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SYSTEMATIC REVIEW AND META-ANALYSIS

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Chinese Herbal Medicine for Improving Quality of Life Among Nonsmall Cell Lung Cancer Patients

Overview of Systematic Reviews and Network Meta-Analysis

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Abstract: For patients with nonsmall cell lung cancer (NSCLC) receiving chemotherapy, current clinical evidence has indicated add-on benefit of Chinese herbal medicine (CHM) in improving quality of life (QoL). However, the relative performance among different CHM is unknown.

The aim of this overview of systematic reviews (SRs) and network meta-analyses (NMA) is to evaluate the comparative effectiveness of different CHM.

Seven electronic databases including both international databases and Chinese databases were searched.

SRs focus on randomized controlled trials (RCTs) with comparison of CHM plus chemotherapy against chemotherapy alone on QoL among NSCLC patients were considered eligible.

Data from RCTs were extracted for random effect pairwise meta-analyses. Pooled relative risk (RR) with 95% confidence interval (CI) was used to quantify the impact of CHM on QoL. NMA was used to explore the most effective CHM for improving QoL when used with chemotherapy.

From 14 SRs, 61 RCTs (n = 4247) assessing 11 different CHM were included. Result from pairwise meta-analyses showed 6 CHM (Kang-lai-te injection, Shei-qi-fu-zheng injection, Compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, and Shen-fu injection) has significant beneficial effect on QoL among NSCLC patients when used with chemotherapy, even after adjustment for publication bias. Pooled RR varied from 1.38 (95% CI: 1.11–1.72, $I^2 = 0.0\%$, Kang-lai-te injection) to 3.36 (95% CI: 1.30–8.66, $I^2 = 0.0\%$, Zi-jin-long tablet). One trial comparing Hai-shen-su (a protein extract from *Tegillarca granosa* L.) plus chemotherapy with chemotherapy also demonstrated beneficial effect of combined treatment (RR = 3.13, 95% CI: 1.41–6.98). Results from NMA showed no differences on the comparative effectiveness among CHM, but Hai-shen-su plus chemotherapy has the highest probability (62.3%) of being the best option for improving QoL.

Use of CHM on top of chemotherapy can significantly improve QoL in NSCLC patients. Although Hai-shen-su showed the highest probability of being the best add-on to chemotherapy, the effectiveness of all 11 CHM reviewed appeared to be similar. In the future, rigorous placebo controlled trials with proper blinding are needed to confirm the effectiveness of CHM.

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Abbreviations: CHM = Chinese herbal medicine, CI = confidence interval, CONSORT = consolidated standards of reporting trials, KPS = Karnofsky Performance Status (KPS), NMA = network meta-analyses, NSCLC = nonsmall cell lung cancer, QoL = quality of life, RCTs = randomized controlled trials, RR = relative risk, SRs = systematic reviews, SUCRA = surface under the cumulative ranking curve, TNM = tumor-node-metastasis stage.

INTRODUCTION

Lung cancer is 1 of the most prevalent cancers worldwide for decades. It is, respectively, the first and third most common cancer in male and female.[1] Lung cancer is estimated to contribute to nearly one-fifth of deaths globally.[2] While the incidence of lung cancer has declined in some regions of the world, but it is increasing quickly in China.[3] Small cell lung cancer and nonsmall cell lung cancer (NSCLC) are the 2 major types, and it is reported that the latter accounts for 85% to 90% of all global lung cancer cases.[4]

Reducing symptom burden caused by lung cancer itself or cancer-related treatment is high on the clinical research agenda[5,6] as such burden is negatively correlated to quality of life (QoL) among lung cancer patients.[5,7] Effectiveness of current cancer symptoms management approaches seems to be limited, with considerable number of patients reporting clinically important reductions in QoL.[8] Lung cancer population is no exception,[5] and poor QoL is considered a negative prognostic factor among elderly patients with advanced NSCLC.[9]

Although an effective treatment for advanced NSCLC patients, chemotherapy can also incur substantial toxicity including nausea and vomiting, fatigue, and sore mouth due to mucositis.[10] The impact of these adverse effects can lead to withdrawal of some patients, representing a missed opportunity for them to benefit from chemotherapy.[10] Interventions for managing majority of these adverse effects are limited and there is an urgent need for addressing this effectiveness gap. For instance, fatigue is a major cause of poor QoL among NSCLC

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patients, with a prevalence of 57%.[11] Unfortunately, this symptom is widely regarded as under-treated because of limited treatment options available from conventional medicine.[12]

Chinese herbal medicine (CHM) is widely used in combination with chemotherapy for mitigating its side effects, especially among Chinese populations.[13,14] Clinical evidence from systematic reviews (SRs) of randomized controlled trials (RCTs) has demonstrated beneficial effect of CHM for improving QoL when used in combination with chemotherapy, with relative risk (RR) values ranging from 1.73 to 12.72 among NSCLC patients.[15,16] Variation in the type of CHM evaluated in these RCTs may contribute to the differences in effect sizes. It is worthwhile to explore which CHM has the best potential in improving QoL in order to guide future research and clinical decision making for NSCLC patients who are receiving chemotherapy.

Using a network meta-analysis (NMA) approach,[17] the aim of this overview of SRs is to evaluate the comparative effectiveness of different CHM for improving QoL among NSCLC patients who are receiving chemotherapy.

METHODS

This overview of SRs and NMA was strictly reported according to the PRISMA checklist. Ethical approval was not necessary for this study since all the analyses were conducted based on the data retrieved from previous published SRs and trials.

Inclusion Criteria

To be included in this overview, SRs had to provide clear reporting of meta-analysis results, and satisfy the criteria list below on participants, interventions, control, and outcome of interest. RCTs' citations were then retrieved from eligible SRs, which is a common approach used in NMA.[18]

Participants

Patients diagnosed with NSCLC using pathology, cytology, or biopsy methods were considered. There was no restriction on tumor stage.

Interventions and Control Groups

Any form of CHM was considered eligible, including both Chinese patent medicine, Chinese materia medica or a single herb, as long as it is mentioned in the 2010 China Pharmacopeia CHM index.[19] Eligible comparisons for this overview were: CHM plus chemotherapy versus chemotherapy alone; CHM plus chemotherapy versus CHM placebo plus chemotherapy; and CHM plus chemotherapy versus another CHM plus chemotherapy. For each RCT, chemotherapy used in all arms must be the same. However, it was acceptable for chemotherapy protocol to vary across studies.

Outcomes of Interest

To be included, RCTs must report QoL as an outcome measured with a validated instrument.

Literature Search

Literature search for SRs was conducted in both international databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Medline, and Embase) and Chinese databases (Wan Fang Digital Journals, Chinese Biomedical Databases, and Taiwan Periodical Literature Databases). Specialized SRs search filters were applied in Medline[20] and Embase.[21]

Literature Selection, Data Extraction, and Risk of Bias Assessment

Two researchers (XW and PL) independently selected eligible SRs, extracted data, and assessed risk of bias of included RCTs as well as the methodological quality of eligible SRs. Any disagreement was resolved by discussion and consensus, with unresolved discrepancy managed by a third reviewer (VCHC).

