



Efficacy and Safety of Chinese Herbal Medicine on Ovarian Cancer After Reduction Surgery and Adjuvant Chemotherapy: A Systematic Review and Meta-Analysis

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Background: Ovarian cancer (OvC) is a malignant tumor which invades ovarian epithelium and interstitium. Reduction surgery combined with adjuvant chemotherapy is standard treatment for OvC patients, but the adverse effects due to chemotherapy still remains a major problem. While Chinese herbal medicine (CHM) therapy has a unique therapeutic effect to reduce side effects of chemotherapy by boosting immune system, the evidence of CHM in the treatment of OvC patients are limited.

Objective: We conducted a systematic review to evaluate the efficacy and safety of CHM in the treatment of OvC after reduction surgery and adjuvant chemotherapy.

Method: Chinese National Knowledge Infrastructure (CNKI) and PubMed up to Dec 31st 2018 were searched to identify relevant studies. Only randomized controlled trials (RCTs) were included, and there was no limitation on language of the publication. Data were extracted from all included studies and meta-analysis was performed with Review Manager 5.3. Study quality was assessed and pooled risk ratios (RR) or mean difference (MD) with 95% CIs were used to evaluate the efficacy and safety of CHM.

Results: A total of 18 RCTs involving 975 participants were included. There was no placebo, no treatment and CHM alone. Compared with Western Medicine (WM) alone, Chinese herbal Medicine combined with WM (CHM-WM) significantly improved TCM syndromes and symptoms, KPS scores, CD4 counts, CA125 levels, and 3-years survival rate ($P < 0.05$). Incidences of gastrointestinal reactions, marrow depression, urinary system symptoms were significantly lower in CHM-WM group than in WM group ($P < 0.01$). There was no significant difference in CD3 counts, CD8 counts, quality of life, liver function, and peripheral neuropathy between the two groups ($P > 0.05$).

Conclusion: The systematic review indicated that CHM combined with WM is effective and safe as a treatment for OvC patients after reduction surgery and adjuvant chemotherapy. However, more high-quality and large-scale RCTs are needed to confirm the efficacy and safety of CHM intervention.

Keywords: meta-analysis, ovarian cancer, Chinese herbal medicine, efficacy, safety

Ovarian Cancer (OvC) is a gynecological malignancy with high prevalence in women aged 50–70. It accounts for about 20% of all female reproductive cancers (1). Although the morbidity in OvC is lower than that in cervical and endometrial cancers, OvC has the highest mortality amongst the three, which is the leading cause of cancer-associated death in women (2). Owing to lack of typical symptoms and early detection methods, diagnosis is often belated. Fewer than one-half of patients can survive beyond 5 years after diagnosis (3). Over 60–70% of patients are diagnosed at advanced stage. In terminal stage, patients always suffer from severe abdominal pain and distension due to peritoneal metastasis.

The National Comprehensive Cancer Network (NCCN) Guidelines recommend removal of the ovary and fallopian tubes as an initial treatment for OvC to patients with FIGO stage I and/or low-grade invasive carcinoma, and debulking surgery for patients with FIGO stage II-IV (4). Adjuvant treatments are necessary to minimize recurrence of OvC, which may include radical surgery (such as hysterectomy, unilateral salpingo-oophorectomy, etc.), radiotherapy (such as high-energy x-rays, etc.), chemotherapy (such as carboplatin plus paclitaxel regimen, cisplatin plus cyclophosphamide regimen, etc.), hormone therapy (such as tamoxifen, letrozole, etc.), tumor-targeted therapy (such as monoclonal antibody therapy, bevacizumab, etc.), and/or Chinese herbal medicine (CHM) (such as Bushenxiaozheng decoction, Lichongshensui decoction, etc.). Most postoperative patients suffer from constitutional debility and other surgery-related complications. While chemotherapy kills both tumor cells and normal cells, leading to many adverse effects, such as marrow depression, gastrointestinal reactions (nausea, vomiting), neurotoxicity, so on. In recent years, a growing number of clinical studies showed CHM could alleviate chemotherapy-related side effects and improves human immunity, which can be a supporting therapy of the adjuvant treatment for OvC (5).

OBJECTIVE

The systematic review aimed to assess the efficacy and safety of CHM for ovarian cancer after reduction surgery and adjuvant chemotherapy.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Inclusion Criteria

- (1) Patients were confirmed with diagnosis of OvC at FIGO stage II-IV by surgery and pathology;

- (2) The tumors were primary, and the patients included should not have any other untreated malignant tumors simultaneously;
- (3) OvC patients carried out reduction surgery and adjuvant platinum-based chemotherapy;
- (4) No contraindications to chemotherapy, including bone marrow depression, fever, liver and renal dysfunction, blood picture, and electrocardiogram abnormalities;
- (5) Study intervention started with comparable baseline;
- (6) Life expectancy was longer than 6 months for observation;
- (7) No serious diseases in major organs and systems;
- (8) Patients participated in the trial voluntarily.

Exclusion Criteria

- (1) Not meeting the diagnostic criteria;
- (2) Allergic to drugs;
- (3) Nursing women;
- (4) With mental diseases not easy or refuse to cooperate;

Shedding cases, such as subjects with poor compliance, were asked to quit the study, etc.

