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Original Article

Meta-analysis of efficacy of Chinese medicine compound combined with concurrent radiotherapy and chemotherapy in the treatment of locally advanced nasopharyngeal carcinoma

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Abstract: Background: Nasopharyngeal carcinoma is a prevalent malignant tumor in clinical practice, with the highest incidence rate among otorhinolaryngological malignant tumors. Objectives: This study aims to comprehensively evaluate the clinical efficacy and safety of traditional Chinese medicine compound (CMC) combined with concurrent radiotherapy and chemotherapy in the treatment of locally advanced nasopharyngeal carcinoma (LA-NPC). Methods: Relevant essays published before November 20, 2021, were retrieved from China National Knowledge Internet (CNKI), China Science and Technology Journal Database (CQVIP), Wanfang database, PubMed, and Web of Science databases. Randomized controlled trials regarding the clinical efficacy of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of LA-NPC were included. Results: A total of 15 publications involving 1324 patients were included in this study, including 665 in the experimental group and 659 in the control group. Meta-analyses revealed that compared with radiotherapy or chemotherapy only, CMC combined with concurrent radiotherapy and chemotherapy for LA-NPC significantly improved the efficacy [risk ratio (RR)=1.15, 95% confidence interval (95% CI) (1.09, 1.20), $P<0.00001$], the quality of life [RR=1.35, 95% CI (1.13, 1.62), $P=0.0009$], immune function indices CD4+ levels [RR=6.2, 95% CI (3.64, 8.76), $P<0.00001$], CD4+/CD8+ [RR=0.33, 95% CI (0.14, 0.53), $P=0.0009$], and alleviated the decrease in white blood cell counts [RR=0.67, 95% CI (0.52, 0.86), $P=0.002$]. Conclusion: CMC combined with concurrent radiotherapy and chemotherapy for the treatment of LA-NPC can significantly improve the efficacy and reduce severe adverse reactions caused by conventional radiotherapy and chemotherapy. However, due to limitations in the quantity and quality of the included studies, more high-quality, multi-center, and large sample-size studies are needed to provide high-level and high-quality medical evidence for systematic evaluation.

Keywords: Locally advanced nasopharyngeal carcinoma, radiotherapy, chemotherapy, Chinese medicine compound, meta-analysis

Introduction

Nasopharyngeal carcinoma is a common malignant tumor in clinical practice, and its incidence ranks first among otorhinolaryngological malignant tumors [1]. Its symptoms mainly include nasal congestion, ear stuffiness, headache, and diplopia, which seriously affect the hearing and vision of patients, and may even damage the brain nerve, resulting in death [2]. It has been shown that approximately 80% of global nasopharyngeal carcinoma cases occur in China, with a higher prevalence observed in southern China. Furthermore, approximately 75% of patients are diagnosed at advanced stages of the disease [3]. Therefore, timely and effective treatment is extremely important for patients with locally advanced nasopharyngeal carcinoma (LA-NPC). Currently, radiotherapy and chemotherapy are treatment options for LA-NPC [4]. Due to the insidious lesions of nasopharyngeal carcinoma and the lack of typical early-stage manifestations, most patients develop symptoms in intermediate and late

Table 1. Literature inclusion according to PICOS strategy

PICOS	Inclusion criteria
Participants (P)	① published literature of randomized controlled clinical studies of CMC combined with concurrent radiotherapy and chemotherapy for the treatment in patients with LA-NPC, whether blinded or not; ② original prospective clinical trial studies; ③ patients who were pathologically confirmed with primary diagnosis as nasopharyngeal carcinoma at primary diagnosis and whose clinical stage was locally advanced
Intervention (I)	CMC, radiotherapy, chemotherapy
Comparison (C)	Radiotherapy, chemotherapy
Outcome (C)	① evaluation efficacy of solid tumor; ② change in the quality-of-life KPS score; ③ immune index functional T-cell subsets CD3+, CD4+, CD8+, CD4+/CD8+
Study design (S)	RTC

stages of the disease, and the treatment efficacy is not very satisfactory. In addition, many clinical studies [5] have shown that adverse reactions are common after radiotherapy and chemotherapy, such as bone marrow suppression, gastrointestinal reactions, anemia, platelet reduction, and oral mucositis, resulting in termination of radiotherapy and chemotherapy. Therefore, further optimization of the treatment protocols for nasopharyngeal carcinoma has been the focus of attention.

To further improve the clinical efficacy, many scholars have combined traditional Chinese medicine compound (CMC) with conventional radiotherapy and chemotherapy for nasopharyngeal carcinoma and achieved satisfying outcomes, including enhanced sensitivity of radiotherapy and chemotherapy, reduced incidence of distant metastasis and adverse reactions, and improved physical function, thus improving the overall efficacy [6]. Studies on CMC combined with concurrent radiotherapy and chemotherapy for LA-NPC are on the rise, but many studies lack sufficient sample size, which may affect the reliability of the results. For this reason, we conducted a meta-analysis on randomized controlled trials (RCTs) related to CMC combined with concurrent radiotherapy and chemotherapy for patients with advanced nasopharyngeal carcinoma, aiming to provide a basis for the safety and efficacy of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of patients with LA-NPC.

Materials and methods

Literature retrieve

The databases for the literature search included China National Knowledge Internet (CNKI), China Science and Technology Journal Database (CQVIP), Wanfang database, PubMed, and Web of Science database. The search period was from the establishment of each database to November 20, 2021. The RCTs about the efficacy of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of patients with LA-NPC were collected. The search terms included "locally advanced nasopharyngeal carcinoma", "Detoxification and pharyngeal soup", "Compound Banmao injection", "Compound Kushen injection", "Zijinlong", "Shenqi Fuzheng injection", "simultaneous radiotherapy and chemotherapy", and "nasopharyngeal tumors", and essays were searched using a combination of keywords and free words. The specific steps were as follows:

#1. "Traditional Chinese medicine" OR "Chinese medicine" OR "Chinese medicine compound" OR "nasopharyngeal tumors".

#2. "Detoxification and pharyngeal soup" OR "Compound Banmao" OR "Compound Kushen injection" OR "Zijinlong" OR "Shenqi Fuzheng injection" OR "simultaneous radiotherapy and chemotherapy" OR "nasopharyngeal tumors".

This study was conducted following the PRISMA statement [7].

Inclusion and exclusion criteria

The literature inclusion was performed according to the PICOS strategy (**Table 1**).

Exclusion criteria: (i) studies involving animal subjects; (ii) there was no control group; (iii) it was not an RCT; (iv) the outcome indicators and outcome measures were not available; (v) the types of studies were review, commentary,

case report, and meta-analysis study, etc.; (vi) literature inconsistent with the study topic.