For literature selection, SRs' citations generated from database searches were screened and assessed for eligibility. For eligible SRs, their lists of included RCTs were retrieved and collated into a single list. To eliminate duplicate or overlapping RCT publications in this list,[22] a single most updated and comprehensive publication of the RCT was selected for further data extraction and other versions were used as supplementary information, if needed.

The following data from each included RCT were then extracted: basic characteristics of the RCT, including trial location, sample size, diagnostic methods, tumor stage, prior treatment, and patient characteristics; nature of intervention in both treatment and control groups, including regimens and dosages for both CHM and chemotherapy, treatment duration, and follow-up duration; information on QoL (including measurement method and treatment effect) and survival data; and information for assessing risk of bias assessment.

Methodological quality of included SRs was evaluated using the AMSTAR instrument.[23] For retrieved RCTs, their risk of bias were assessed with the latest version of the Cochrane risk of bias tool.[24] Six risk of bias domains were assessed, including sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Each domain was judged as having low, unclear, or high risk of bias according to information provided by the publication or its protocol (if available).

Data Synthesis

Pairwise random-effect meta-analyses were used to synthesize data separately for each individual CHM.[25] For dichotomous data extracted from RCTs, pooled RR with 95% confidence interval (CI) was used to quantify the impact of CHM on QoL and survival time. Heterogeneity across RCTs was tested with χ^2 test. Level of heterogeneity was measured with I^2 statistic, with $I^2 < 25\%$ considered as low level, 25% to 50% as moderate level, $>50\%$ as high level.[26]

Then, NMA was conducted to evaluate the comparative effectiveness of different CHM for improving QoL in NSCLC patients. Using the common comparator of chemotherapy, indirect comparison between different CHM on QoL was implemented with *mvmeta* command in STATA.[27,28] Results from NMA were reported as RR for each possible pair of comparisons.

Effectiveness ranking of all included CHM was also devised. We calculated the probability of each CHM being the most effective regimen, the second best regimen, the third best regimen and so on by calculating the RR for each CHM as compared to chemotherapy alone. The surface under the cumulative ranking curve (SUCRA)[29] and mean ranks were used to obtain an effectiveness hierarchy. STATA Version 13.0 (STATA Corporation, College Station, TX) was used for this data analysis.

The possible presence of publication bias was assessed with Egger's funnel plots, and the Egger's test was used to assess symmetry of the funnel plot. Trim and fill methods[30]

were used as sensitivity analysis to adjust for publication bias when it was detected.[31] All statistical tests were 2-tailed with significance level of 0.05, except for the heterogeneity test ($P = 0.10$).

RESULTS

Results on Literature Search and Selection

We identified 14 SRs through the literature search (Appendix 1, http://links.lww.com/MD/A593). These 14 SRs included a total of 120 RCTs. Fifty-nine RCTs were excluded due to following reasons: duplicate publications (n = 17); not reporting a time point for outcome measurement (n = 13); non-RCT design (n = 11); did not use a validated instrument for measuring QoL (n = 8); did not report any QoL outcome (n = 6); provided no details on the composition of CHM (n = 3); and both chemotherapy and radiotherapy were used as control intervention (n = 1). Hence, 61 RCTs were included in this overview (Appendix 2, http://links.lww.com/MD/A593). Details on the literature selection are presented in Figure 1.

Characteristics of Included RCTs

The 61 RCTs included a total of 4247 NSCLC patients, with sample sizes varying from 43 to 135. All RCTs were conducted among Chinese populations in China. The majority of included RCTs (82%) recruited NSCLC patients with TNM III–IV stage, 6 RCTs (10%) at TNM II–IV stage, and the remaining 5 RCTs (8%) did not report the TNM stage information. All RCTs compared CHM plus chemotherapy versus chemotherapy alone, except for 1 RCT which used CHM placebo plus chemotherapy as control interventions.[32]

A total of 11 CHM were evaluated in these 61 RCTs, including Shen-qi-fu-zheng injection (n = 22), Kang-ai injection (n = 9), Compound ku-shen injection (n = 8), Kang-la-te injection (n = 7), Xiao-ai-ping injection (n = 5), Zi-jin-long tablet (n = 3), Shen-fu injection (n = 3), Yi-fei-bai-du decoction (n = 1), Fei-liu-ping extract (n = 1), Hai-shen-su (a protein extract from *Tegillarca granosa* L. n = 1), and Fu-zheng-jie-du decoction (n = 1). The CHM were prescribed as either oral medication or as intravenous injection, with treatment duration of 15 to 112 days (median = 42 days).

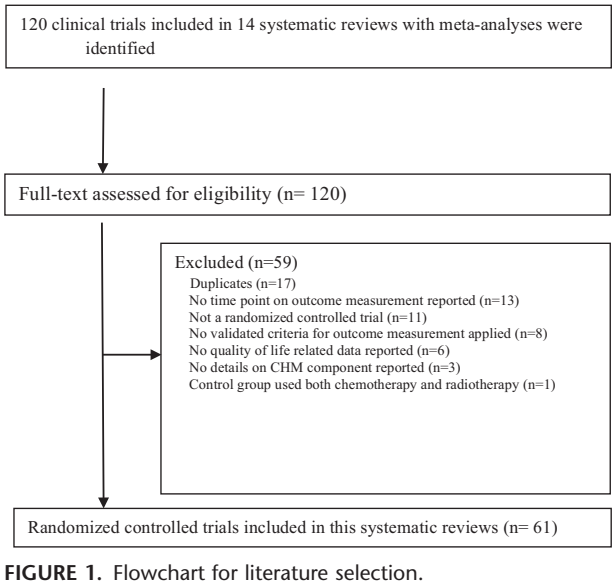

FIGURE 1. Flowchart for literature selection.

All the RCTs assessed QoL immediately after treatment completion, except for 1 RCT,[33] which evaluated QoL 7 days after treatment completion. Characteristics of included RCTs were shown in Table 1.

Methodological Quality of Included SRs and Risk of Bias of Included RCTs

Methodological quality of the 14 SRs was moderate. All the included SRs conducted comprehensive literature search, with 92.9% assessing scientific quality of the primary studies and using appropriate method to combine the results. On the other hand, none of the SRs fulfilled the following 3 AMSTAR criteria: providing an ''a priori'' design, providing lists of both included and excluded studies, and stating conflicts of interests for both the SR and included studies (details on the methodological quality of the 14 SRs are presented in Appendix 3, http://links.lww.com/MD/A593).

Among all the included trials, only 17 (28%) provided details on sequence generation, of which 16 of them (26%) used appropriate methods and thus judged as having low risk of bias. Forty-four (72%) trials did not provide information on sequence generation and 58 (95%) RCTs did not describe allocation concealment and were judged as having unclear risk of bias. Only 2 (3%) trials reported using sequentially numbered, sealed, and opaque envelopes to ensure allocation concealment. For blinding, 58 (95%) RCTs were judged as having high risk of bias for blinding of participants and study personnel to intervention assignment, as well as blinding of outcome assessment. The included RCTs generally performed well in incomplete outcome data and selective reporting, with 95% and 100% judged as having low risk of bias, respectively. Details on risk of bias are shown in Figure 2.

Add-On Effect of CHM for Improving QoL

All included RCTs measured patients' QoL with Karnofsky Performance Status (KPS) scale, which scores patients' QoL status from 0 to 100, where 0 represents death and 100 represents perfect health.[34] Patients with an increment of KPS score >10 were considered to have clinically relevant improvement on QoL,[32] and hence, it is used as cut off in the calculation of RR.