Types of Research

Only randomized controlled trials (RCTs) were included.

Interventions and Comparison

- (1) CHM vs. placebo;
- (2) CHM vs. no treatment;
- (3) CHM vs. WM;
- (4) CHM combined with WM vs. WM alone; and
- (5) CHM vs. other interventions (bed rest, nutritional support, etc.).

Literature Search

Database

We performed a comprehensive search from CNKI and PubMed databases for all the potentially eligible trials of CHM for OvC. All databases were searched from 31st January, 1966 to Dec 31st, 2018.

Search Strategy

Keywords for the search included “Chinese Medicine,” “Chinese Herbal Medicine,” “Traditional Chinese Medicine,” and “Ovarian Cancer.” For the CNKI database, the key words were searched in Chinese characters and Pinyin. There was no limitation on the languages.

Data Extraction

Based on a pre-designed and standardized data collection form, two authors (WRY & LL) reviewed the titles and abstracts

of all the clinical studies independently for study inclusion. Subsequently, two authors read the full texts for study inclusion. Any non-conformity would be solved by discussion with the third author (CTH) to make a consensus. The following information was extracted from the included studies: first author, year, sample size, study design, baseline information, randomization, therapeutic outcomes, and adverse effects.

Quality Assessment

Assessment of methodological quality was conducted in accordance with Cochrane Reviewers' Handbook 5.0, including the randomization method, allocation concealment, description of inclusion criteria, evaluation on the curative effect with blinding, description of withdrawal and loss of follow-up, baseline consistency, and whether the intention-to-treatment (ITT) analysis was performed.

Data Synthesis and Analysis

We processed and analyzed the data using the Review Manager software (Revman 5.3, provided by the Cochrane Collaboration). Random-effects models were used to calculate pooled effects. Fixed-effect models were used for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e., where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Dichotomous data were presented as pooled Risk Ratio (RR) with 95% confidence intervals (95% CIs), while continuous data were presented as Mean Difference (MD) with 95% CIs. We performed forest plot and funnel plot analysis to test heterogeneity, and assess reporting biases. $P < 0.05$ was considered statistically significant.

Heterogeneity was assessed through the I^2 statistic, which estimates the fraction of variance that is due to heterogeneity and by Q test. The level of significance for the Q test was defined as $P < 0.10$.

RESULTS

Literature Search

480 clinical studies were identified in the literature search. After screening the titles and abstracts, 38 RCTs were selected initially according to the inclusion, and exclusion criteria. Subsequently, full texts of these studies were further reviewed, 20 studies were further excluded, and 18 studies were finally included for meta-analysis (6–23). Amongst these excluded studies, 14 studies applied wrong randomization (24–37), 4 trials reported only recruit FIGO stage II-IV patients but mixed with FIGO stage I patients in their outcome reports (38–41), 1 study used wrong intervention (42), and 1 study included non OvC patient (43). Besides, the subjects and study design of 2 trials (12, 18) were same, but the outcomes were different. We failed to get the responses and clarifications from the original authors. After discussion, we included all of these studies. **Figure 1** summarizes the process of the study selection.

Characteristics and Quality of the Studies

Table 1 shows a summary and quality assessment of all included studies. In total 18 studies with 975 patients were analyzed, whereas 488 patients were from study group (treated with combined CHM and WM), and the other 487 patients were from control group (treated with WM alone). There was no study group treated with CHM alone, and no placebo and no treatment in control group. CHM included Shenlingbaizhu decoction, Guizhifuling capsules, so on, where WM included Docetaxel, Cisplatin, so on. There were no significant differences in ages, BMI, clinical stages, pathological types, histological grade between the groups ($P > 0.05$). The baselines of patients' information between groups were similar, but blinding, allocation concealment and ITT were not reported in all studies.