Data extraction

A data extraction form was created, and two investigators independently performed literature screening, data extraction, and cross-checking based on predefined inclusion and exclusion criteria. In case of any doubt or disagreement, a third researcher joined the discussion, and the decision was made through consensus. Data extraction: title of literature, first author, year of publication, sample size and interventions, course of treatment, primary outcome indicators, and secondary outcome indicators. The primary outcome indicators included efficacy, while the secondary outcome indicators included Karnofsky performance status (KPS) score regarding the quality of life, immune function related T-cell subpopulation indicators, adverse reactions, such as the decrease in white blood cells (WBC), nausea and vomiting, hepatic damage, oral mucositis, thrombocytopenia, and anemia.

Quality evaluation

The quality of the included literature was assessed using the risk of bias assessment tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions. The assessment evaluated various aspects such as randomization, allocation concealment, blinding, integrity of outcome data, selective reporting of study results, and other potential sources of bias. Each item was categorized as "high risk", "low risk" and "unclear". Risk propensity was produced by RevMan5.4.

Statistical analysis

The data were combined and tested for heterogeneity using RevMan 5.4 software, and a meta-analysis was performed. Statistical heterogeneity among literature was analyzed by the I^2 test. $P<0.05$ and $I^2\geq50\%$ indicated statistical heterogeneity among literature, and meta-analysis was performed with a random effect model; $P\geq0.05$ or $I^2<50\%$ indicated that there was no statistical heterogeneity among literature, and meta-analysis was performed with a fixed-effects model. Categorical variables were described by risk ratio (RR) with 95% confidence interval (CI), and continuous variables were described by standardized mean difference (SMD) with 95% CI. When $I^2\geq50\%$, subgroup analysis and sensitivity analysis were performed to explore the source of heterogeneity. Funnel plots were plotted to analyze whether there was a publication bias in the included literature, and Egger's test was carried out on the symmetry of the funnel plot. $P<0.05$ was considered to be statistically significant.

Results

Search process and results

A total of 2021 papers were initially identified from multiple databases, and 15 studies involving 1297 patients were finally included after a hierarchical screening process. The literature screening process and assessment of bias are presented in **Figures 1** and **2**, respectively.

Inclusion of studies

A total of 15 studies were included [8-22], covering 1324 patients, with 665 in the experimental group and 659 in the control group. The maximum/minimum number of patients included in each study was 79/30, and the treatment duration for the included patients ranged from 4 weeks to 12 weeks. The specific characteristics and quality evaluation of the included literature are shown in **Table 2**.

Meta-analysis results

Short-term efficacy: The 15 included papers [8-22] (1324 cases) had observed the efficacy of CMC combined with concurrent radiotherapy and chemotherapy for LA-NPC. Due to the small heterogeneity ($P=0.02$, $I^2=48\%$), a meta-analysis was performed using a fixed effect model. The results showed that CMC combined with concurrent radiotherapy and chemotherapy could significantly improve the efficacy compared with the control group [RR=1.15, 95% CI (1.09, 1.20), $P<0.00001$] (**Figure 3**).

KPS score regarding the quality of life: A total of 6 papers [8, 13, 14, 16, 18, 21] reported the KPS scores, including 266 patients in the experimental group and 263 patients in the control group. No statistical heterogeneity was found between studies ($P=0.39$, $I^2=4\%$). Compared with the control group, CMC combined with concurrent radiotherapy and chemothera-

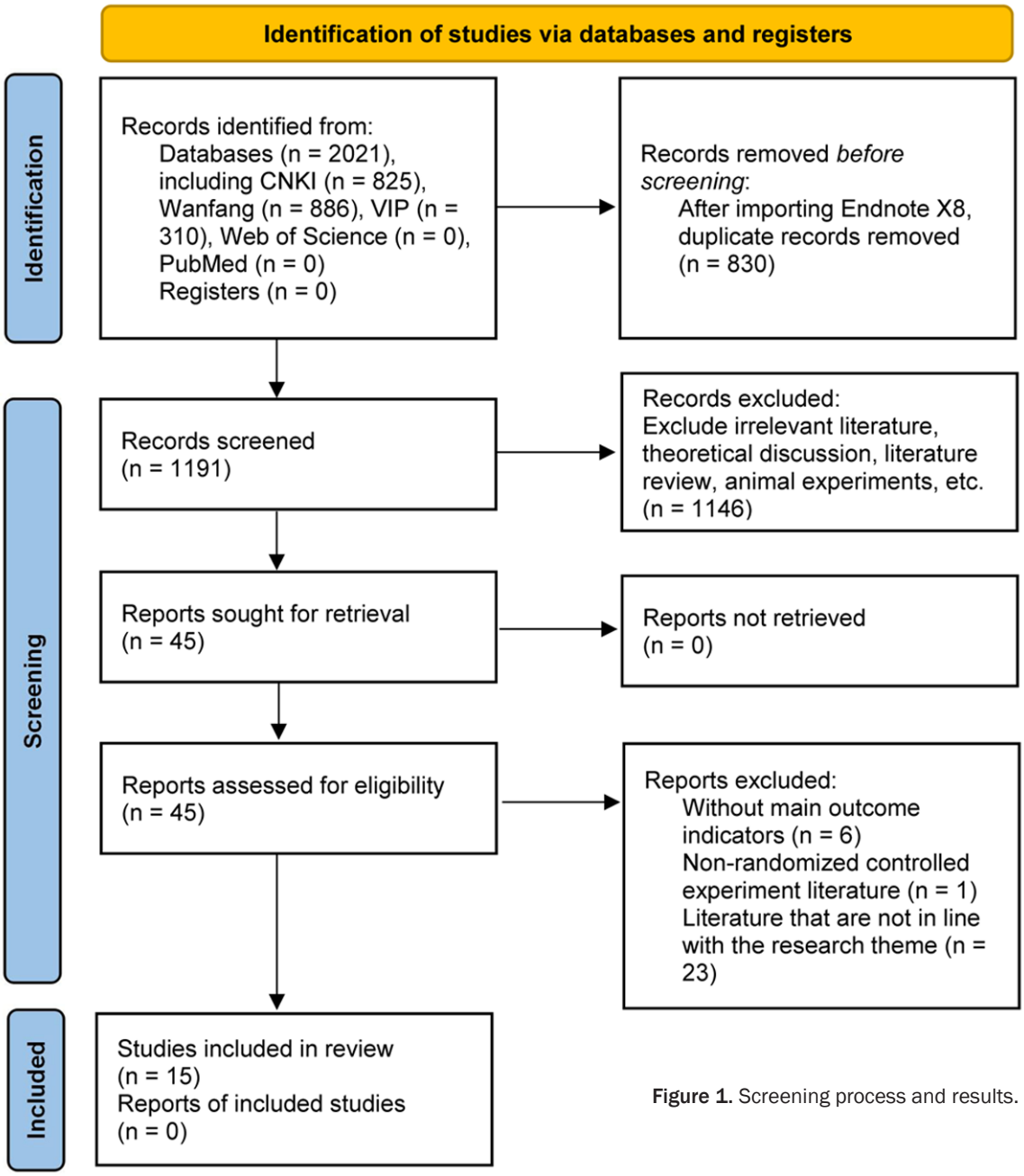


Figure 1. Screening process and results.

py could significantly improve the quality of life of the patients [RR=1.35, 95% CI (1.13, 1.62), *P*=0.0009, **Figure 4**].