Results of Pairwise Meta-Analyses

Overall, results from pairwise meta-analyses showed the add-on benefit of CHM for improving QoL among NSCLC patients (Table 2). Statistically significant results favoring combined treatment were reached in all the 7 pairwise meta-analyses. Pooled RR varied from 1.38 (95% CI: 1.11–1.72, $I^2 = 0.0\%$, Kang-lai-te injection) to 3.36 (95% CI: 1.30–8.66, $I^2 = 0.0\%$, Zi-jin-long tablet). Favorable results were also observed in 1 RCT comparing Hai-shen-su plus chemotherapy with chemotherapy (RR = 3.13, 95% CI: 1.41–6.98). Significant add-on effect was not observed in the pooling results of Yi-fei-bai-du decoction, Fei-liu-ping extract, and Fu-zheng-jie-du decoction. Heterogeneity was not observed in all 7 meta-analyses, with all the I^2 values equal to 0.0%. Detailed results were shown in Table 2.

Results of Network Meta-Analysis

Comparative effectiveness of 11 CHM was evaluated against a common comparator of chemotherapy. A star-shape

TABLE 1. Characteristics of Included Randomized Controlled Trials

First Author, Year of Publication, Country	Sample Size	Tumor Stage	Characteristics of Patients: Male/Female, Mean or Median Age, y	Interventions in the Treatment Group	Interventions in the Control Group	Time of QoL Assessment
Jiang, 2002, China	86	TNM III–IV	T: 39/17, 53.4 ± 11.5 C: 19/11, 51.6 ± 12.4	Yi-fei-bai-du decoction + MVP Twice/d, oral, d_{1-30}, 30 d/cycle, 2 cycles	MVP only Mitomycin 6–8 mg/m^2, iv, d_1, Vindesine 3 mg/m^2, iv, $d_{1,8}$, Cisplatin 40 mg/m^2, iv, d_{1-3}, 21–28 d/cycle, 2 cycles	Immediately after the treatment
Zhang, 2012, China	135	TNM IIIb–IV	T: 45/22, 62.5 ± 9.8 C: 43/25, 62.5 ± 9.4	Fei-liu-ping extract + NP or TP or chemotherapy 15 g/time, oral, 3 times/d for 42 d	NP or TP or GP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_{1-3}, OR Taxol 135–175 mg/m^2, iv, d_1, Cisplatin 80 mg/m^2, iv, d_{1-3}, OR Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Li, 2009, China	83	TNM III–IV	T: 33/9, 59.3 ± 5.9 C: 32/9, 59.2 ± 5.8	Hai-sheng-su + MVP 2.4 mg/d, iv, 15 d	Placebo + MVP Mitomycin 10 mg/m^2, iv, d_1, Vindesine 4 mg/m^2, iv, $d_{1,8}$, Cisplatin 40 mg/m^2, iv, d_{1-3}, 28 d/cycle, 2 cycles	Immediately after the treatment
Sun, 2011, China	60	TNM III–IV	T: NR, NR C: NR, NR	Fu-zheng-jie-du decoction + NP NR, treat for 9 wk	NP only NR, treat for 9 wk	Immediately after the treatment
Lv, 2004, China	60	TNM IIIb–IV	T: NR, 49 (median) C: NR, 49 (median)	Kang-lai-te injection + NP 100 mL/time, once/d, iv, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/kg per m^2, iv, $d_{1,8}$, Cisplatin 40 mg/kg per m^2 d_{1-3}, iv, 21 d/cycle, 2 cycles	Immediately after the treatment
Yang, 2003, China	57	TNM IIIa–IV	T: NR, 58 (median) C: NR, 56 (median)	Kang-lai-te injection + NP 200 mL/time, once/d, iv, d_{8-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Deng, 2006, China	43	TNM III–IV	T: 16/6, 48.6 ± 13.8 C: 12/9, 54.7 ± 15.3	Kang-lai-te injection + GC 200 mL/d, iv, d_{1-21}, 21 d/cycle, 3 cycles	GC only Gemzar 1000 mL/m^2, iv, $d_{1,8}$, Carboplatin, dosage was calculated according to AUC = 5, d_1, 21 d/cycle, 3 cycles	Immediately after the treatment
Tong, 2007, China	60	TNM IIIa–IV	T: NR, 49 (median) C: NR, 49 (median)	Kang-lai-te injection + GP 100 mL/d, d_{1-21}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Xie, 2003, China	87	NR	T: NR, 58 (median) C: NR, 58 (median)	Kang-lai-te injection + NP 100 mL, iv, once/d, d_{1-30}, 30 d/cycle, 1 cycle	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 75 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	During 7 d follow up after the treatment
Hou, 2008, China	68	TNM IIIb–IV	T: 20/14, 49 (median) C: 21/13, 50 (median)	Kang-lai-te injection + NP 100 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Ren, 2010, China	127	TNM IIIb–IV	T: 40/24, 56 (median) C: 43/20, 51 (median)	Kang-lai-te injection + NP 200 mL/time, once/d, iv, d_{1-21}, 21 d/cycle, 4 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_{1-3}, 21 d/cycle, 4 cycles	Immediately after the treatment
Hao, 2008, China	128	NR	T: NR, 60 (NR) C: NR, 63 (NR)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 75 mg/m^2, iv, d_{2-4}, 21 d/cycle, 2 cycles	Immediately after the treatment
Gong, 2008, China	65	TNM III–IV	T: NR, 49 (median) C: NR, 49 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-10}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2007, China	55	TNM IIIb–IV	T: NR, 58.6 (median) C: NR, 58.6 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 3 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 300–500 mg, iv, d_1, 21 d/cycle, 3 cycles	Immediately after the treatment
Li, 2009, China	69	NR	T: 25/11, 58 (NR) C: 21/12, 55 (NR)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-28}, 28 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-3}, 28 d/cycle, 2 cycles	Immediately after the treatment
Lv, 2008, China	80	TNM IIIb–IV	T: 32/8, 65.2 (median) C: 33/7, 63.8 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Yu, 2007, China	62	TNM III–IV	T: 21/9, 57 (median) C: 22/10, 54 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-10}, 21–28 d/cycle, 4 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 40 mg/m^2, iv, d_{1-3}, 21–28 d/cycle, 4 cycles	Immediately after the treatment
Miao, 2010, China	79	TNM IIIb–IV	T: 28/10, 61 (median) C: 32/9, 61 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-4}, 28 d/cycle, 2 cycles	Immediately after the treatment
Li, 2010, China	85	TNM IIIb–IV	T: 29/14, 57.1 ± 4.8 C: 27/15, 55.6 ± 5.4	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	NP only Vinorelbine 35 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_1, or 35 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Zou, 2005, China	48	TNM IIIb–IV	T: 17/7, 56 (median) C: 16/8, 55 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Carboplatin 300–350 mg/m^2, iv, d_1, 21–28 d/cycle, 2 cycles	Immediately after the treatment
Luo, 2006, China	50	TNM IIIb–IV	T: 16/9, 55 (median) C: 17/8, 54 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Luo, 2007, China	60	TNM IIIa–IV	T: 20/10, 55 (median) C: 19/11, 54 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment