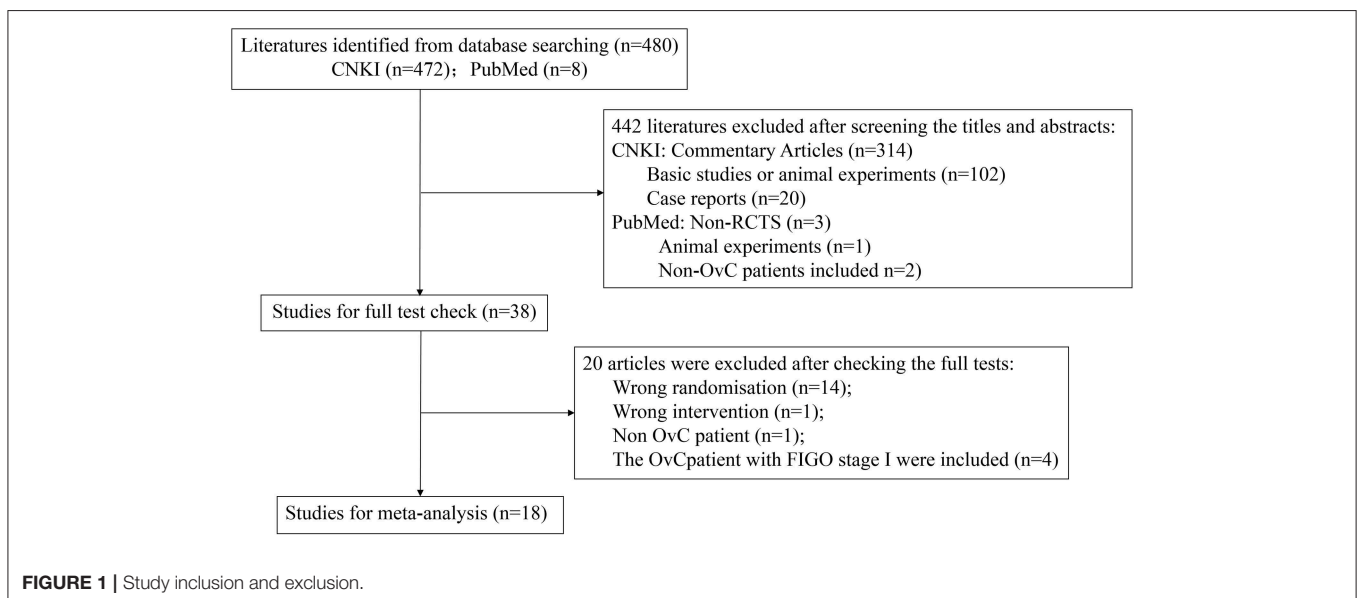


TABLE 1 | Summary of characteristics of included studies.

| Study ID | T/C (n) | Interventions | Control | Follow-up | Baseline similarity | Randomization | Blinding | Drop-off (%) |
|---------------------|---------|---|--|--------------|-----------------------|-------------------|--------------|--------------|
| Chen (6) | 20/20 | 1. CHM formula, 200 ml, po, BID, 8 weeks; 2. Docetaxel, 70–100 mg/m ² , ivgtt, day 1 and day 8, 21 days*2 courses; 3. Cisplatin, 60 mg/m ² , ivgtt, day 1 and day 8, 21 days*2 courses | 1. Docetaxel, 70–100 mg/m ² , ivgtt, day 1 and day 8, 21 days*2 courses; 2. Cisplatin, 60 mg/m ² , ivgtt, day 1 and day 8, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Chen (7) | 30/29 | 1. CHM formula, 100 ml, po, BID, 18 days*2 courses; 2. Taxol, 175 mg/m ² , ivgtt, day 1, 21 days*2 courses; 3. Carboplatin, 300 mg/m ² , ivgtt, Day 2, 21 days*2 courses | 1. Taxol, 175 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 2. Carboplatin, 300 mg/m ² , ivgtt, Day 2, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Number randomized | Not reported | 1.7 |
| Cheng and Zhang (8) | 31/31 | 1. CHM formula, po, BID, 21 days; 2. Pemetrexed, 500 mg/m ² , ivgtt, Day 1, 1 course; 3. Carboplatin, AUC = 5, ivgtt, Day 1, 1 course | 1. Pemetrexed, 500 mg/m ² , ivgtt, Day 1, 1 course; 2. Carboplatin, AUC = 5, ivgtt, Day 1, 1 course | 1 month | Comparable (P > 0.05) | Number randomized | Not reported | 0 |
| Guo (9) | 27/27 | 1. Puerarin injection, 400 mg, ivgtt, QD, 21 days; 2. Docetaxel, 75 mg/m ² , ivgtt, Day 1, day 8, and day 15, 21 days*1–6 courses; 3. Cisplatin, 30 mg/m ² , ivgtt, Day 1–3, 21 days*1–6 courses | 1. Docetaxel, 75 mg/m ² , ivgtt, Day 1, day 8, and day 15, 21 days*1–6 courses; 2. Cisplatin, 30 mg/m ² , ivgtt, Day 1–3, 21 days*1–6 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Han et al. (10) | 25/25 | 1. CHM formula, 200 ml, po, BID, 21 days*3 courses; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*3 courses; 3. Carboplatin, 300–500 mg/m ² , ivgtt, Day 2, 21 days*3 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*3 courses; 2. Carboplatin, 300–500 mg/m ² , ivgtt, Day 2, 21 days*3 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Hao (11) | 20/21 | 1. CHM formula, 200 ml, PO, BID, 3 weeks; 2. Taxol, 135 mg/m ² , ivgtt, 1 course; 3. Carboplatin, AUC = 5, ivgtt, 1 course; | 1. Taxol, 135 mg/m ² , ivgtt, 1 course; 2. Carboplatin, AUC = 5, ivgtt, 1 course; | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Li (12) | 19/20 | 1. CHM Capsule, 0.31 g *3, po, TID, 21 days*2 courses; 2. Earthworm, 10 g, po, QD, 21 days*2 courses; 3. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 4. Carboplatin, AUC = 5, ivgtt, Day 1, 21 days*2 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 2. Carboplatin, AUC = 5, ivgtt, Day 1, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 2.5 |
| Li (13) | 30/30 | 1. CHM formula, 200 ml, po, BID, 6 weeks; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 3. Carboplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*2 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 2. Carboplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Liu et al. (14) | 30/30 | 1. CHM formula, 150 ml, po, BID, 4 weeks; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 1 course; 3. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 1 course | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 1 course; 2. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 1 course | Not reported | Comparable (P > 0.06) | Randomized | Not reported | 0 |