Immune function-related T-cell subpopulation indicators

CD4+: A total of 7 papers on CD4+ were screened, but only 4 [8, 11, 17, 21] papers were included in this study. As they were continuous variables, the mean difference (MD) was used for meta-analysis, and due to the large heterogeneity (*P*<0.00001, I^2=96%), a random effect model was used. The results showed that compared with the control group, CMC combined with concurrent radiotherapy and chemotherapy produced a significant increase in CD4+ activity [RR=6.2, 95% CI (3.64, 8.76), *P*<0.00001, **Figure 5A**].

CD4+/CD8+: A total of 7 papers on CD4+/CD8+ were screened, but only 6 [8, 10, 11, 17, 21,

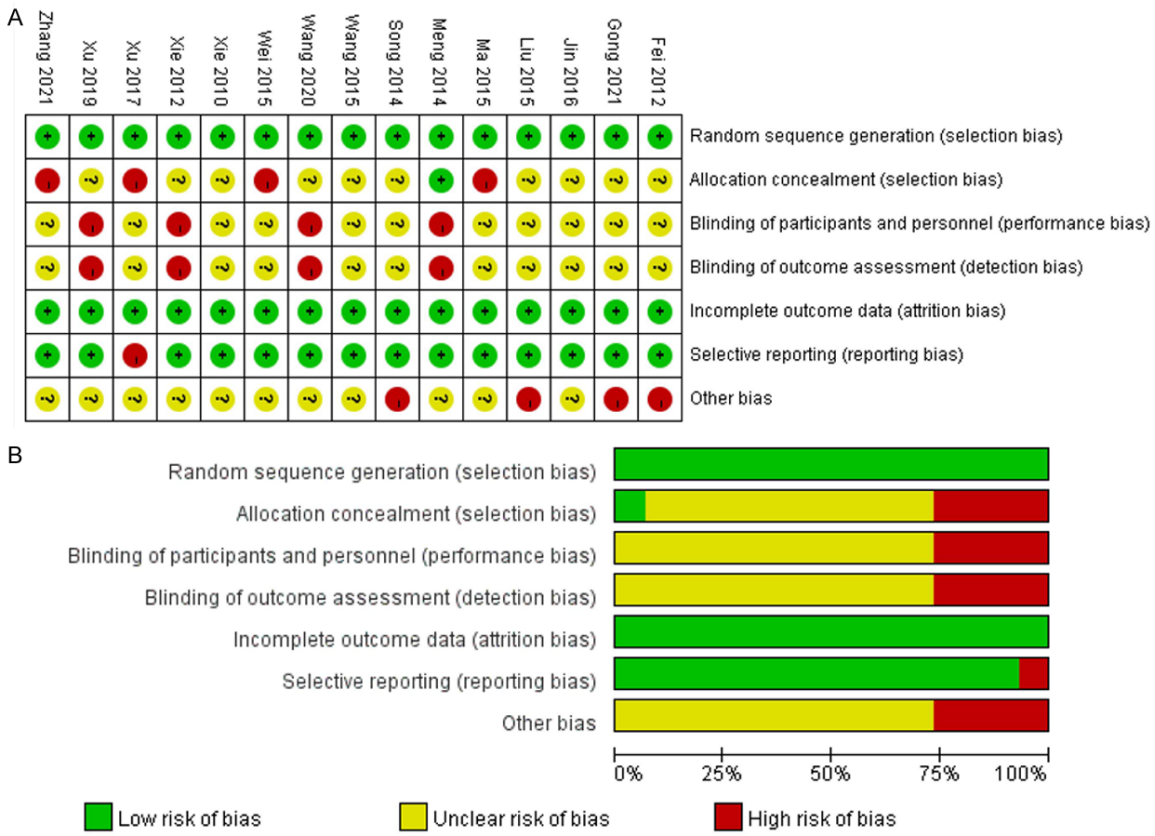


Figure 2. Quality evaluation of included studies. A. Risk of bias assessment of included studies: low-risk bias (+), high-risk bias (-), unclear risk bias (?); B. Bar graph of the comparison of the percentage of risk bias for each included study, with green indicating low risk of bias, yellow indicating unclear risk of bias, and red indicating high risk of bias.

22] papers were included in this study, comprising 259 patients in the experimental group and 251 patients in the control group. There was large heterogeneity among studies ($P<0.00001$, $I^2=94\%$). Analysis of the results showed that CMC combined with concurrent radiotherapy and chemotherapy produced a significant increase in CD4+/CD8+ compared with the control group [RR=0.33, 95% CI (0.14, 0.53), $P=0.0009$, **Figure 5B**].

Adverse reactions

Decrease in WBC: Nine papers reported a decrease in WBC [8-10, 12, 14, 16, 18, 21, 22], including 415 patients in the experimental group and 411 patients in the control group. There was large heterogeneity among studies ($P<0.00001$, $I^2=86\%$). The analysis of the results showed that CMC combined with concurrent radiotherapy and chemotherapy significantly alleviated the decrease in WBC compared with the control group [RR=0.67, 95% CI (0.52, 0.86), P=0.002, **Figure 6A**].

Nausea and vomiting: Six papers reported nausea and vomiting [8, 10, 12, 18, 21, 22], including 270 patients in the experimental group and 269 patients in the control group. There was large heterogeneity among studies ($P<0.0001$, $I^2=82\%$). Analysis of the results showed that CMC combined with concurrent radiotherapy and chemotherapy significantly improved nausea and vomiting compared with the control group [RR=0.76, 95% CI (0.6, 0.97), $P=0.03$, **Figure 6B**].

Hepatic damage: Five papers reported hepatic damage [8, 9, 12, 16, 21], including 231 patients in both the experimental and control groups. There was small heterogeneity among studies ($P=0.69$, $I^2=0\%$). Analysis of the results showed that CMC combined with concurrent radiotherapy and chemotherapy significantly