First Author, Year of Publication, Country	Sample Size	Tumor Stage	Characteristics of Patients: Male/Female, Mean or Median Age, y	Interventions in the Treatment Group	Interventions in the Control Group	Time of QoL Assessment
Zhang, 2008, China	60	TNM IIIa–IV	T: 22/8, 53 (median) C: 21/9, 54 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Zhao, 2009, China	80	Moderate to advanced stage	T: 22/18, 55.0 ± 9.6 C: 25/15, 56.6 ± 10.8	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 3 cycles	TP only Taxol 135–175 mg/m^2, iv, d_1, Cisplatin 60–80 mg/m^2, iv, d_{1-3}, 21 d/cycle, 3 cycles	Immediately after the treatment
Chen, 2007, China	80	TNM III–IV	T: 30/11, NR C: 27/12, NR	Shen-qi-fu-zheng injection + TP or NP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	TP or NP only Taxol 135–175 mg/m^2, iv, d_1, L-OHP 100–130 mg/m^2, iv, d_1, OR Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Shi, 2007, China	59	TNM IIIb–IV	T: NR, 56 (median) C: NR, 56 (median)	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-15}, 21 d/cycle, 2 cycles	NP only Vinorelbine 30 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Jiang, 2005, China	67	TNM III–IV	T: 27/8, 57 (median) C: 26/6, 56 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 4 cycles	TP only Taxol + Cisplatin, no details, 21 d/cycle, 4 cycles	Immediately after the treatment
Wang, 2009, China	80	TNM IIIa–IV	T: 31/9, 54 (median) C: 28/12, 52 (median)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 150 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Cui, 2010, China	60	TNM IIb–IV	T: 30/12, 62.6 (NR) C: 16/12, 58.4 (NR)	Shen-qi-fu-zheng injection + TP 250 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 25 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Zhong, 2011, China	72	TNM IIIb–IV	T: NR, 65 (median) C: NR, 65 (median)	Shen-qi-fu-zheng injection + GP 250 mL/d, iv, d_{1-19}, 21 d/cycle, 2 cycles	GP only Gemzar 1000 mg/m^2, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-4}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2011, China	52	TNM IV	T: 17/7, 56.6 ± 10.3 C: 25/15, 57.1 ± 11.1	Shen-qi-fu-zheng injection + DP 250 mL/d, iv, d_{1-10}, 21 d/cycle, 2 cycles	DP only Docetaxel 75 mg/m^2, iv, d_1, Cisplatin 75 mg/m^2, iv, d_{1-5}, 21 d/cycle, 2 cycles	Immediately after the treatment
Lu, 2010, China	60	TNM IIIb–IV	T: 21/9, 65.2 ± 1.5 C: 23/7, 65.3 ± 1.4	Shen-qi-fu-zheng injection + NP 250 mL/d, iv, d_{1-10}, 28 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 40 mg/m^2, iv, d_{1-3}, or 35 mg/m^2, iv, d_{1-3}, 28 d/cycle, 2 cycles	Immediately after the treatment
Liu, 2011, China	100	TNM IIb–IV	T: 27/23, 57.1 ± 5.3 C: 24/26, 56.8 ± 6.2	Shen-qi-fu-zheng injection + DP 250 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	DP only Docetaxel 75 mg/m^2, iv, d_1, Cisplatin 75 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Song, 2010, China	47	TNM IIIb–IV	T: 13/14, NR C: 10/10, NR	Compound ku-shen injection + NP 20 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2009, China	90	TNM III–IV	T: 30/15, 50.3 (NR) C: 28/17, 52.1 (NR)	Compound ku-shen injection + NP 20 mL/d, iv, d_{1-10}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 80 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Zhou, 2009, China	65	TNM II–IIIb	T: 26/7, 75.4 ± 3.4 C: 24/8, 74.5 ± 4.6	Compound ku-shen injection + NP 20 mL/d, iv, d_{1-14}, 28 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 28 d/cycle, 2 cycles	Immediately after the treatment
Zhang, 2008, China	50	TNM IIIa–IV	T: 18/12, 46.9 (NR) C: 13/7, 46.3 (NR)	Compound ku-shen injection + NP 20 mL/d, iv, d_{1-21}, 21 d/cycle, 3 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 60–80 mg/m^2, iv, d_{1-3}, 21 d/cycle, 3 cycles	Immediately after the treatment
Li, 2008, China	100	TNM III–IV	T: 35/25, 56 (median) C: 25/15, 58 (median)	Compound ku-shen injection + NP 20 mL/d, iv, d_{1-14}, 15–16 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 75 mg/m^2, iv, d_{2-5}, 15–16 d/cycle, 2 cycles	Immediately after the treatment
Yang, 2008, China	105	TNM III–IV	T: 32/18, 56.0 ± 13.2 C: 33/22, 53.0 ± 15.6	Compound ku-shen injection + DP 20 mL/d, iv, d_{1-14}, 14 d/cycle, 2 cycles	DP only Docetaxel 40 mg/m^2, iv, d_{1-8}, Cisplatin 75 mg/m^2, iv, d_1, 21 d/cycle, 2 cycles	Immediately after the treatment
Liu, 2010, China	64	TNM IIIa–IV	T: 20/12, 55 (median) C: 19/13, 58 (median)	Compound ku-shen injection + TP 15 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Xu, 2007, China	66	TNM III–IV	T: 26/10, 53 (median) C: 16/14, 55 (median)	Compound ku-shen injection + TP 20 mL/d, iv, d_{1-14}, 15–16 d/cycle, 2 cycles	TP only Taxol 90 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2010, China	64	TNM III–IV	T: 24/8, 53 (NR) C: 22/10, 53 (NR)	Kang-ai injection + TP 50 mL/d, iv, d_{1-7}, 21 d/cycle, 4 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 80–100 mg/m^2, iv, d_1, 21 d/cycle, 4 cycles	Immediately after the treatment
Zhang, 2010, China	60	TNM IIIa–IV	T: 22/8, 65.2 (median) C: 23/7, 63.8 (median)	Kang-ai injection + TP 40 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Li, 2009, China	56	TNM IIIb–IV	T: NR, 55 (median) C: NR, 55 (median)	Kang-ai injection + TP 60 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 175 mg/m^2, iv, d_1, Cisplatin 25 mg/m^2, iv, d_{1-5}, 21 d/cycle, 2 cycles	Immediately after the treatment
Zhang, 2009, China	120	TNM IIIa–IV	T: 39/21, NR C: 37/23, NR	Kang-ai injection + TP 40 mL/d, iv, NR, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wu, 2009, China	56	TNM IIIb–IV	T: 22/6, 58 (median) C: 21/7, 56 (median)	Kang-ai injection + TP 50 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	TP only Taxol 135 mg/m^2, iv, d_1, Cisplatin 100 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2009, China	56	TNM IIIb–IV	T: NR, 66 (median) C: NR, 66 (median)	Kang-ai injection + GP 60 mL/d, iv, d_{1-10}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-4}, 21 d/cycle, 2 cycles	Immediately after the treatment