(Continued)

TABLE 1 | Continued

| Study ID | T/C (n) | Interventions | Control | Follow-up | Baseline similarity | Randomization | Blinding | Drop-off (%) |
|-----------------|---------|---|--|--------------|-----------------------|-------------------------|--------------|--------------|
| Ma (15) | 15/15 | 1. CHM formula, 150 mg, po, BID, 8 weeks; 2. Docetaxel, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 3. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*2 courses | 1. Docetaxel, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 2. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Mei (16) | 20/20 | 1. TCM formula, 250 ml, po, BID, 6 weeks; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 3 weeks*2 courses; 3. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 3 weeks*2 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 3 weeks*2 courses; 2. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 3 weeks*2 courses | Not reported | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Qiu (17) | 20/20 | 1. CHM formula, 100 ml, PO, BID, 21 days; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 1 course; 3. Carboplatin, the dose according to patient, ivgtt, Day 2, 1 course; | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 1 course; 2. Carboplatin, the dose according to patient, ivgtt, Day 2, 1 course; | Not reported | Comparable (P > 0.05) | Number table randomized | Not reported | 0 |
| Zhao (18) | 19/20 | 1. CHM Capsule, 0.31 g *3, po, TID, 21 days*2 courses; 2. Earthworm, 10 g, po, QD, 21 days*2 courses; 3. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 4. Carboplatin, AUC = 5, ivgtt, Day 1, 21 days*2 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*2 courses; 2. Carboplatin, AUC = 5, ivgtt, Day 1, 21 days*2 courses | Not reported | Comparable (P > 0.05) | Number table randomized | Not reported | 2.5 |
| Jia (19) | 42/42 | 1. CHM formula, 200 ml, po, BID, 6 months; 2. Day 1–3, Docetaxel (60 mg/m ²) + Cisplatin (50 mg/m ²), ivgtt, From day 4, Docetaxel (90 mg/m ²) + Cisplatin (60 mg/m ²), IPT [#] , Once or twice a day, 6 months | Days 1–3, Docetaxel(60 mg/m ²) +Cisplatin (50 mg/m ²), ivgtt, From day 4, Docetaxel (90 mg/m ²) + Cisplatin (60 mg/m ²), IPT [#] , Once or twice a day, 6 months | 3 years | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Yi et al. (20) | 30/30 | 1. CHM formula, 100 ml, po, BID, 4 weeks; 2. IL-2 (2 million U) + 0.9% NaCl (20 ml), Intraperitoneal perfusion, QW, 4 weeks | IL-2 (2 million U) + 0.9%NaCl(20 ml), intraperitoneal perfusion, QW, 4 weeks | Not reported | Comparable (P > 0.05) | Number table randomized | Not reported | 0 |
| Mao et al. (21) | 36/35 | 1. CHM formula 150 ml, po, BID, 30 days*6; 2. Matrine Injection (4 ml) + Shenmai injection (50 ml), ivgtt, Day 1–9, Once per months, 6 months | Matrine injection (4 ml) + Shenmai injection (50 ml), ivgtt, Day 1–9, Once per months, 6 months | 6 months | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Xu (22) | 40/40 | 1. TCM formula, 100 ml, po, BID, 5 weeks; 2. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*3 courses; 3. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*3 courses 4. Taxol + Cisplatin, 60 mg/m ² , IPT [#] , once per course, 21 days*3 courses | 1. Taxol, 135 mg/m ² , ivgtt, Day 1, 21 days*3 courses; 2. Cisplatin, 75 mg/m ² , ivgtt, Day 1, 21 days*3 courses 3. Taxol + Cisplatin, 60 mg/m ² , IPT [#] , once per course, 21 days*3 courses | 3 months | Comparable (P > 0.05) | Randomized | Not reported | 0 |
| Zhang (23) | 34/32 | 1. CHM formula, Accupoint application, QD, 1 week; 2. Normal nursing | Normal nursing | Not reported | Comparable (P > 0.05) | Number table randomized | Not reported | 0 |

[#]IPT, intraperitoneal perfusion chemotherapy.

Efficacy and Safety

Outcomes of efficacy and safety were separately analyzed as below and summarized as in **Supplementary Table 1**. Comparisons and meta-analysis were only available and performed between combined Chinese herbal Medicine and Western Medicine (CHM-WM) group and Western Medicine alone (WM) group.

Efficacy

Syndromes and symptoms

Ten trials (6, 7, 10, 11, 13, 15–18, 21) evaluated the efficacy in the improvement of TCM syndromes and symptoms (such as poor appetite, fatigue, etc.) between the two groups. Meta-analysis showed that the symptoms were significantly improved in CHM-WM group when compared with WM group (RR = 0.29, 95% CI: 0.21–0.37, $P < 0.00001$, **Figure 2A**).