Table 2. Basic characteristics

No.	Author/year	Number (experimental group/control group)	Staging	Intervention (experimental group/control group)	Duration of treatment (experimental/control group)	Outcome indicators
1	Liu et al. 2015	30/30	III to IVa	Shenqi Fuzheng Injection+RT+CT/RT+CT	6 weeks/6 weeks	①②③④⑤⑥⑦⑧⑨⑩
2	Meng et al. 2014	40/40	III~IVb	Compound banmao Capsules+RT+CT/RT+CT	6 weeks/6 weeks	①④⑤⑨⑩⑪⑰
3	Gong et al. 2021	79/78	III~IVb	Compound banmao injection+RT+CT/RT+CT	7 weeks/7 weeks	①③④⑤⑥⑦⑧⑪⑫⑬⑭
4	Xu et al. 2019	30/30	III to IVa	Compound Kushen injection+RT+CT/RT+CT	12 weeks/12 weeks	①③⑯
5	Song et al. 2014	56/56	III~IVb	Compound Kushen injection+RT+CT/RT+CT	4 weeks/4 weeks	①④⑤⑥⑦⑧⑨⑰⑱
6	Wang et al. 2015	56/56	III~IVb	Compound Kushen injection+RT+CT/RT+CT	4 weeks/4 weeks	①②⑰
7	Xie et al. 2012	45/42	III to IVa	Compound Kushen injection+RT+CT/RT+CT	7 weeks/7 weeks	①②④⑲
8	Jin et al. 2016	42/40	III to IVa	Compound Kushen injection+RT+CT/RT+CT	6 weeks/6 weeks	①③⑳
9	Fei et al. 2012	60/60	III to IVa	Compound Kushen injection+RT+CT/RT+CT	8 weeks/8 weeks	①②④⑨⑩⑫⑮⑲
10	Zhang et al. 2021	55/55	III~IVb	Detoxification and pharyngeal soup+RT+CT/RT+CT	9 weeks/9 weeks	①③
11	Xie et al. 2010	30/30	III to IVa	Shenqi Fuzheng Injection+RT+CT/RT+CT	6 weeks/6 weeks	①②④⑤⑦⑧
12	Xu et al. 2017	40/40	III to IVa	Chinese herbal compound soup+RT+CT/+RT+CT	7 weeks/7 weeks	①⑦⑫⑲⑳
13	Wei 2015	27/27	III to IVa	Compound Kushen injection+RT+CT/RT+CT	6 weeks/5 weeks	①⑦⑫⑳
14	Ma et al. 2015	45/45	III to IVa	ZiLongJin tablets+RT+CT/RT+CT	6 weeks/6 weeks	①②③④⑤⑥⑦⑧⑨⑩
15	Wang et al. 2020	30/30	III to IVa	Qing Run Liyan Decoction+RT+CT/RT+CT	6 weeks/6 weeks	①③④⑥⑦⑧⑪⑰⑲

Note: ① efficacy evaluation of solid tumors; ② change in quality of life KPS score; ③ immune index functional T-cell subsets CD3+, CD4+, CD8+, CD4+/CD8+; ④ leukopenia; ⑤ decreased platelets; ⑥ anemia; ⑦ oral mucositis; ⑧ nausea and vomiting; ⑨ liver impairment; ⑩ renal impairment; ⑪ neutropenia; ⑫ gastrointestinal reaction; ⑬ fatigue; ⑭ alanine aminotransferase, aspartate transaminase elevation; ⑮ Candida albicans infection; ⑯ serum matrix metalloproteinase-2, bone alkaline phosphatase, and vascular endothelial growth factor levels; ⑰ survival rate; ⑱ cervical dermatitis; ⑲ cutaneous radiation injury; ⑳ bone marrow suppression; Parotid EI; Head and neck cancer (quality-of-life instruments for cancer patients-head and neck cancer, QLICP-HN) score; RT: radiotherapy; CT: chemotherapy.

improved liver impairment compared with the control group [RR=0.40, 95% CI (0.24, 0.67), P=0.0005, **Figure 6C**].

Oral mucositis: Oral mucositis is an adverse reaction, which was reported in 8 papers [8, 10, 12, 18-22], including 337 patients in the experimental group and 336 patients in the control group. There was large heterogeneity among studies (P<0.00001, I^2=89%). CMC combined with concurrent radiotherapy and chemotherapy didn't reduce significantly the incidence of oral mucositis compared with the control group [RR=0.95, 95% CI (0.82, 1.09), P=0.43, **Figure 6D**].

Thrombocytopenia: Thrombocytopenia is an adverse reaction, which was reported in 6 papers [8-10, 12, 18, 21], including 290 patients in the experimental group and 289 patients in the control group. There was large heterogeneity among studies (P=0.02, I^2=62%). CMC combined with concurrent radiotherapy and chemotherapy didn't significantly reduce

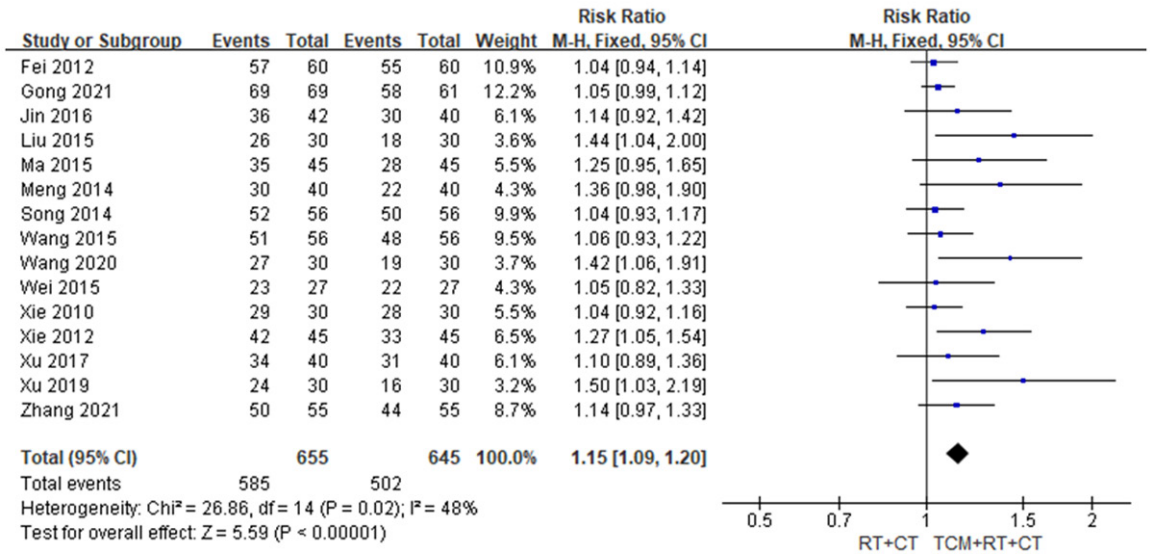


Figure 3. Meta-analysis of the efficacy of CMC combined with concurrent radiotherapy and chemotherapy for locally advanced nasopharyngeal carcinoma. CMC: Chinese medicine compound.

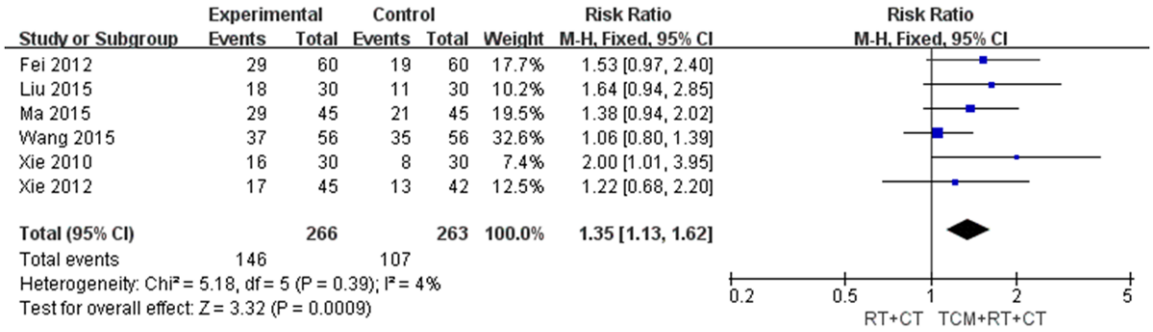


Figure 4. Meta-analysis of quality-of-life KPS scores. KPS: Karnofsky performance status.