First Author, Year of Publication, Country	Sample Size	Tumor Stage	Characteristics of Patients: Male/Female, Mean or Median Age, y	Interventions in the Treatment Group	Interventions in the Control Group	Time of QoL Assessment
Ge, 2011, China	64	TNM III–IV	T: 24/8, NR C: 23/9, NR	Kang-ai injection + GP 30 mL/d, iv, d_{1-21}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1250 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Cai, 2007, China	60	TNM IIIb–IV	T: NR, 43 (NR) C: NR, 43 (NR)	Kang-ai injection + NP 40 mL/d, iv, d_{1-15}, 15 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wen, 2006, China	78	TNM IIIb–IV	T: 34/6, 60 (median) C: 33/5, 56 (median)	Kang-ai injection + NP 50 mL/d, iv, d_{1-14}, 21 d/cycle, 4 cycles	NP only Vinorelbine NR, Cisplatin NR, 21 d/cycle, 4 cycles	Immediately after the treatment
Chen, 2011, China	48	TNM IIIa–IV	T: 14/11, 53.8 (NR) C: 10/13, 53.5 (NR)	Zi-jin-long tablet + DP 4 tablets/time, 3 times/d, oral, d_{1-21}, 21 d/cycle, 2 cycles	DP only Docetaxel 75 mg/m^2, iv, $d_{1,8}$, Cisplatin 20 mg/m^2, iv, d_{2-6}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2008, China	63	TNM IIa–IV	T: 18/14, 63 (median) C: 19/12, 62 (median)	Zi-jin-long tablet + NP or MVP 4 tablets/time, 3 times/d, oral, d_{1-28}, 28 d/cycle, 2 cycles	NP or MVP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-3}, OR Mitomycin 6 mg/m^2, iv, d_1, Vindesine 3 mg/m^2, iv, $d_{1,8}$, Cisplatin 60 mg/m^2, iv, d_{1-2}, 21 d/cycle, 2 cycles	Immediately after the treatment
Guo, 2002, China	45	TNM II–IV	T: 25/5, 64.3 (NR) C: 14/1, 60.4 (NR)	Zi-jin-long tablet + MVP 4 tablets/time, 3 times/d, oral, d_{1-28}, 28 d/cycle, 2 cycles	MVP only Mitomycin 6–8 mg/m^2, iv, d_1, Vindesine 4 mg/m^2, iv, $d_{1,8}$, Cisplatin 70–80 mg/m^2, iv, d_1, 28 d/cycle, 2 cycles	Immediately after the treatment
Liu, 2008, China	68	TNM IIIb–IV	T: 22/12, 58 (median) C: 24/10, 56 (median)	Xiao-ai-ping injection + NP 20 mL/d, iv, d_{1-10}, 28 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 28 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2009, China	56	TNM IIIb–IV	T: 17/10, 59.5 (median) C: 20/9, 61.0 (median)	Xiao-ai-ping injection + TP 80 mL/d, iv, d_{1-7}, 21 d/cycle, 2 cycles	TP only Taxol 150–175 mg/m^2, iv, d_1, Cisplatin 70 mg/m^2, iv, d_2, 21 d/cycle, 2 cycles	Immediately after the treatment
Zhang, 2011, China	48	TNM IIIb–IV	T: NR, 65 (median) C: NR, 65 (median)	Xiao-ai-ping injection + GP 40–60 mL/d, iv, d_{1-15}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2009, China	56	TNM IIIb–IV	T: NR, NR C: NR, NR	Xiao-ai-ping injection + NP 40–60 mL/d, iv, d_{1-15}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Wang, 2012, China	56	NR	T: NR, 56 (median) C: NR, 56 (median)	Xiao-ai-ping injection + GP 40–60 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Gao, 2012, China	86	TNM IIIa–IV	T: 27/16, 58 (median) C: 25/18, 59 (median)	Shen-fu injection + GP 60 mL/d, iv, d_{1-10}, 21 d/cycle, 2 cycles	GP only Gemcitabine 1000 mg/m^2, iv, $d_{1,8}$, Cisplatin 40 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Liu, 2011, China	60	TNM IIIa–IV	T: 22/8, 56.4 ± 5.6 C: 24/6, 58,5 ± 6.2	Shen-fu injection + NP 60 mL/d, iv, d_{1-14}, 14 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 30 mg/m^2, iv, d_{1-3}, 21 d/cycle, 2 cycles	Immediately after the treatment
Tang, 2008, China	52	TNM IV	T: NR, NR C: NR, NR	Shen-fu injection + NP 50 mL/d, iv, d_{1-14}, 21 d/cycle, 2 cycles	NP only Vinorelbine 25 mg/m^2, iv, $d_{1,8}$, Cisplatin 25 mg/m^2, iv, d_{1-3}, 21–28 d/cycle, 2 cycles	Immediately after the treatment

AUC = area under curve, C = control, DP = Docetaxel + Cisplatin, GC = Gemzar + Carboplatin, GP = Gemzar + Cisplatin, MVP = Mitomycin + Vindesine + Cisplatin, NP = Vinorelbine + Cisplatin, NR = not reported, OHP = Oxaliplatin, QoL = quality of life, T = treatment, TNM = tumor-node-metastasis stage, TP = Taxol + Cisplatin.

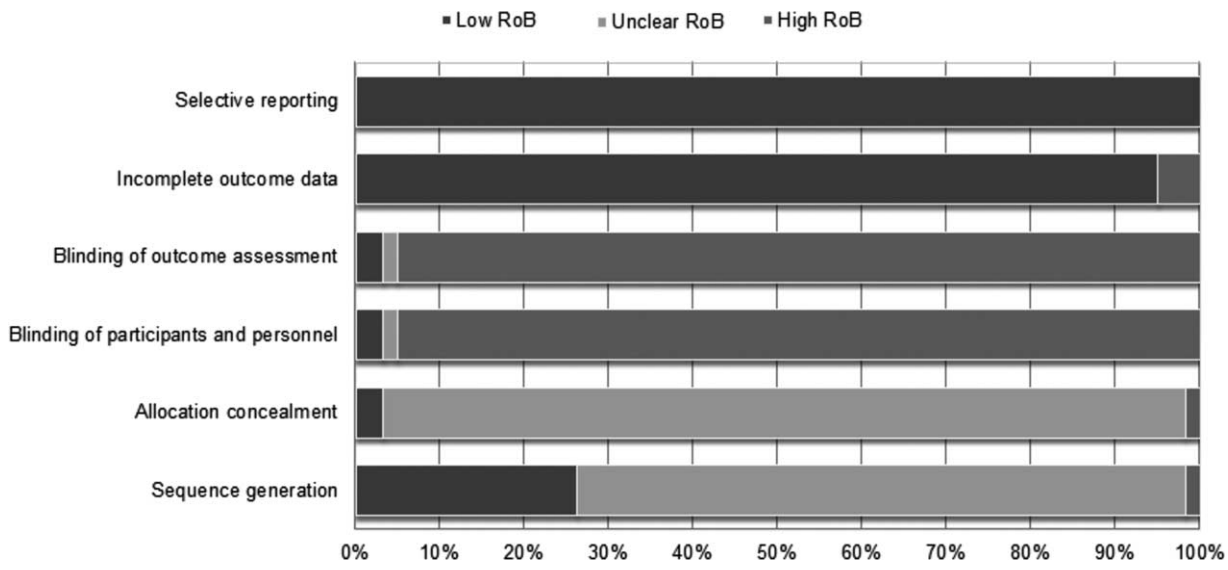

FIGURE 2. Risk of bias among included randomized controlled trials.

network was devised as chemotherapy was the only node that connects with all other CHM treatments (Figure 3).

