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A network meta-analysis

The best Yiqi Fuzheng Chinese herbal injections for use based on the NP regimen to treat NSCLC

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Abstract

Background: Chinese herbal injections (CHIs) have been proven beneficial to patients with non-small cell lung cancer (NSCLC) in combination with chemotherapy. The network meta-analysis (NMA) was designed to update and expand on previous work to better evaluate the effectiveness and safety of different Yiqi Fuzheng (YQFZ) CHIs combined with the Vinorelbine plus cisplatin (NP) regimen versus NP alone for NSCLC.

Methods: We searched multiple electronic databases and identified randomized controlled trials (RCTs) concerning different YQFZ CHIs combined with the NP regimen for treating NSCLC up to March 1st, 2019. The outcomes are the objective response rate, performance status and adverse reactions (ADRs). Two individuals accomplished the quality assessment of this NMA based on the Cochrane risk of bias tool and the methodological section of the CONSORT statement. Random effects models were generated to estimate efficacy and safety outcomes. Odds ratios and corresponding 95% confidence intervals were calculated via Stata 14 software. Furthermore, the rankings for the efficacy and safety of different YQFZ CHIs for each outcome were determined by the surface under the cumulative ranking curve (SUCRA).

Results: Initially, a total of 4775 citations were retrieved through comprehensive searching, and 88 eligible articles involving 6695 participants and 8 CHIs were ultimately included. The cluster analysis results of the current evidence indicated that the NP regimen combined with Delisheng, Shenfu and Shenmai injections have a higher clinical effectiveness rate and better performance status compared with the NP regimen alone. Additionally, the NP regimen combined with Shenqifuzheng, Shengmai and Shenfu injections may be considered a favorable choice for reliving ADRs among patients with NSCLC.

Conclusions: The current evidence demonstrated that the combination of Shenfu injection plus NP regimen could produce better outcomes than other YQFZ CHIs groups in terms of efficacy and safety. However, meticulously designed, strictly executed, high-quality trials are still required to further assess and confirm the results due to the inadequacy of the included RCTs.

Abbreviations: ADRs = adverse reactions, CBMdisc = China Biology Medicine disc, CHI = Chinese herbal injection, CHM = Chinese herbal medicine, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure Database, MDR = multidrug resistance, NMA = network meta-analysis, NP = Vinorelbine plus cisplatin, NSCLC = non-small cell lung cancer, PS = performance status, RCTs = randomized controlled trials, ROS = reactive oxygen species, SUCRA = cumulative ranking curve, TCM = Traditional Chinese medicine, VIP = VIP Database, YQFZ = Yiqi Fuzheng.

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HL and WZ have the same contribution to this research and should be regarded as the co-first author.

HL and WZ contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Keywords: Chinese herbal injections, network meta-analysis, non-small cell lung cancer, NP regimen, randomized controlled trials, Yiqi Fuzheng

1. Introduction

Lung cancer is a global health problem, which is also being the leading cause of cancer incidence and mortality. With 2.1 million new lung cancer cases and 1.8 million deaths predicted a year, accounting for nearly one fifth (18.4%) cancer deaths.[1] Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer.[2] Most NSCLC patients with stages I/II would benefit from surgical resection, which is the only possible way to cure. Nevertheless, close to 70% of patients with locally advanced or metastatic disease at the time of diagnosis, which was the main reason for the low cure rate of NSCLC.[3] Patients with advanced NSCLC who have an excellent performance status (PS) would benefit from chemotherapy, generally with a platinum-based regimen. It can significantly lighten and control the clinical symptoms of patients, prolong overall survival, and improve the quality of life.[4–6] The benefits of improving the quality of life are to promote the acceptance and adherence of chemotherapy among these patients. Vinorelbine plus cisplatin (NP) are one of the first-line treatment of patients with advanced NSCLC, which can prolong the overall survival among patients.[7–9] However, previous studies have demonstrated that patients with NSCLC treated with the NP regimens are often accompanied by severe adverse reactions (ADRs), such as hematologic toxic, fatigue, anorexia, nausea, and vomiting. The intolerable agony causing by the emergence of these ADRs may induce some patients to withdraw from the treatment, which means missing the opportunity to benefit from chemotherapy.