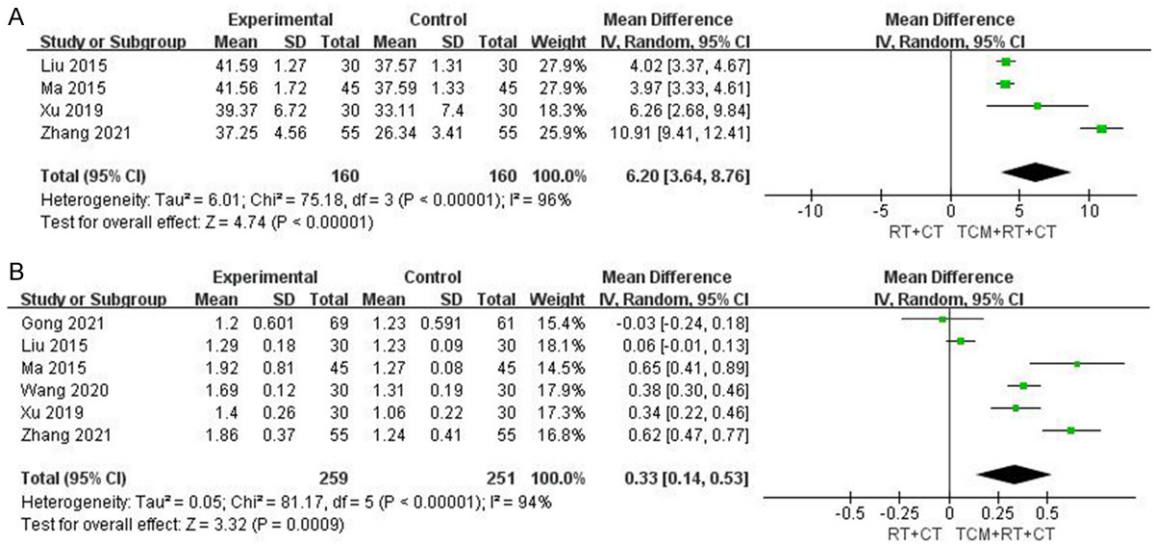
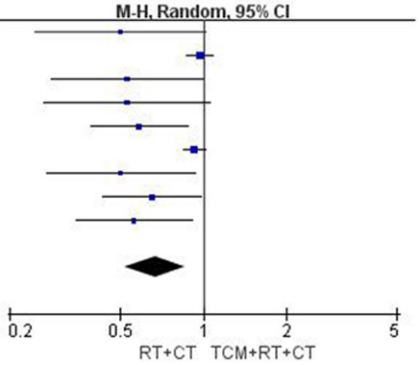


Figure 5. Meta-analysis of CD4+ and CD4+/CD8+ levels. A. CD4+; B. CD4+/CD8+ levels.

A

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fei 2012	9	60	18	60	7.2%	0.50 [0.24, 1.02]
Gong 2021	69	79	70	78	17.0%	0.97 [0.87, 1.09]
Liu 2015	9	30	17	30	8.3%	0.53 [0.28, 0.99]
Ma 2015	9	45	17	45	7.4%	0.53 [0.26, 1.06]
Meng 2014	17	40	29	40	12.0%	0.59 [0.39, 0.88]
Song 2014	51	56	55	56	17.2%	0.93 [0.85, 1.01]
Wang 2020	9	30	18	30	8.4%	0.50 [0.27, 0.93]
Xie 2010	15	30	23	30	11.9%	0.65 [0.43, 0.98]
Xie 2012	15	45	25	42	10.6%	0.56 [0.35, 0.91]
Total (95% CI)		**415**		**411**	**100.0%**	**0.67 [0.52, 0.86]**
Total events	203		272			

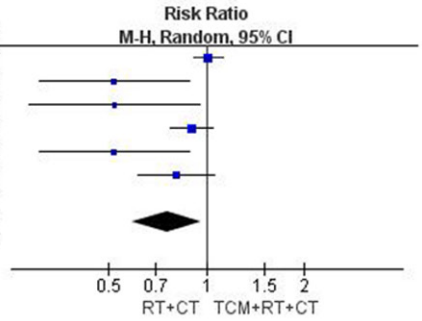
Heterogeneity: Tau² = 0.09; Chi² = 55.18, df = 8 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.16 (P = 0.002)



B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gong 2021	72	79	70	78	24.3%	1.02 [0.92, 1.12]
Liu 2015	11	30	21	30	11.6%	0.52 [0.31, 0.89]
Ma 2015	11	45	21	45	9.9%	0.52 [0.29, 0.96]
Song 2014	46	56	51	56	23.3%	0.90 [0.78, 1.04]
Wang 2020	11	30	21	30	11.6%	0.52 [0.31, 0.89]
Xie 2010	21	30	26	30	19.2%	0.81 [0.61, 1.06]
Total (95% CI)		**270**		**269**	**100.0%**	**0.76 [0.60, 0.97]**
Total events	172		210			

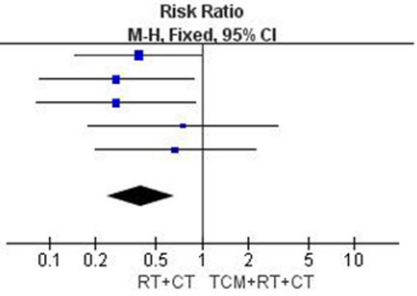
Heterogeneity: Tau² = 0.06; Chi² = 27.27, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 2.23 (P = 0.03)



C

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fei 2012	5	60	13	60	28.9%	0.38 [0.15, 1.01]
Liu 2015	3	30	11	30	24.4%	0.27 [0.08, 0.88]
Ma 2015	3	45	11	45	24.4%	0.27 [0.08, 0.91]
Meng 2014	3	40	4	40	8.9%	0.75 [0.18, 3.14]
Song 2014	4	56	6	56	13.3%	0.67 [0.20, 2.24]
Total (95% CI)		**231**		**231**	**100.0%**	**0.40 [0.24, 0.67]**
Total events	18		45			

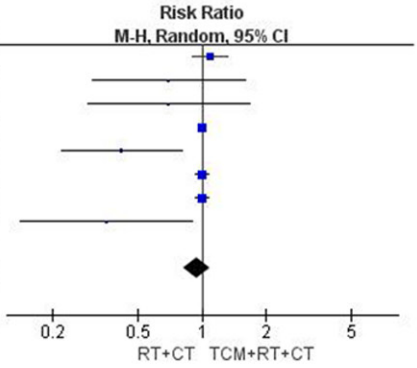
Heterogeneity: Chi² = 2.23, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)