Figure 4 summarized NMA results. Although some CHM showed better effectiveness in improving QoL than others (eg, the add-on effect of Hai-shen-su is higher than that of the Fei-liu-ping extract [RR = 2.13, 95% credibility interval: 0.58–3.67]), no significant differences were observed between each of the 11 CHM. Figure 5 shows the cumulative probabilities (SUCRA results) of each CHM being the most effective when added to chemotherapy. Hai-shen-su has the highest probability (62.3%), followed by Zi-jin-long tablet (34.3%). Chemotherapy alone had the lowest probability (0.0%) of being the best treatment.

Add-On Effect of CHM for Prolonging Survival Time

Only 5 RCTs provided survival data of cancer patients, of which 4 reported data on 1-year survival rate, the remaining 1 reported 1-, 2-, and 3-year survival rates (Table 3). Results showed that although patients in the combined CHM and

TABLE 2. Meta-Analyses and Trim and Fill Sensitivity Analyses: Effectiveness of Chinese Herbal Medicine Combined With Chemotherapy vs Chemotherapy Alone for Improving Quality of Life* in Nonsmall Cell Lung Cancer Patients

		No. of Patients in the Combined Group		No. of Patients in the CT Group			Heterogeneity Test		Trim and Fill Sensitivity Analyses	
Comparison	No. of Studies	Improved	Total	Improved	Total	Pooled RR** or RR (95% CI)	I^2, %	*P*	No.†	Pooled RR (95% CI)
Yi-fei-bai-du decoction + CT vs CT	1	30	56	7	30	1.84 (0.89, 3.81)	NA			NA
Fei-liu-ping extract + CT vs CT	1	9	63	6	56	1.29 (0.49, 3.43)	NA			NA
Hai-shen-su + CT vs CT	1	28	42	6	41	*3.13 (1.41, 6.98)*	NA			NA
Fu-zheng-jie-du decoction + CT vs CT	1	5	30	4	29	1.18 (0.35, 4.02)	NA			NA
Kang-la-te injection + CT vs CT	7	144	245	87	245	*1.38 (1.11, 1.72)*	0.00	0.93	10	*1.31 (1.07, 1.60)*
Shen-qi-fu-zheng injection + CT vs CT	22	374	774	173	776	*1.73 (1.47, 2.03)*	0.00	0.88	29	*1.52 (1.32, 1.76)*
Compound ku-shen injection + CT vs CT	8	155	313	81	281	*1.47 (1.17, 1.85)*	0.00	0.91	10	*1.38 (1.11, 1.70)*
Kang-ai injection + CT vs CT	9	205	310	114	304	*1.43 (1.19, 1.73)*	0.00	0.90	9	*1.43 (1.19, 1.73)*
Zi-jin-long tablet + CT vs CT	3	45	84	8	69	*3.36 (1.30, 8.66)*	0.00	0.91	3	*3.36 (1.30, 8.66)*
Xiao-ai-ping injection + CT vs CT	5	76	141	44	139	*1.43 (1.05, 1.96)*	0.00	0.96	8	*1.17 (0.88, 1.56)*
Shen-fu injection + CT vs CT	3	48	99	26	99	*1.56 (1.04, 2.35)*	0.00	0.94	3	*1.56 (1.04, 2.35)*

CI = confidence interval, CT = chemotherapy, NA = not applicable, RR = risk ratio.

* Quality of life measured with Karnofsky Performance Status (KPS) scale. KPS score increment >10 points was defined as improved, with improvement rate = number of patients had KPS increased > 10 points/total number of patients.

** Random-effect model was used for all meta-analyses.

† This column reports the number of studies pooled after the application of trim and fill adjustments. Italicized values indicate $p < 0.05$.

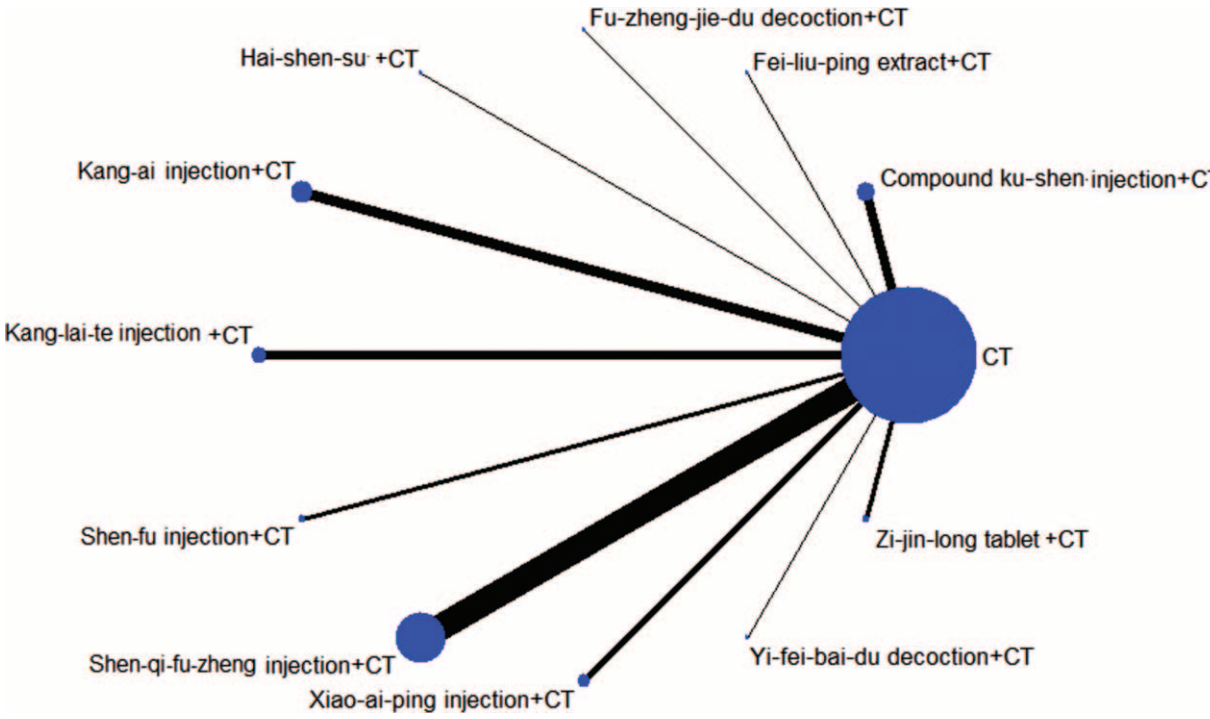

FIGURE 3. Network of included comparisons. The width of the lines represents the proportion of the number of trials for each comparison to the total number of trials and the size of the nodes represents the proportion of the number of randomized patients (sample sizes). CT = chemotherapy.

chemotherapy group had higher 1-, 2-, and 3-year survival rates, no significant difference were found.

Publication Bias and Sensitivity Analysis

There was an asymmetrical funnel plot (Figure 6) and results from Egger's test indicated the presence of a publication bias ($t = 5.94$, $P < 0.001$). Results from trim and fill sensitivity analysis indicated that among the 7 pairwise meta-analyses, all the add-on use of CHM still showed significant effect in improving QoL when compared to chemotherapy alone, except for Xiao-ai-ping injection (pooled RR: 1.17, 95% CI: 0.88–1.56). Detailed results on sensitivity analysis were reported in Table 2.