Traditional Chinese medicine (TCM) believes that chemotherapy will attack the "Zhengqi" from the human body, and Yiqi Fuzheng (YQFZ, 1 of the treatment methods of Chinese medicine, means Boosting Qi and inspiring Zheng) Chinese herbal medicine (CHM) can help to improve the bodys weakness. Some researchers have found that combining CHM with platinum-based chemotherapy for advanced NSCLC may enhance the efficacy and reduce the toxicity. For this reason, many CHMs have been widely used to connect with chemotherapy in the treatment of advanced NSCLC to reduce ADRs and enhance efficacy.[10,11] LevistolideA, a main bioactive compound in the CHM Ligusticum chuanxiong Hort, triggers the endoplasmic reticulum stress response and induces apoptosis by activating the reactive oxygen species (ROS)-mediated PERK/eIF2α/CHOP pathway.[12] Furthermore, LevistolideA has been proven to significantly enhanced vincristine-induced G2/M arrest and apoptosis. And it also can reverse P-glycoprotein -mediated multidrug resistance (MDR) in human breast carcinoma Bcap37/MDR1 cells.[13] Schisandra sphenanthera extract has a protective effect against cisplatin-induced nephrotoxicity via activating the Nrf2-mediated defense response, reducing the levels of ROS and increasing levels of glutathione.[14] As a bioactive compound present in Scutellaria, wogonin can selective activating PLCγ_1 (a key enzyme involved in Ca^{2+} signaling) via H_2O_2 signaling, leading to sustained elevation of cytosolic Ca^{2+}, then resulting in Ca^{2+} overload and mitochondrial apoptosis sequentially. Hence, it can induce apoptosis of malignant but not normal T cells.[15] Wogonin downregulates antiapoptotic proteins by causing the accumulation of ROS, thereby enhancing the antitumor activity of tumor necrosis factor-related apoptosis-inducing ligand.[16] In recent years, TCM has gradually been recognized worldwide, and it represents a ray of hope for patients with advanced cancer. Moreover, TCM is widely used to improve the side effects of conventional treatments, such as chemotherapy or surgery for cancer.[17,18] Chinese herbal injection (CHI) is the active ingredient extracted and purified from CHM by modern scientific techniques, which is a new type of TCM preparation. The studies have shown that they can improve the objective response rate of tumors, improve PS and decrease chemotherapy toxicity.[19–21]

Currently, most randomized controlled trials (RCTs) are double-arm trials, which emphasize on the comparisons between CHI plus chemotherapy and chemotherapy alone. The existing meta-analyses have indicated that the combination of CHI and chemotherapy can contribute to improving the efficacy and safety of patients with NSCLC, but none of them have investigated the comparative effectiveness of different CHIs. The head-to-head comparison research of different CHIs about their efficacy is relatively lacking. The advantage of network meta-analysis (NMA) is that it can integrate direct and indirect comparisons from clinical trials and summarize the evidence of each intervention for identifying the best treatment strategy based on the rankings of discrete outcomes.[22–24] YQFZ CHIs combined with chemotherapy is increasingly used in China, so it is necessary to explore the effectiveness of different YQFZ CHIs plus the NP regimens. This article aims to compare the efficacy and safety of treating NSCLC between different CHIs with the purpose of strengthening guidance for clinical practice in the future.

2. Materials and methods

The procedure of the current NMA includes establishing the strategy of literature search, setting inclusion and exclusion criteria, completing data extraction, making the quality assessment, and performing statistical analysis, followed by Cochrane criteria and PRISMA Checklist.[25] Ethical approval was not required for this study since the article was conducted based on the data retrieved from previously published RCTs.

2.1. Database and retrieval strategies

The literature up to March 1, 2019 were systematically searched using the PubMed, Embase, the Cochrane Library, Web of Science, the China National Knowledge Infrastructure Database (CNKI), the Wan-fang Database, the VIP Database (VIP), and the China Biology Medicine disc (CBMdisc). The inclusion criteria of the literature were unlimited to the publication year, language and blinding methods. The search term is composed of 3 domains:

1. NSCLC,
2. CHIs,
3. Study type (RCTs).

The search strategy used a combination of subject words and free-text words. The following terms were used for NSCLC: "lung carcinoma," "carcinoma of the lungs," "lung cancer," "non-small cell lung cancer," "non small cell lung cancer," "non small cell lung carcinoma," "non-small cell lung carcinoma," and "NSCLC." All investigators work together to develop appropri-

ate retrieval strategies. Supplement Part 1, http://links.lww.com/MD/E312 shows the specific Chinese and English search terms for each CHI, and some of the particular retrieval strategies.

