.47 [0.31; 0.72]	0.88 [0.35; 2.18]	0.91 [0.62; 1.33]	0.72 [0.58; 0.90]	0.63 [0.41; 0.95]	C	-

Figure 8. Pairwise comparisons of the efficacy of 10 kinds of OCPM combined with C. Drugs are reported in alphabetical order. Data are RRs and 95% CIs in each grid. The results show comparisons of column-defining drug versus row-defining drug.

cellular mitotic division and inhibit proliferation and promote cancer cell apoptosis.[56]

TCM as a complementary medicine is based on a well-developed theory,[57] Reinforcing the fundamental and cultivating the vital energy to resist and dispel pathogenic factors, and adjusting yin and yang to maintain their balance are the principle of treating cancer in TCM. According to TCM, qi and pathogens are not only related to the occurrence of a disease, but also directly affect its development and final outcome. Victory or failure in the struggle between vital qi and pathogens determines the aggravation or alleviation of a disease. One of the important principles in clinical treatment is to change the relative strength of vital qi and pathogens. OCPM are a form of TCM preparation that is based on extracting and purifying the effective and active compounds from herbs or decoction

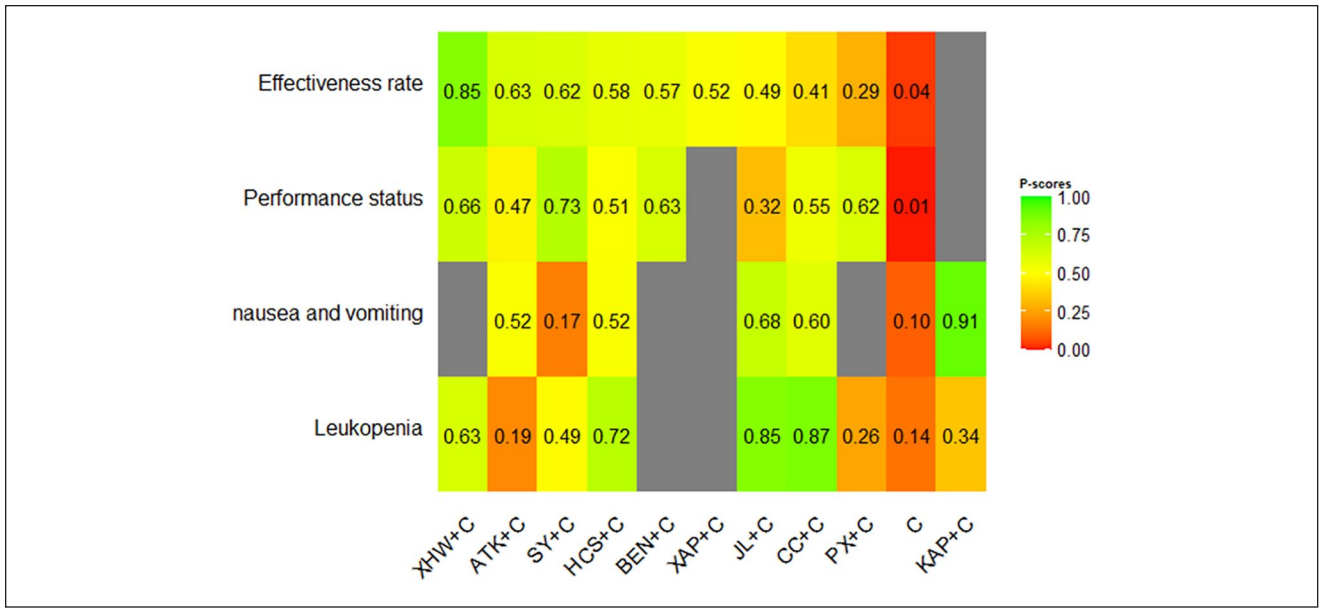

Figure 9. Ranking of effectiveness and safety of 10 kinds of OCPM combined with C.