Performance status (KPS scores)

Nine trials (6, 10–16, 20) compared patients' performance status by KPS scores before and after the treatments. Meta-analysis showed that the KPS scores were significantly increased in CHM-WM group when compared with WM group (MD = 3.75, 95% CI: 0.85–6.65, $P = 0.01$, **Figure 2B**).

Tumor evaluation

Five trials (6, 8, 9, 15, 16) evaluated the tumor by Response Evaluation Criteria in Solid Tumors (RECIST) between two groups. Meta-analysis showed that the pathological change of tumor was significantly more stable in the CHM-WM group when compared with WM group (RR = 1.30, 95% CI: 1.01–1.67, $P = 0.04$, **Figure 2C**).

Immunologic function

Four trials (13, 15–17) evaluated the immunologic function by CD3, CD4, and CD8 counts before and after the treatments. Meta-analysis showed that ① CD4 counts level were significantly higher in CHM-WM group when compared with WM group (MD = 4.16, 95% CI: 1.25–7.06, $P = 0.005$, **Figure 2D**). ② CD3 and CD8 counts were not significantly different between CHM-WM group and WM group (WM) (MD = 3.74 CI: –0.43–7.91, $P = 0.08$, **Figure 2E**, MD = –0.76 CI: –4.07–2.54, $P = 0.65$, **Figure 2F**).

CA125

Four trials (10, 12, 13, 16) evaluated CA125 before and after the treatments. Meta-analysis showed that CA125 was significantly lower in CHM-WM group when compared with WM group (MD = –7.76, 95% CI: –12.57 to –2.95, $P = 0.002$, **Figure 2G**).

Quality of life

Quality of life was reported in 3 trials (6, 10, 16). Meta-analysis showed that there was no significant difference in quality of life between CHM-WM group and WM group (MD = 2.55, 95% CI: 0.01–5.10, $P = 0.05$, **Figure 2H**).

Three-year survival rate

Three-year survival rate was reported in 2 trials (19, 22). Meta-analysis indicated that the 3-year survival rate in CHM-WM group was significantly higher than in WM group (RR = 1.29, 95% CI: 1.06–1.57, $P = 0.01$, **Figure 2I**).

Safety

Gastrointestinal reactions

Gastrointestinal reactions (including nausea or vomiting, diarrhea) were recorded in 7 trials (6, 7, 10, 11, 14–16). Meta-analysis showed that the incidence of gastrointestinal reactions was significantly lower in CHM-WM group when compared with WM group (RR = 0.74, 95% CI: 0.56–0.93, $P = 0.01$, **Figure 3A**).

Bone marrow depression

Bone marrow depressions (parameters such as nausea or vomiting, diarrhea) were recorded in 10 trials (6, 7, 10–13, 15–18). Meta-analysis showed that the bone marrow depression in CHM-WM group was significantly lower than that in WM group (RR = 0.70, 95% CI: 0.62–0.79, $P < 0.00001$, **Figure 3B**).

Urinary system symptoms

Symptoms and markers in the urinary system including hematuria, proteinuria, urea nitrogen and creatinine, were recorded in 6 trials (6, 10, 12, 13, 18, 19). Meta-analysis results showed that incidence of urinary system symptoms in CHM-WM group was significantly lower than that in WM group (RR = 0.47, 95% CI: 0.32–0.70, $P = 0.0002$, **Figure 3C**).

Liver function

Liver function (parameters such as ALT) was recorded in 4 trials (6, 12, 15, 16). Meta-analysis indicated that there was no significant difference in liver function between two groups (RR = 0.72, 95% CI: 0.44–1.17, $P = 0.18$, **Figure 3D**).

Peripheral neuropathy

Peripheral neuropathy (such as loss of sensation, muscle weakness and atrophy, loss of tendon reflexes, and vasomotor symptoms) was recorded in 3 trials (9, 15, 16). Meta-analysis showed that there was no significant difference in peripheral neuropathy between two groups (RR = 1.11, 95% CI: 0.81–1.50, $P = 0.52$, **Figure 3E**).

Others

Additionally, one study (23) compared appetite score by daily intake between the two groups, and reported that the appetite score of the CHM-WM group (4.54 ± 1.22) was significantly higher than the score of the WM group (2.12 ± 1.23), ($P < 0.05$, **Figure 4A**). Another study (10) recorded the incidence rate of hair loss, infection and oral ulcer. It showed that the incidence rate of hair loss in CHM-WM group was significantly lower than that in WM group ($P = 0.005$, **Figure 4B**), but there was no significant difference in incidence rate of infection and oral ulcer between two groups ($P > 0.05$, **Figures 4C,D**).