2.2. Inclusion criteria

All RCTs of comparing YQFZ CHIs plus the NP regimen with NP alone for treating NSCLC were considered as eligible research for this NMA. All articles were independently reviewed by 2 investigators (Huiyan Luo, Qian Yan). RCTs that satisfied the following criteria will be included:

1. Unrestricted by age, race, gender, region or nationality, age, race, the participants who involved in the study met NSCLC pathological or cytological diagnostic criteria. Besides, patients had no contraindication to chemotherapy and apparent abnormalities in their liver and kidney functions, meanwhile.
2. Interventions involved the administration of YQFZ CHIs combined with the NP regimen. The YQFZ CHIs (such as Delisheng, Huangqi, Kangai, Renshenduotang, Shenfu, Shengmai, Shenmai, and Shenqifuzheng injections) has been authorized by the China Food and Drug Administration and applied in clinics for treating tumors.
3. This study was compared with NSCLC patients who received chemotherapy only. The YQFZ CHIs plus NP regimens were utilized to treat the CHIs group, while the NP group solely received the NP regimen.
4. The study described efficacy outcomes, such as the clinical effectiveness rate and PS. The clinical effectiveness rate was defined as the objective response rate, which is the sum of complete response and partial response. More than 10 points increasing of Karnofsky performance score after completed treatment was considered to be an improvement of PS. Besides, safety outcomes, including leucopenia, nausea and vomiting were evaluated in our study.
5. The study was an RCT that compared with the different results of YQFZ CHIs combined with chemotherapy.

2.3. Exclusion criteria

The exclusion criteria were as follows:

1. Participants have other primary tumors.
2. Interventions include surgery, radiotherapy, immunotherapy, interventional therapy, or other cancer treatment; the NP regimen or YQFZ CHIs were not used.
3. Relevant outcomes were not reported.
4. Different non-RCT study types were excluded, such as reviews, duplicate publications, pharmacological experiments, case reports, qualitative studies, observational studies, meta-analyses, single-arm trials, editorials, and letters.

2.4. Data extraction and quality assessment

All potential articles were managed via EndNote software. After removing duplicate records, 2 researchers (Huiyan Luo, Qian Yan) independently screened the initial search results that might qualify. Then retrieve all identified articles and extract the following data using Microsoft Excel:

1. Publication date, title, the name of the first author, the publication year, and literature sources.
2. Characteristics of the enrolled patients with NSCLC: number, age, gender, intervention, Karnofsky performance score before treatment and stage of cancer.
3. Information on the intervention: the drug, dosage, duration, and treatment cycle.
4. Outcomes: the measured data on the objective response rate and PS outcomes.

These outcomes were calculated using the following formula: the objective response rate = (number of complete response patients + number of partial response patients)/ total number of patients × 100%).[26] The improvement of PS was deemed to be an increase in the Karnofsky performance score of more than 10 points after completed treatment.[27] The safety outcomes were the ADRs, involving leucopenia, nausea and vomiting. The criterion of ADRs met the requirements of the toxicity criteria of chemotherapy drugs issued by WHO in 1981. ADRs = (number of patients occurred ADRs)/ total number of patients × 100%. (5) Description of studying design: blinding, randomized allocation methods, and other items for assessing the risk of bias assessment.

The bias risk assessment was independently completed by 2 investigators (Huiyan Luo and Qian Yan) using Review Manager (Rev Man, version 5.3) statistical software based on the criteria of the Cochrane Risk of Bias Tool (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0).[28,29] When there is a discrepancy, it is resolved through negotiation or by the third investigator (Wenjiang Zheng). The quality assessment of the included RCTs focused on the following essential information: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. According to content provided by the publication, each domain was judged as having a low, unclear or high risk of bias. Additional information, such as randomized methods, inclusion and exclusion criteria, follow-up, reasons for withdrawal and statistical methods, was used to the quality evaluation in each RCT.