D

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gong 2021	61	79	55	78	17.2%	1.10 [0.91, 1.32]
Liu 2015	7	30	10	30	2.5%	0.70 [0.31, 1.59]
Ma 2015	7	45	10	45	2.3%	0.70 [0.29, 1.68]
Song 2014	56	56	56	56	24.7%	1.00 [0.97, 1.04]
Wang 2020	8	30	19	30	3.8%	0.42 [0.22, 0.81]
Wei 2015	27	27	27	27	23.6%	1.00 [0.93, 1.07]
Xie 2010	30	30	30	30	23.8%	1.00 [0.94, 1.07]
Xu 2017	5	40	14	40	2.1%	0.36 [0.14, 0.90]
Total (95% CI)		**337**		**336**	**100.0%**	**0.95 [0.82, 1.09]**
Total events	201		221			

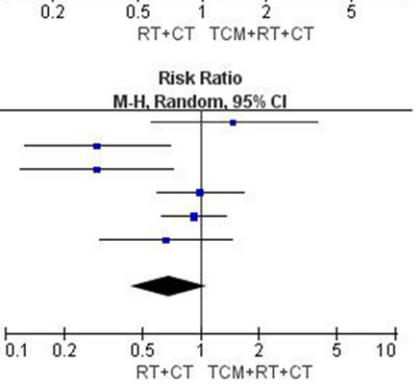
Heterogeneity: Tau² = 0.02; Chi² = 60.95, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.79 (P = 0.43)



E

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gong 2021	9	79	6	78	12.2%	1.48 [0.55, 3.96]
Liu 2015	5	30	17	30	14.1%	0.29 [0.12, 0.69]
Ma 2015	5	45	17	45	13.3%	0.29 [0.12, 0.73]
Meng 2014	17	40	17	40	21.1%	1.00 [0.60, 1.66]
Song 2014	26	56	28	56	23.8%	0.93 [0.63, 1.36]
Xie 2010	8	40	12	40	15.5%	0.67 [0.31, 1.45]
Total (95% CI)		**290**		**289**	**100.0%**	**0.69 [0.44, 1.09]**
Total events	70		97			

Heterogeneity: Tau² = 0.19; Chi² = 13.28, df = 5 (P = 0.02); I² = 62%
Test for overall effect: Z = 1.60 (P = 0.11)



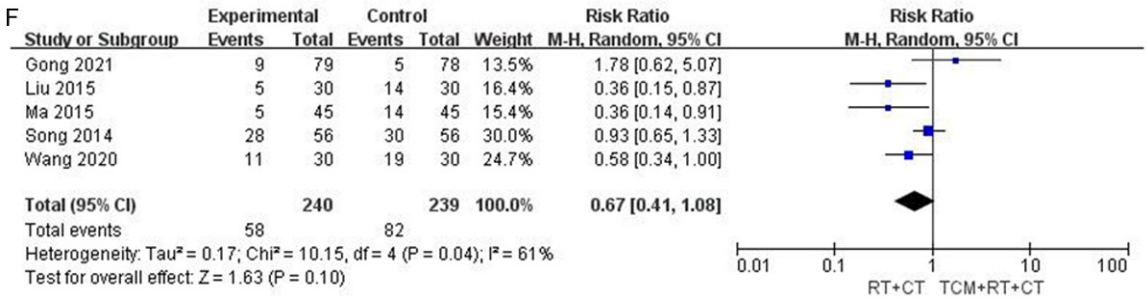


Figure 6. Meta-analysis of the incidence of WBC decrease, nausea and vomiting, hepatic damage, oral mucositis, thrombocytopenia, and anemia. A. Decrease in WBC; B. Nausea and vomiting; C. Hepatic damage; D. Oral mucositis; E. Thrombocytopenia; F. Anemia. WBC: white blood cells.

the incidence of thrombocytopenia compared with the control group [RR=0.69, 95% CI (0.44, 1.09), *P*=0.11, **Figure 6E**].

Anemia: Anemia is an adverse reaction, which was reported in 5 papers [8, 10, 12, 21, 22], including 161 patients in both the experimental and control groups. There was large heterogeneity among studies (*P*=0.04, I^2=61%). Analysis of the results showed that there was no significant difference in anemia between the two groups [RR=0.67, 95% CI (0.41, 1.08), *P*=0.10, **Figure 6F**].

Sensitivity analysis

According to the meta-analysis results of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of LA-NPC, for the outcome indicators with heterogeneity, one study was arbitrarily excluded for sensitivity analysis, and effect sizes were combined again respectively. The new combined results were compared with the combined results before exclusion. No significant change was observed in the effect size and *P* value of each outcome measurement, indicating that the results of this study had high stability, so the reliability of this study was high.

Subgroup analysis

In the 15 included studies, Compound Kushen injection, Compound Banmao capsule, Compound Banmao injection, Shenqi Fuzheng injection, detoxification and pharyngeal soup, self-designed prescription, and other prescriptions combined with radiotherapy and chemotherapy were used for the treatment of the disease. Therefore, the subgroup analysis was carried out with the traditional Chinese medicine prescriptions used in the study.

The results showed that among the included literature, Compound Kushen injection was used in 7 literataure [11-16, 20], Compound Banmao capsule/injection was used in 2 literature [9, 10], Shenqi Fuzheng injection was used in 2 literature [8, 18], detoxification and pharyngeal soup was used in 2 literature [17, 22], and other traditional Chinese medicines were used in 2 literature [19, 21]. The results showed a significant difference in efficacy between the control group and the experimental group in the studies using Compound Kushen injection and detoxification and pharyngeal soup, but no significant difference in efficacy between the control group and the experimental group in the subgroups of other traditional Chinese medicines, as detailed in **Figure 7**.

Analysis of publication bias

With a standard error of RR and logRR as variables, funnel plots were drawn for the therapeutic efficacy of the included studies, and the results showed that the left and right funnel plots were asymmetrical and presented a skewed distribution, as shown in **Figure 8**. Egger's test was carried out, and the result showed that P<0.005, suggesting that there might be some publication bias, as shown in **Table 3** and **Figure 9**. This may be due to the use of different types of traditional Chinese medicine prescriptions.