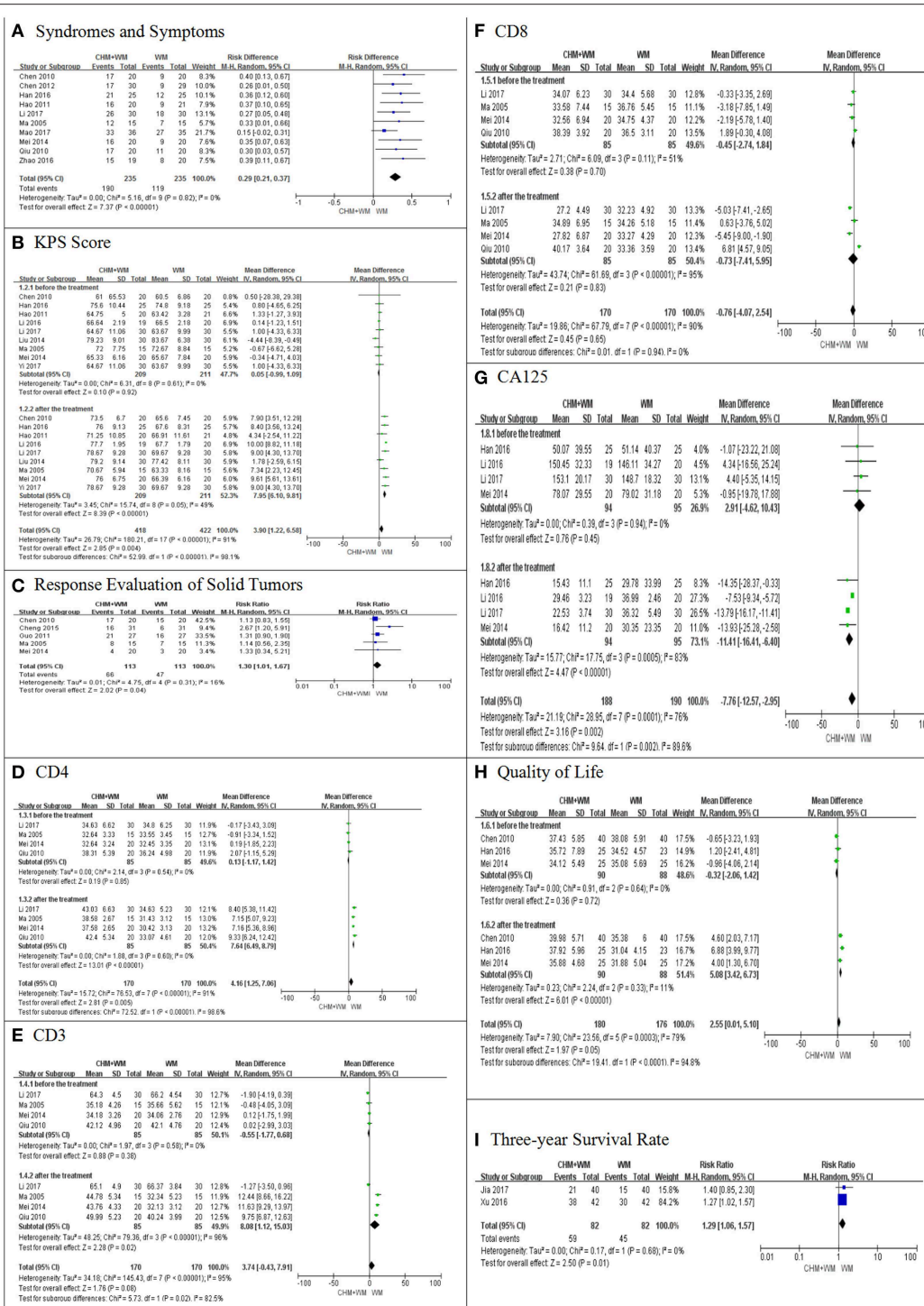


FIGURE 2 | Meta-analysis on efficacy. (A–I) showed the comparisons and meta-analyses on efficacy between CHM-WM group and WM group. The I2 statistic described the percentage of total variation across studies that was due to heterogeneity rather than chance. CI indicated the confidence interval. Dichotomous data were presented as pooled Risk Ratio (RR) with 95% confidence intervals (95% CIs), while continuous data were presented as Mean Difference (MD) with 95% CIs.

DISCUSSION

In this study, we reviewed the efficacy and safety of CHM in the treatment of OvC after reduction surgery and adjuvant chemotherapy. A total number of 18

trials involved 975 patients were included, 488 patients in CHM-WM group, and 487 patients in WM group. Meta-analysis indicated that using CHM combined with WM improves the efficacy and safety of treatment on OvC patients.