2.5. Statistical analysis

We expressed the efficacy and safety outcomes measures as odds ratios with 95% confidence intervals (CIs). When the 95% CIs do not include 1, it means that the difference between the comparison groups was significant. According to the within-study and between-study methodological, the random-effects model of NMA was selected.[30,31] Moreover, since there is no loop connecting the 3 arms in our study, it is no need to evaluate the inconsistency between direct and indirect comparisons.[32] Additionally, all calculations and graphs were conducted by Stata 14.0 software. The relationship between the different treatments was described as a network map.[33–35] The thickness of the lines in the network map was proportional to the number of trials, and the size of the node reflects the total sample sizes. Meanwhile, the areas under the cumulative ranking curve (SUCRA) are used to rank the outcomes of different CHIs. Moreover, the larger area under SUCRA means the better effect of the treatment. The SUCRA values of 100% and 0% assigned to the best and the worst treatments, respectively.[36,37] Besides, the potential of publication bias was graphically accessed via a comparison-adjusted funnel plot.[38] Furthermore, cluster analysis was conducted for choosing the optimal YQFZ CHIs, considering both the efficacy and safety of each intervention simultaneously.

Table 1

Include basic information of literature.

Study	KPS	TNM stages	The age		The Sample Size	Gen	Intervention		Outcome
			A1	A2	N1/ N2	M/F	T1	T2	
Bai CH 2014[1]	NR	III–IV	44–79 (59.7 ± 3.1)	NR	59/50	NR	I	A	(1)
Bian L 2005[2]	50–80	III–IV	32–68	24–76	30/30	45/15	H	A	(1)(2)(4)
Chen AN 2006[3]	NR	IIIB–IV	45–78	20/20	22/18	D	A	(1)(3)	
Chen HA 2010[4]	NR	III–IV	48–76 (59)	50–75 (54)	24/23	31/16	F	A	(1)(3)
Chen L 2014[5]	>60	III–IV	(62.4 ± 10.5)	41/42	53/30	D	A	(1)	
Chen QS 2010[6]	>60	III–IV	29–65 (52.48 ± 9.39)	26–64 (54.5 ± 8.2)	30/30	51/9	H	A	(1)(2)
Chen QS 2011[7]	≥60	IIIB–IV	46–69 (56.77 ± 6.56)	47–69 (55.83 ± 5.89)	30/30	42/18	G	A	(2)
Chen RS 2004[8]	>60	IIB–IV	42–72 (56)	44–75 (57)	21/20	30/11	F	A	(1)
Chen YF 2018[9]	NR	III–IV	42–76 (55.6 ± 5.1)	42–77 (55.2 ± 5.2)	40/40	45/35	I	A	(1)
Chen YZ[10]	NR	III–IV	39–74 (63.2)	29–75 (60.1)	42/40	53/29	G	A	(1)
Ding LM 2007[11]	≥60	IIIB–IV	34–76	35–75	25/25	33/17	D	A	(1)(2)(4)
Ding PQ 2016[12]	NR	III–IV	63–79 (70.5 ± 4.0)	62–80 (70.2 ± 3.6)	60/60	78/42	I	A	(1)(3)
Ding XM 2007[13]	≥60	III–IV	35–68 (52)	34–68 (51)	32/28	39/21	B	A	(1)
Geng D 2007[14]	≥60	III–IV	40–72 (59)	35–68 (58)	42/26	45/23	I	A	(2)
Geng L 2004[15]	≥70	III–IV	25–64 (43)	25–68 (45)	25/15	25/15	I	A	(1)
Gong HW 2008[16]	≥50	IIIB–IV	65–79 (73.2)	66–80 (73.8)	30/30	41/19	F	A	(1)(3)
Gong ZM 2008[17]	>60	IIIB–IV	34–74 (49)	33/32	48/17	I	A	(1)(2)(3)(4)	
Hao XL 2008[18]	≥70	NR	60	63	60/68	NR	I	A	(2)(3)(4)
Hu DX 2007[19]	>60	III–IV	NR	21/22	29/14	D	A	(1)(2)(3)(4)	
Hu W 2008[20]	<70	III–IV	(61.2 ± 5.3)	(60.5 ± 4.3)	40/40	48/32	H	A	(1)
Huang RW 2006[21]	≥60	IIIB–IV	35–75 (55)	36–78 (57)	25/25	34/16	D	A	(1)(2)(3)(4)