Discussion

LA-NPC has a great impact on patient's health and quality of life [23]. Due to its concealed

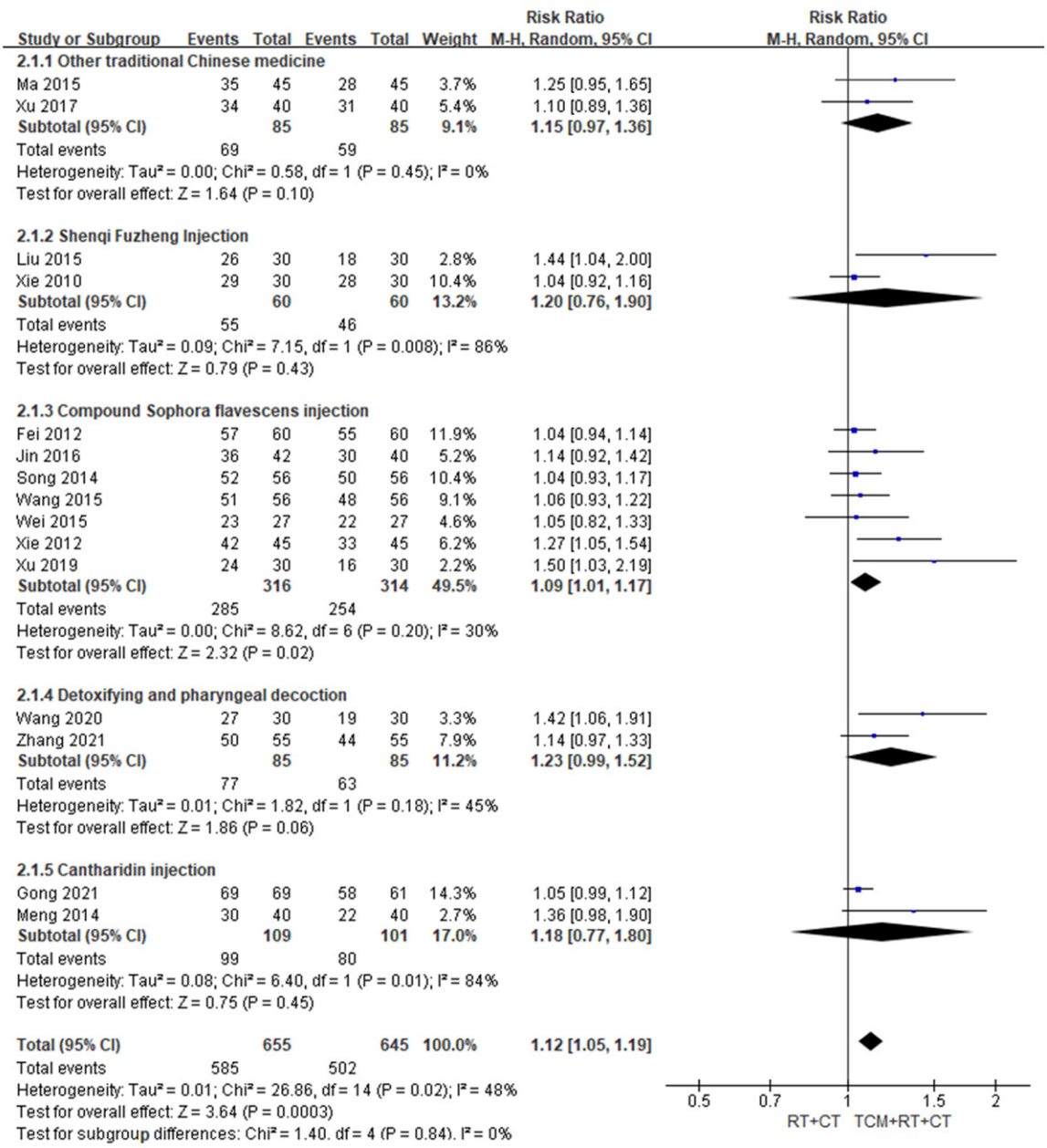


Figure 7. The subgroup analysis of the studies on the compatibility of different prescriptions.

location and insidious early symptoms, most patients have progressed to a locally advanced stage by the time of first diagnosis [24]. Therefore, it is imperative to provide timely and effective treatment. While the term "locally advanced nasopharyngeal carcinoma" does not exist in ancient Chinese medical books, it can be classified into the categories of "glanders", "rhinopolypus" and "upper stony flat abscess" according to its clinical manifestations and signs [25]. Ancient doctors have recognized that it is an extremely dangerous disease with a very poor prognosis. With the continuous development of medical science and technology, patients with nasopharyngeal carcinoma can survive longer through radiotherapy and chemotherapy. However, the adverse reactions of chemotherapy drugs and radiation on patients greatly affect the quality of life of patients. A large number of clinical studies have shown that TCM combined with concurrent radiotherapy and chemotherapy

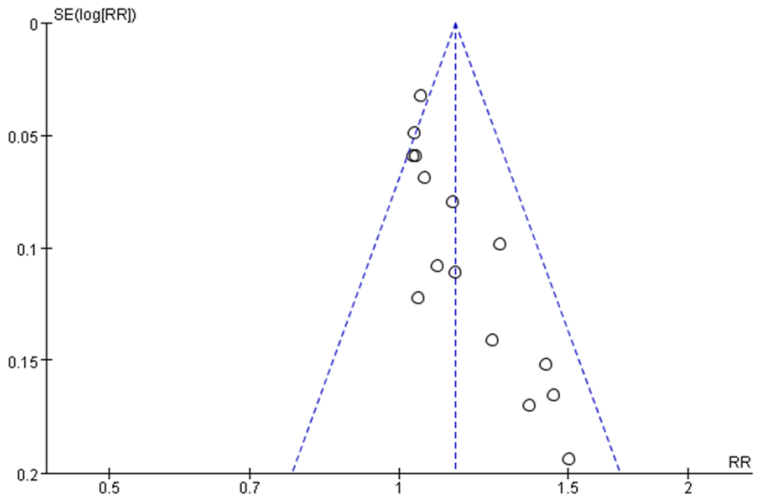


Figure 8. Funnel plots of therapeutic efficacy.

Table 3. Egger's test

Std_Eff	Coef.	Std. Err.	*t*	*P*>|*t*|	[95% Conf. Interval]	
Slope	0.9459555	0.0308985	30.61	0.000	0.8792032	1.012708
Bias	2.214618	0.4236915	5.23	0.000	1.299288	3.129948

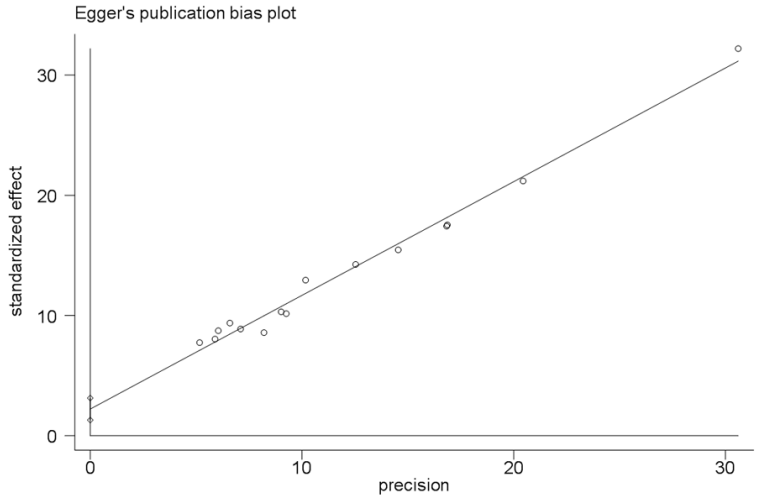


Figure 9. Egger's publication bias plot of therapeutic efficacy.

can significantly improve the recent and long-term efficacy than radiotherapy or chemotherapy alone, which can inhibit the survival of residual cancer cells, enhance the sensitivity of tumors to radiotherapy and chemotherapy, improve patients' quality of life, and reduce the adverse reactions of radiotherapy and chemotherapy [26, 27]. Many meta-analyses of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of tumors have shown that CMC combined with concurrent radiotherapy and chemotherapy can significantly improve the efficacy and quality of life of patients.