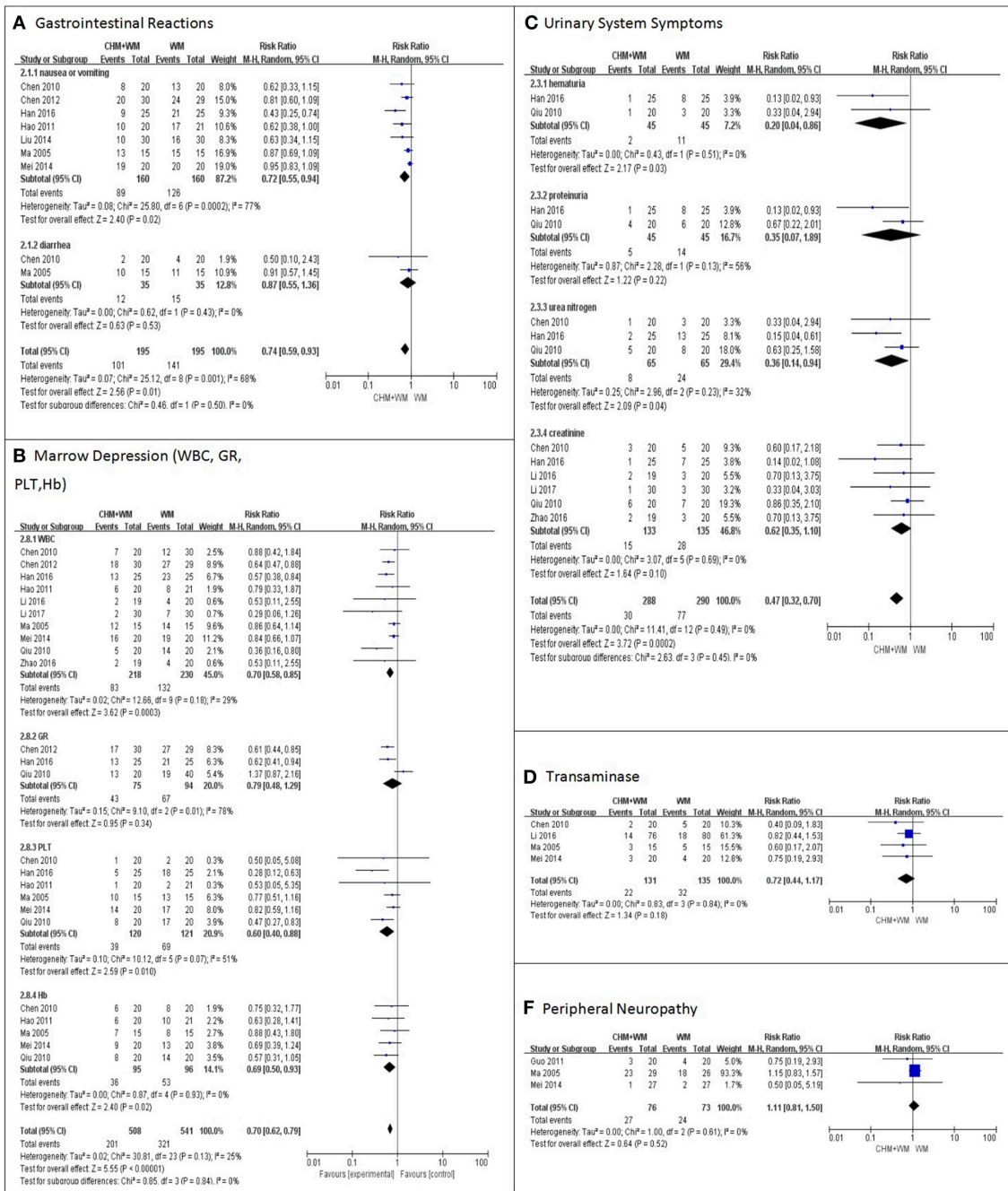


FIGURE 3 | Meta-analysis on safety. (A–F) shown the comparisons and meta-analysis on safety between CHM-WM group and WM group. The I2 statistic described the percentage of total variation across studies that was due to heterogeneity rather than chance. CI indicated the confidence interval. Dichotomous data were presented as pooled Risk Ratio (RR) with 95% confidence intervals (95% CIs).

The meta-analysis showed that the improvements of TCM syndromes and symptoms, KPS Scores, CD4, CA125, and 3-years survival rate in CHM-WM group were significantly better than WM group. These results implied that, compared with WM alone treatment, CHM combined with WM treatment can improve the symptoms and quality of life, consolidating the curative effects and alleviating the pain of OvC patients. There are no special symptoms in the early stage of OvC, and

the methods for screening and early detection of OvC are still lacking. Therefore, most of the OvC patients were diagnosed at late stage, resulting in a poor prognosis (44). Although the adjuvant platinum-based chemotherapy is a therapeutically effective treatment after tumor debulking reduction surgery, adverse effects of chemotherapy, and high tumor recurrence are still a major problems for OvC patients (45). The application of CHM is extensive and profound, and there are a solid theoretical