Huang YN 2011[22]	NR	III–IV	43–70 (58.5)	42–71 (57.2)	144/142	194/92	D	A	(1)(2)(3)(4)
Huang YN 2012[23]	≥60	III–IV	60–77 (67.9)	60–76 (67.7)	80/72	94/58	D	A	(1)(3)
Jia YL 2012[24]	≥60	III–IV	60–77 (67.9)	60–76 (67.7)	72/71	98/45	I	A	(1)(2)(3)(4)
Jiang PP 2008[25]	NR	IIIB–IV	32–71 (55)	35–69 (54)	20/20	29/11	I	A	(3)(4)
Jin JZ 2017[26]	NR	III–IV	29–74 (55.47 ± 6.26)	30–72 (56.52 ± 6.07)	43/43	60/26	I	A	(1)(2)
Jing H 2007[27]	≥60	III–IV	35–73 (58.12 ± 19.1)	38–70 (56.43 ± 16.4)	51/46	61/36	D	A	(3)(4)
Kang GY 2006[28]	≥60	III–IV	45–71 (62)	52–87 (69)	36/36	40/32	I	A	(1)(3)(4)
Li AM 2006[29]	≥60	III–IV	32–78 (62)	30–75 (59)	34/31	42/23	D	A	(2)(3)
Liang HY 2013[30]	NR	III–IV	60–73 (67)	26/24	24/26	E	A	(3)	
Li FC 2007[31]	50–80	III–IV	45–70 (58.8)	43–69 (57.6)	28/24	37/15	C	A	(1)(2)(3)
Li GX 2011[32]	>60	NR	46–75	32/20	27/25	I	A	(1)	
Li H 2015[33]	≥60	III–IV	63–85 (66.1 ± 7.5)	61–81 (68.7 ± 6.0)	34/12	27/19	I	A	(3)(4)
Li J 2014[34]	≥60	III–IV	53–65 (61.4)	55–67 (62.7)	30/30	37/23	F	A	(1)(2)
Li SL 2005[35]	≥50	IIIB–IV	38–76 (54)	38–75 (52)	30/30	50/10	H	A	(1)
Li TW 2009[36]	30–70	NR	31–72 (58)	32–70 (55)	36/33	46/23	I	A	(2)(3)
Li Y 2007[37]	>60	NR	42–81 (71)	44/43	65/22	I	A	(1)(3)(4)	
Li YQ 2010[38]	>60	IIIB–IV	47–72 (57.1 ± 4.8)	45–75 (55.6 ± 5.4)	43/42	56/29	I	A	(2)
Li ZJ 2009[39]	>50	IIIB–IV	NR	72/68	NR	D	A	(1)(2)(3)	
Li ZJ 2013[40]	≥60	III–IV	45–75 (65)	43–74 (63)	35/33	45/23	D	A	(1)(2)(3)(4)
Liao XD 2015[41]	NR	II	42–74 (61.2 ± 5.7)	43–76 (63.5 ± 6.4)	45/45	58/32	I	A	(1)(2)(3)(4)
Liu CL 2004[42]	≥60	II–IV	60–75 (69.5)	60–76 (68)	60/60	87/33	I	A	(1)(3)
Liu HM 2007[43]	NR	NR	NR	51/50	53/48	H	A	(1)(3)	
Liu JB 2011[44]	≥70	III–IV	50–75 (56.4 ± 5.6)	48–63 (58.5 ± 6.2)	30/30	46/14	F	A	(2)
Liu ZH 2004[45]	>60	IIIB–IV	42–72 (56)	44–75 (57)	21/20	30/11	F	A	(1)(3)
Lu QY 2011[46]	>60	III–IV	46–64 (50.0 ± 7.6)	40–62 (47.2 ± 8.3)	30/30	49/11	H	A	(3)
Lu XA 2010[47]	>60	III–IV	38–70 (50.3 ± 16.7)	40–69 (56.58 ± 9.97)	30/30	43/17	F	A	(1)(3)(4)
Lu XA 2011[48]	≥60	III–IV	32–70 (52)	36–69 (52)	30/30	48/12	G	A	(3)
Lv J 2008[49]	≥50	IIIB–IV	52–78 (65.2)	51–78 (63.8)	40/40	65/15	I	A	(1)(2)
Miao SR 2010[50]	60–85	IIIB–IV	38–71	40–70	38/41	61/18	I	A	(1)(2)(3)(4)
Ran RZ 2009[51]	NR	III–IV	54	55	66/62	86/42	D	A	(1)(3)(4)
Shen JJ 2012[52]	≥60	III–IV	45–72 (60.2 ± 5.3)	43–70 (60.7 ± 5.2)	30/30	50/10	H	A	(1)(3)(4)
Shi ZY 2008[53]	≥60	III–IV	42–79 (61.58 ± 7.95)	43–75 (58.91 ± 6.11)	30/30	42/18	H	A	(1)(3)(4)
Song ZY 2006[54]	≥60	III–IV	30–70 (51)	28–70 (50)	26/26	32/20	D	A	(1)(3)(4)
Tian J 2008[55]	≥60	III–IV	NR	21/22	29/14	D	A	(1)(2)(3)	
Wang HX 2016[56]	>70	III–IV	(55.4 ± 16.7)	45/41	45/41	E	A	(2)(3)(4)	
Wang K 2007[57]	>50	IIIB–IV	38–75 (58.3 ± 7.3)	34–73 (56.7 ± 7.2)	18/18	26/10	I	A	(1)(3)
Wang XY 2007[58]	>60	III–IV	61–82 (72)	35/34	51/18	I	A	(1)(3)(4)	
Wang YX 2014[59]	>70	III–IV	45–80 (56.1 ± 4.6)	43–78 (55.7 ± 5.1)	41/41	60/22	I	A	(2)(3)(4)
Wang YZ 2007[60]	≥60	IIIB–IV	46–75 (58.6)	28/27	37/12	I	A	(1)(2)	
Wei HD 2012[61]	≥60	IIIB–IV	44–72 (58.6 ± 8.4)	50/50	58/42	D	A	(2)(3)(4)	