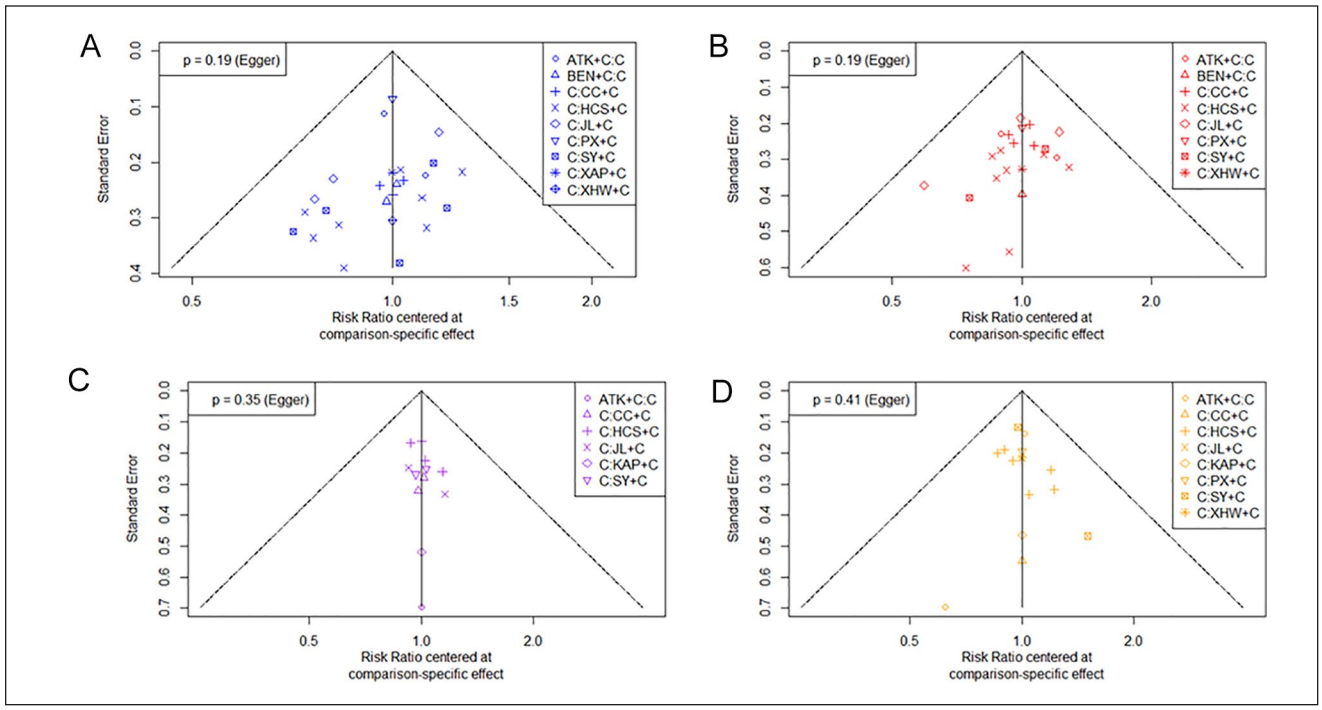

Figure 10. The comparison-adjusted funnel plots of 10 kinds of OCPM combined with C. (A) ORR. (B) Performance status. (C) Nausea and vomiting. (D) Leukopenia.

pieces via the theory of TCM and modern medical techniques and methods.[58] A total of 10 OCPM involved in the study can be classified into 3 categories according to the TCM therapeutic principle: The first category strengthens vital qi and eliminates pathogens, simultaneously, ATK and BER fall into this category; The second type only strengthens the body resistance, such as SY. The third one expels pathogens; most of the OCPM (XHW, JL, PX, CC, KAP,

XAP, and HCS) included in this study belong to this category. Although OCPM is only widely used in China at present, it is a promising complementary therapy for patients with CRC.

Some limitations of this NMA have to be acknowledged. First, the quality of the included studies might not be high, and the confidence rating evaluated by CINeMA is ranged from "very low" to "low" for various comparisons, which reduced the reliability of research results. Second, from the methodology point of view, the involved studies are all Chinese literature, and there may be language bias, which is not beneficial to the international promotion of study outcomes. However, the literature search of our study was extensive as well as thorough. Third, there was a lack of direct study on comparisons between diverse OCPM combined with C. Fourthly, the reliability of our study was limited by sample size, especially for some types of OCPM, namely, PX, XAP, KAP, XHW, for which only 1 clinical trial was included in the present study. Lastly, the limitations of "frequentist" analysis cannot be ignored.[15]

Conclusion

Taken together, this NMA provides evidence supporting diverse OCPM plus oxaliplatin-based chemotherapy for CRC patients. Among different types of OCPM, ATK + C, SY + C, KAP + C, and JL + C demonstrated the maximum probability of being the optimal choice for CRC patients. However, the results of this study have been plagued by some limitations of the included studies. Thus the selection of OCPM in a given situation will continue to depend upon clinicians until multicenter and high-quality studies to support our findings.

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Author Contributions

All authors take responsibility for the integrity of the data and the accuracy of data analysis. Performed the experiments: TM ZJW WL. Analyzed the data: TM ZJW. Contributed reagents/materials/analysis tools: TM ZJW WL HB. Wrote the paper: TM ZJW WL HB.

Declaration of Conflicting Interests

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Supplemental Material

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