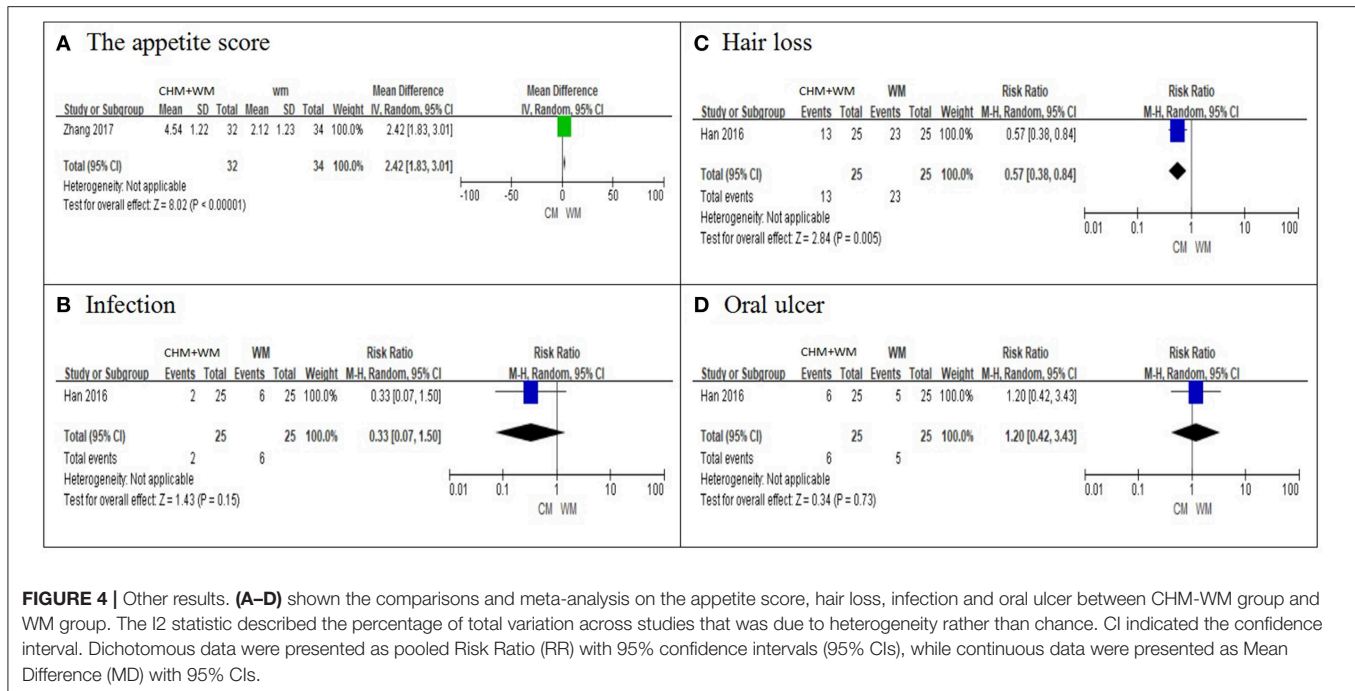


FIGURE 4 | Other results. (A–D) show the comparisons and meta-analysis on the appetite score, hair loss, infection and oral ulcer between CHM-WM group and WM group. The I² statistic described the percentage of total variation across studies that was due to heterogeneity rather than chance. CI indicated the confidence interval. Dichotomous data were presented as pooled Risk Ratio (RR) with 95% confidence intervals (95% CIs), while continuous data were presented as Mean Difference (MD) with 95% CIs.

foundation and rich clinical experience in the treatment of cancer with CHM. Although CHM cannot inhibit the growth of tumors, CHM plays an important role in reinforcing healthy Qi, regulating the disharmony of Yin-Yang, Qi-Blood, and Zang-Fu, enhancing the patients' resistance, etc. These could be reflected by the improvement of performance status, TCM syndromes, and symptoms in the clinical trials.

Compared with WM group, the adverse effects including gastrointestinal reaction, marrow suppression, liver and kidney dysfunction and infection were significantly reduced in CHM-WM group. It implied that CHM combined with WM treatment could reduce the side effects caused either by the cancer itself or by the chemotherapy used in treating OvC. The toxic effects, medical complications and the poor quality of life are common, though surgery, radiotherapy, and chemotherapy have very good anti-cancer outcomes. Clinically, CHM combined with WM treatment not only provides higher clinical efficacy and longer survival time for patients, but also have therapeutically effects on alleviating and preventing the side effects of surgery, radiotherapy and chemotherapy. The mechanisms could be the formula was aimed at reducing the chemotherapy-induced side-effects, and some of the individual herbs included were also shown to have anti-oxidant and cytotoxic activities and they might also enhance cellular immunity

There are limitations in the study. Firstly, the methodology quality of the included RCTs was generally not high. Although all the studies claimed that randomization has been applied, only one study list the details of the randomized schemes and instructions. Six studies mentioned the application of "random number table" but without further details. The rest of studies only mentioned "randomization," and we failed to get confirmation by contacting the original authors. Secondly, only one study reported blinding. We considered blinding was not carried out

in most of the clinical studies due to clinical trial ethics on the treatment for cancer patients. Additionally, the included studies were mostly small sample sized. Thirdly, the CHM formula included studies which were different or not exactly the same. Based on TCM theory, personalized individual treatment plan should be applied according to the patient's condition individually. So, our conclusion of this review is referring to the general concept of CHM, but not to individual CHM formula or individual herb.

CONCLUSION

In conclusion, the results showed that CHM significantly improved symptoms and enhanced curative effects. CHM also showed the unique superior chemotherapy tolerance in quality of patient's life and minimal toxic and adverse effects due to chemotherapy. So, our review and meta-analysis have provided evidence on the efficacy and safety of CHM for ovarian cancer after reduction surgery and adjuvant chemotherapy, but rigorously designed and large-scale RCTs are still needed in the future.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

LL contributed conception and design of the study. LL, YL, RW, and QS organized the databases. RW, QS, FW, YL, HT, and WH performed the statistical analysis and prepared the figures and tables. LL, RW, QS, and FW wrote the first draft of the

manuscript. YL, XL, TC, XW, HT, MZ, SZ, and YX wrote the sections of the manuscript. CW modified the English of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2019.00730/full#supplementary-material>

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