(*continued*)

Table 1
(continued).

Study	KPS	TNM stages	The age		The Sample Size	Gen	Intervention		Outcome
			A1	A2	N1/ N2	M/F	T1	T2	
Wei JN 2008[62]	≥60	III–IV	28–60 (50.5)	27–60 (51.3)	30/30	45/15	H	A	(1)(2)
Wen JY 2006[63]	>60	IIIB–IV	24–76 (60)	30–75 (58)	40/38	67/11	D	A	(1)(2)
Xiao ZY 2011[64]	≥60	IIIB–IV	35–74 (57.3)	36–73 (56.6)	60/61	82/39	B	A	(2)(3)
Xie WG 2010[65]	≥60	III–IV	60–73	25/25	26/24	F	A	(3)(4)	
Yang HP 2006[66]	NR	IIIB–IV	33–71 (56)	31–73 (57)	58/60	73/45	B	A	(1)(2)(3)
Yang XH 2017[67]	NR	III–IV	46–78 (56.7 ± 4.9)	45–79 (56.8 ± 4.7)	40/40	55/25	I	A	(2)
Yang ZJ 2012[68]	≥60	III–IV	35–67 (52)	32–66 (51)	30/30	50/10	G	A	(1)(4)
Yao JT 2007[69]	>60	III–IV	40–70 (56)	39–70 (55)	32/32	45/19	G	A	(1)(2)
Yao XQ 2014[70]	NR	IIIB–IV	38–71 (55.3)	40/40	62/18	H	A	(1)(3)	
Yin B 2007[71]	>70	NR	35–80 (56)	40–78 (54)	31/40	41/30	D	A	(1)(3)
Yun XY 2012[72]	NR	NR	NR	48/37	56/29	I	A	(1)(3)	
Zha MB 2006[73]	NR	NR	44–78 (61)	43–76 (59.5)	30/30	43/17	H	A	(1)(4)
Zhang CM 2016[74]	≥60	III–IV	41–65 (53.4 ± 4.6)	38–66 (51.2 ± 5.8)	30/30	47/13	G	A	(2)(3)(4)
Zhang CR 2008[75]	>60	IIIB–IV	65–82 (71)	25/25	40/10	D	A	(1)(2)	
Zhang LL 2009[76]	≥70	NR	45–70 (55.4)	30/30	32/28	I	A	(1)(2)	
Zhang LL 2013[77]	≥60	III–IV	45–71 (62)	47–69 (60.3)	27/27	36/18	H	A	(3)
Zhang QH 2008[78]	≥50	IIIB–IV	49–78 (63.5)	50–77 (64)	32/34	45/21	G	A	(1)(3)
Zhang XL 2005[79]	>60	III–IV	35–74 (57)	37–76 (54)	30/32	43/19	D	A	(1)(2)(3)
Zhao CH 2008[80]	>60	NR	25–75 (55.7)	28–73 (54.2)	56/56	64/48	H	A	(3)(4)
Zhao D 2015[81]	NR	III–IV	44–75 (58.2 ± 4.7)	45–73 (57.8 ± 4.9)	40/40	48/32	D	A	(1)
Zhao LL 2017[82]	≥60	III–IV	52–69 (63.5 ± 1.2)	51–67 (61.5 ± 2.1)	50/50	61/39	F	A	(1)(2)
Zhao ZY 2007[83]	>60	III–IV	61–82 (72)	35/54	51/18	I	A	(1)(3)(4)	
Zheng HY 2012[84]	60–90	III–IV	36–73	39–73	30/30	38/22	D	A	(2)(3)
Zheng JH 2009[85]	≥60	NR	42–74 (61.2 ± 5.7)	47–79 (67.35 ± 12.6)	42/42	52/32	I	A	(1)
Zhong FH 2011[86]	NR	NR	36–75 (51.6)	37–74 (53.2)	40/40	57/23	C	A	(3)
Zhu DP 2012[87]	≥70	III–IV	41–76 (59)	40/37	49/28	I	A	(1)(2)(3)(4)	
Zou Y 2013[88]	≥60	III–IV	52–74 (66.3 ± 6.8)	53–71 (64.5 ± 6.1)	38/38	52/24	D	A	(3)