CT alone	YFBDD+CT	FLPD+CT	HSS+CT	FZJDD+CT	KLT+CT	SFI+CT	KS+CT	KA+CT	ZJL+CT	XAP+CT	Shenfu+CT
1.33(0.34, 2.32)											
0.33(-0.77, 1.43)	-1.00(-2.49,0.48)										
2.45(1.38, 3.53)	1.12(-0.34,2.59)	2.13(0.58,3.67)									
0.22(-1.20,1.65)	-1.11(-2.84,0.63)	-0.11(-1.91,1.70)	-2.23(-4.02,-0.45)								
1.05(0.66,1.45)	-0.28(-1.35,0.79)	0.72(-0.45,1.89)	-1.40(-2.58,-0.23)	0.83(-0.65,2.31)							
1.23(1.00, 1.46)	-0.10(-1.12,0.92)	0.90(-0.22,2.03)	-1.23(-2.33,-0.12)	1.01(-0.44,2.45)	0.18(-0.28,0.63)						
0.99(0.63,1.35)	-0.34(-1.40,0.72)	0.66(-0.50,1.82)	-1.47(-2.61,-0.33)	0.77(-0.70,2.24)	-0.06(-0.60,0.47)	-0.24(-0.67,0.19)					
1.25(0.90,1.59)	-0.09(-1.14,0.97)	0.92(-0.24,2.07)	-1.21(-2.34,-0.08)	1.02(-0.45,2.49)	0.19(-0.33,0.72)	0.01(-0.40,0.43)	0.25(-0.25,0.76)				
2.15(1.27, 3.03)	0.82(-0.51,2.14)	1.82(0.42,3.23)	0.30(-1.69,1.08)	1.93(0.26,3.60)	1.10(0.14,2.06)	0.92(0.02,1.83)	1.16(0.22,2.11)	0.91(-0.03,1.85)			
1.04(0.52,1.56)	-0.30(-1.42,0.83)	0.71(-0.51,1.93)	-1.42(-2.62,-0.22)	0.81(-0.70,2.33)	-0.02(-0.67,0.64)	-0.19(-0.76,0.37)	0.05(-0.59,0.68)	0-.21(-0.83,0.42)	-1.12(-2.13,-0.10)		
1.00(0.40,1.61)	-0.33(-1.50,0.84)	0.67(-0.58,1.93)	-1.45(-2.69,-0.22)	0.78(-0.77,2.33)	-0.05(-0.77,0.67)	-0.23(-0.88,0.42)	0.01(-0.69,0.72)	-0.24(-0.94,0.46)	-1.15(-2.22,-0.09)	-0.03(-0.83,0.76)	

FIGURE 4. Comparative effectiveness of 11 Chinese herbal medicines for improving quality of life among nonsmall cell lung cancer patients receiving chemotherapy: Results of indirect comparisons. Results are the relative risks (RRs) and related 95% credibility intervals in the row-defining treatment compared with the RRs in the column-defining treatment. RRs higher than 1 favor the column-defining treatment, and vice versa. Significant results are in bold and are underlined. CT = chemotherapy, FLPD = Fei-liu-ping extract, FZJDD = Fu-zheng-jie-du decoction, HSS = Hai-shen-su, KA = Kang-ai injection, KLT = Kang-la-te injection, KS = Compound Ku-shen injection, SFI = Shen-qi-fu-zheng injection, Shenfu = Shen-fu injection, XAP = Xiao-ai-ping injection, YFBDD = Yi-fei-bai-du decoction, ZLJ = Zi-jin-long tablet.

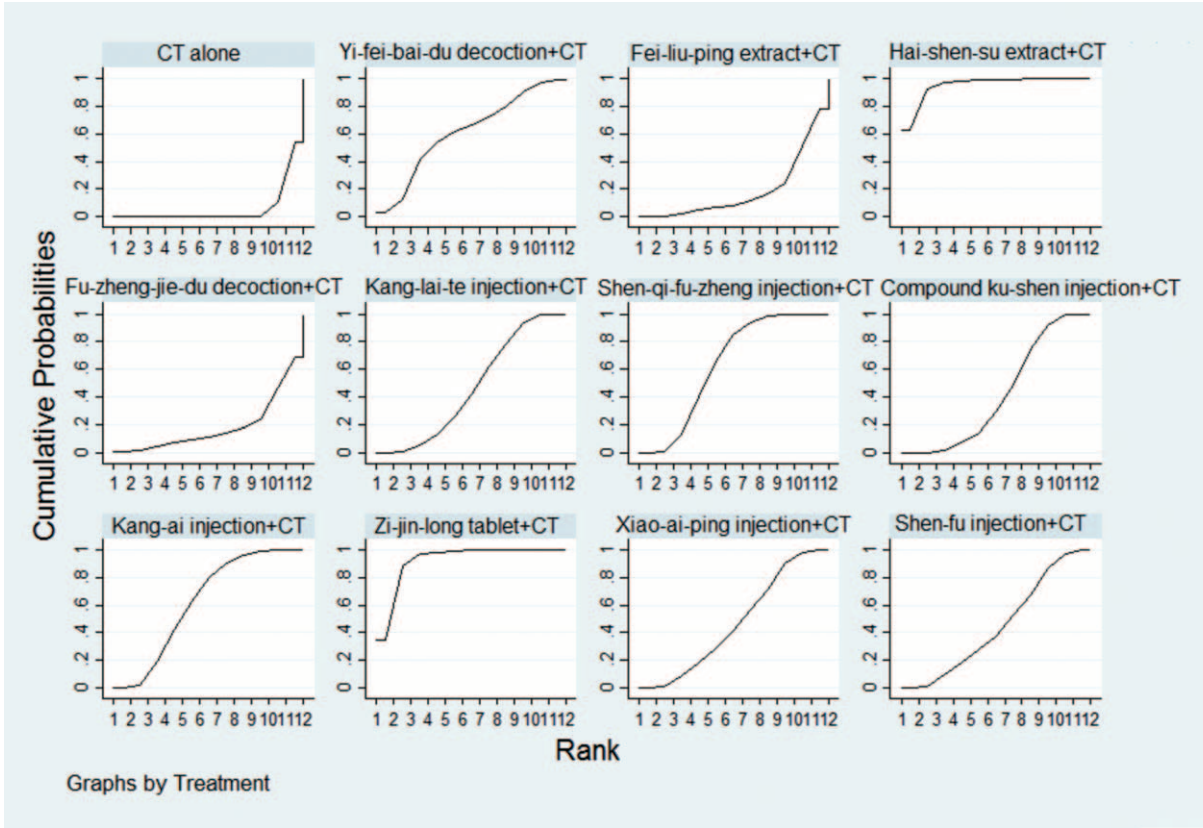

FIGURE 5. Surface under the cumulative ranking curves (SUCRA) for improving quality of life in nonsmall cell lung cancer patients. The x-axis represents the possible rank of each treatment (from the first best rank to the worst according to the improvement on quality of life). The y-axis indicates the cumulative probability for each treatment to be the best treatment, the second best treatment, the third best treatment, and so on.

Adverse Effect of CHM

Among the 61 included RCTs, 43 reported results on adverse effects. None of the RCTs specifically attributed the adverse effect to CHM treatment, as CHM was used together with chemotherapy in all included RCTs.