In this study, a meta-analysis of 15 RCTs of CMC combined with concurrent radiotherapy and chemotherapy in the treatment of LA-NPC was conducted. Among them, 7 studies used Compound Kushen injection, 2 studies used Compound Banmao capsule/injection, 2 studies used Shenqi Fuzheng injection, 2 studies used detoxification and pharyngeal soup, and 2 studies used other traditional Chinese medicines in combination with radiotherapy and chemotherapy. Shenqi Fuzheng injection is a traditional Chinese medicine injection with active ingredients extracted from radix astragali and Dangshen [28], in which radix astragali can enhance the function of T lymphocytes and regulate the immune function of tumor patients by increasing CD4 and CD8 levels, and Dangshen can increase the levels of leukocytes and hemoglobin in the body. Both radix astragali and Dangshen have anti-platelet aggregation effects and can reduce blood viscosity, which can play a certain effect in activating blood circulation and improving microcirculation [29]. Compound Kushen injection is a traditional CMC preparation extracted from matrine and Rhizoma heterosmilacis by modern technology [30]. Studies have shown that matrine can directly kill tumor cells, promote tumor cell differentiation and apoptosis without damaging normal cells, regulate the immune function of T cells and B cells, and relieve cancer pain and the adverse reactions caused by radiotherapy and chemotherapy [31]. Compound Banmao

capsule [32] is composed of 11 herbs such as rhizoma sparganii, ginseng, curcuma zedoary, Barbed Skullcap Herb, radix astragali, and glossy privet fruit, which contain a variety of antitumor active substances such as scirpusin, ginsenoside, oil of zedoary turmeric, and astragaloside, which can effectively inhibit the differentiation, proliferation, and migration of tumor cells, and also induce apoptosis of cancer cells and modulate the immunity of the body to achieve antitumor effects [33]. Detoxification and pharyngeal soup [34] is composed of 12 Chinese herbs, including Dangshen, radix rehmanniae recen, radix ophiopogonis, Radix Salviae Miltiorrhizae, upright ladybell root, coastal Glehnia root, Thunberg Fritillary Bulb, Schisandra chinensis, radix scrophulariae, Bunge corydalis herb, peppermint, and liquorice. Modern pharmacological studies have found that in this prescription, radix rehmanniae recen can accelerate the proliferation of stem cells, have anti-inflammation and antitumor effects, and can promote the synthesis of liver and kidney tissue protein, and both Danshen and Bunge corydalis herb can enhance the bactericidal and anti-inflammatory functions, etc. The whole formula has strong anti-inflammatory, antiseptic, and anti-tumor effects, improves cellular immune activity, enhances the immune function of tumor patients, improves the quality of life of patients, alleviates the adverse reactions caused by radiotherapy, and improves prognosis. It can be seen that the prescriptions used in the literature included in this study all have anti-inflammatory, anti-tumor, and immune function-enhancing abilities. In traditional Chinese medicine, prescriptions of Compound Kushen injection, Compound Banmao capsule, Shenqi Fuzheng injection, detoxification and pharyngeal soup, and self-designed prescription have been used as adjuvant therapy for patients with LA-NPC. However, the effectiveness of CMC as an adjunct therapy is still controversial in Western medicine. Therefore, this meta-analysis was conducted to evaluate the effect of CMC on patients with LA-NPC.

In this study, we conducted a meta-analysis on 15 RCTs regarding CMC combined with concurrent radiotherapy and chemotherapy for the treatment of patients with LA-NPC, including 665 experimental cases and 659 control cases. From the results, CMC combined with concurrent radiotherapy and chemotherapy could significantly improve the efficacy and improve the quality of life of patients. In addition, it could also improve the immune function of patients, which is the first line of defense against cancer and can eliminate cancer cells in normal tissues. However, radiotherapy and chemotherapy are also cytotoxic to normal cells in the body, and cannot selectively target cancer cells and normal cells, so it is very important to improve the body's immunity [35]. T cells composed of CD4+, CD8+, and other cell subsets can reflect the immune function of the body, among which CD4+ is an important regulatory cell subset, responsible for regulating immune response under normal conditions [36, 37], and the ratio of CD4+/CD8+ can reflect the immune function of the body, with a low ratio indicating low immunity. The results of this study showed that CMC combined with concurrent radiotherapy and chemotherapy in the treatment of LA-NPC could significantly improve the activity of CD4+ and the ratio of CD4+/CD8+, thus improving the cellular immune function of patients. Furthermore, the toxicity and adverse reactions during radiotherapy and chemotherapy are still important problems troubling physicians, which seriously affect the psychological and physical health of patients. Therefore, Chinese researchers are committed to exploring the advantages of traditional Chinese medicine to reduce the occurrence of adverse reactions to radiotherapy and chemotherapy. In our meta-analysis, it was also confirmed that the intervention of TCM preparations could reduce the related toxic and adverse effects associated with radiotherapy and chemotherapy, such as nausea and vomiting, leukocyte decline, and liver function damage, but there was no significant improvement in oral mucositis, thrombocytopenia, and anemia, which may be due to the relatively small number of studies included. The results of this meta-analysis were similar to the findings of CMC combined with concurrent radiotherapy and chemotherapy, indicating the general applicability of Chinese medicine in the treatment of nasopharyngeal carcinoma with high efficiency and low toxicity.

Limitations of study

There are some limitations: (1) although all studies adopted the treatment protocol of CMC

combined with concurrent radiotherapy and chemotherapy, there may be a certain degree of bias due to the inconsistency of the specific drugs used in radiotherapy and chemotherapy, as well as the inconsistency of the treatment duration; (2) many of the included studies only mentioned the term "randomization" without specifying the randomization method; (3) the number of studies and patients included was relatively small; (4) there was certain publication bias as indicated by funnel plots.

Conclusions

Through a meta-analysis of RCTs regarding CMC combined with concurrent radiotherapy and chemotherapy for LA-NPC patients, we found that CMC combined with concurrent radiotherapy and chemotherapy can effectively improve the treatment efficacy, and also reduce the severe adverse reactions caused by multiple sessions of radiotherapy and chemotherapy, thus improving the quality of life and immune function. However, due to the small number of included studies and the low quality in some of the literature, more high-quality, multi-center, and large-sample studies are still needed to provide high-level and high-quality evidence for systematic evaluation.

Disclosure of conflict of interest

None.

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