DISCUSSION

While existing SRs have indicated the add-on benefits of individual CHM in improving QoL among NSCLC patients undergoing chemotherapy,[35–37] none of them have investigated the comparative effectiveness of different CHM. This

TABLE 3. Effectiveness of Chinese Herbal Medicine Combined With Chemotherapy vs Chemotherapy Alone for Prolonging Survival Time in Nonsmall Cell Lung Cancer Patients

			Combined Group	CT Alone Group	
Study	Comparison	Survival Time, year(s)	No. of Patients Survived/No. of Patients	No. of Patients Survived/No. of Patients	Risk Ratio (95% Confidence Interval)
Jiang, 2002	Yi-fei-bai-du decoction + CT vs CT	1	43/56	12/30	1.52 (0.90, 2.58)
		2	20/56	7/30	1.39 (0.65, 2.99)
		3	13/56	3/30	2.07 (0.63, 6.78)
Yang, 2003	Kang-la-te injection + CT vs CT	1	12/28	9/29	1.27 (0.60, 2.66)
Luo, 2007	Shen-qi-fu-zheng injection + CT vs CT	1	21/30	16/30	1.31 (0.87, 1.98)
Li, 2008	Compounds ku-shen injection + CT vs CT	1	11/60	4/40	1.83 (0.63, 6.36)
Zhang, 2012	Fei-liu-ping + CT vs CT	1	44/63	32/56	1.22 (0.92, 1.62)

CT = chemotherapy.

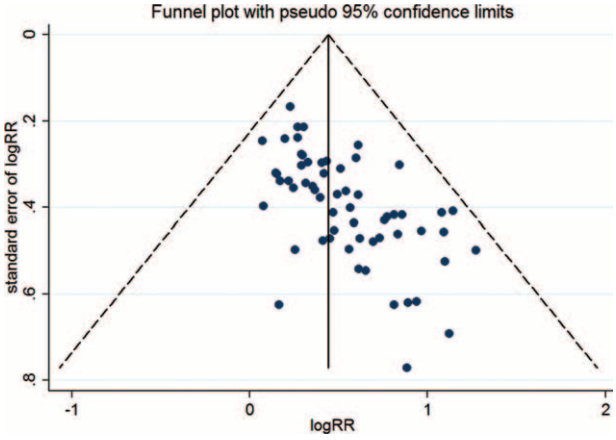

FIGURE 6. Funnel plot for assessing publication bias among included randomized controlled trials. RR = relative risk.

comprehensive overview of 14 SRs summarized the effectiveness of a wide range of CHM, and more importantly, provided a rank of effectiveness among these therapy options. Our analyses were based on 11 CHM identified from 61 RCTs (n = 4247). Pairwise meta-analyses showed 8 of the 11 CHM significantly improved QoL among NSCLC patients receiving chemotherapy. Results from NMA suggested Hai-shen-su has the highest probability of being the best add-on treatment to chemotherapy. In the present overview, the majority of included RCTs (82%) recruited patients at TNM III–IV stages. With most NSCLC patients being diagnosed at this advanced stage of disease, improving QoL, and managing symptoms may be more important than curing the cancer itself.[38] Hence, evidence from this overview is likely to have high relevance to many newly diagnosed NSCLC patients. However, since all the included RCTs were conducted in China among Chinese populations, it is uncertain whether the effect may change when CHM is used in populations of other ethnicity and in different geographical locations. Also, none of the included RCTs reported changes in QoL outcome beyond 1 week. The longer term impact of add-on CHM is uncertain.

Overall, the only RCT that had low risk of bias for all methodological domains was the 1 evaluating Hai-shen-su. Other results presented in this overview have certain shortcomings that may affect trustworthiness of the conclusions. First, due to poor reporting, we were unable to ascertain the risk of bias levels of many included RCTs. Indeed, poor reporting is a prevalent problem in both Chinese[39] and conventional[40] medicine publications and we cannot make any solid conclusion on whether there are real defects in the process of sequence generation and allocation concealment. Nevertheless, it was noted that CHM placebo was not used in all but 1 RCT.[32] This lack of blinding is a significant limitation as it is impossible to blind participants and study personnel without a placebo. Under this circumstance, blinding of the outcome assessment is a key strategy for reducing risk of bias.[41] Unfortunately, only 2 (3.3%) studies mentioned blinding of outcome assessment.

Second, although this overview included 61 RCTs, the number of RCTs investigating each CHM was not equal. Shenqi-fu-zheng injection was evaluated by the largest number of RCTs (22 trials), while only 1 RCT was identified for 4 CHM (Yi-fei-bai-du decoction, Fei-liu-ping extract, Hai-shen-su, and Fu-zheng-jie-du decoction). The small number of trials led to imprecision of effect estimation for these 4 CHM and larger trials are needed to further confirm the effectiveness of these modalities.

Third, we were unable to assess the consistency of direct evidence (head-to-head comparison of different CHM) and indirect evidence (comparison between CHM via chemotherapy) in the NMA. This is due to a lack RCTs that directly compared the add-on effect of CHM with each other in our literature search. Since a key assumption of NMA is the consistency of direct and indirect evidence in the same comparison, researchers in the future will need to use a loop-specific approach to evaluate the presence of inconsistency,[27] when RCTs results from head-to-head comparisons become available. This approach will assess the consistency of each individual closed loop of the network by comparing the direct and indirect estimates of a specific comparison. Magnitude of the difference and their 95% CI could then be used to measure the presence of the inconsistency of each loop.[42] This can be easily implemented using the *ifplot* command in STATA.[27]

Fourth, based on the eligibility criteria, we included RCT that measured QoL with a validated instrument. However, we only identified RCTs that measure such outcome using KPS. Although there is significant positive correlation between KPS and the Short Form 36 (SF-36) scorings,[43] it is controversial that whether KPS is sufficient for measuring QoL comprehensively.[44] KPS is useful in assessing overall physical QoL,[45] but it does not capture emotional, relational, spiritual implications of cancer. Future trials are suggested to use more comprehensive scales such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core 30.[46]

Lastly, anecdotal evidence has suggested that the alleviation of chemotherapy-related adverse effects by CHM is mediated via a reduction of chemotherapy concentration in the body. This raises concerns on whether improved QoL may come with a price of reduced survival.[48] RCTs reporting both QoL and survival outcomes can resolve this uncertainty, and results from 5 trials have suggested no trade-off between QoL improvement and survival. This provides preliminary evidence on how CHM may act synergistically with chemotherapeutic drugs without comprising the latter's effect.

In conclusion, clinical evidence synthesized in this overview of SRs suggested that the use of CHM with chemotherapy can significantly improve QoL among NSCLC patients. Among all the 11 reviewed CHM treatments, Hai-shen-su has the highest probability of being the best add-on treatment for improving QoL. Methodological limitations of RCTs have limited the trustworthiness of these conclusions and future RCTs should address the following: use a CHM placebo in the control group; ensure blinding of outcome assessment; measuring patient outcomes comprehensively using validated scales; report trial implementation and results according to the CONSORT statement[47]; and reducing publication bias by releasing RCT protocols on trial registries. To combat underreporting of results, researchers, funders, industry, and journal editors are encouraged to publish all available RCTs results.[48]

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