A = NP regimen, A1 = age of experimental group, A2 = age of control group, B = NP + Delisheng injection, C = NP regimen + Huangqi injection, D = NP regimen + Kangai injection, E = NP regimen + Renshenduotang injection, F = NP regimen + Shenfu injection, G = NP regimen + Shengmai injection, Gen = gender, H = NP regimen + Shenmai injection, I = NP regimen + Shenqifuzheng injection, KPS = Karnofsky performance score, M = male, N1 = number of experimental group, N2 = number of control group, NR = not reported, F = female, T1 = treatment in the experimental group, T2 = treatment in the control group, (1) = the clinical effectiveness rate, (2) = the improvement of performance status, (3) = leucopenia, (4) = nausea and vomiting.

3. Results

3.1. Literature search and study characteristics

Initially, we used the above-described search strategy to obtain 4775 citations from electronic databases. After deleting duplicates articles with EndNote X9, 771 studies remained. Next, screening titles and abstracts to remove the irrelevant items and reading the full text to remove articles that did not meet the inclusion criteria. Eventually, the 88 RCTs involving 8 YQFZ CHIs met our selection criteria. The study identification, screening, and inclusive process were illustrated in the Study flow diagram. The number of studies included for different CHIs was as follows: Shenqifuzheng injection (30 trials), Kangai injection (22 trials), Shenmai injection (13 trials), Shenfu injection (9 trials), Shengmai injection (7 trials), Delisheng injection (3 trials), Huangqi injection (2 trials) and Renshenduotang injection (2 trials).

Table 1 summarizes the baseline characteristics of each RCT included. Overall, the present NMA involved 6695 NSCLC patients from 88 RCTs. In the experimental group, 3394 patients received a combination of YQFZ CHIs plus NP regimens, while 3301 patients received only the NP regimen in the control group. The sample size of patients was reported in all RCTs, of which 85 trials (96.59%), 83 trials (94.32%), 76 trials (86.36%), and 68 trials (77.27%) provided information on gender, the age, TNM stages and Karnofsky performance score before treatment, respectively. There was no significant difference in patient's characteristics between the different treatment groups. Figure 1 depicts a network map of the interventions included in the the network-meta analysis.

We rigorously assessed the methodological quality of the included RCTs under the guidance of the Cochrane risk of bias tool. Although randomization was adopted in all trials, only 27 RCTs provided the details of information on the random grouping method. 23 RCTs used a random number table, so these trials were rated low risk (26.14%). 3 RCTs used the difference of hospital time for randomization, and 3 RCTs used the methods of treatment to group, which were rated as high risk (6.82%). The risk of remaining RCTs is considered unclear (67.04%). Regarding allocation concealment, 23 RCTs used a random number table, so it was rated as high risk (26.14%); 1 RCT used an envelopes method that without providing the details information was rated as unclear. All RCTs identified the inclusion and exclusion criteria for NSCLC patients, whereas none of them described the impact of blinding. Data reported from 1 RCT was incomplete, so the trial was rated as a high risk of attrition bias (1.14%). None of the included RCTs explicitly showed reporting bias in terms of selective reporting. For other biases, the included trials did not provide the messages. Therefore, they are regarded as unclear in this domain. The risk of bias assessment was completed by 2 independent reviewers (Huiyan Luo, Qian Yan), and the third reviewer (Wenjiang

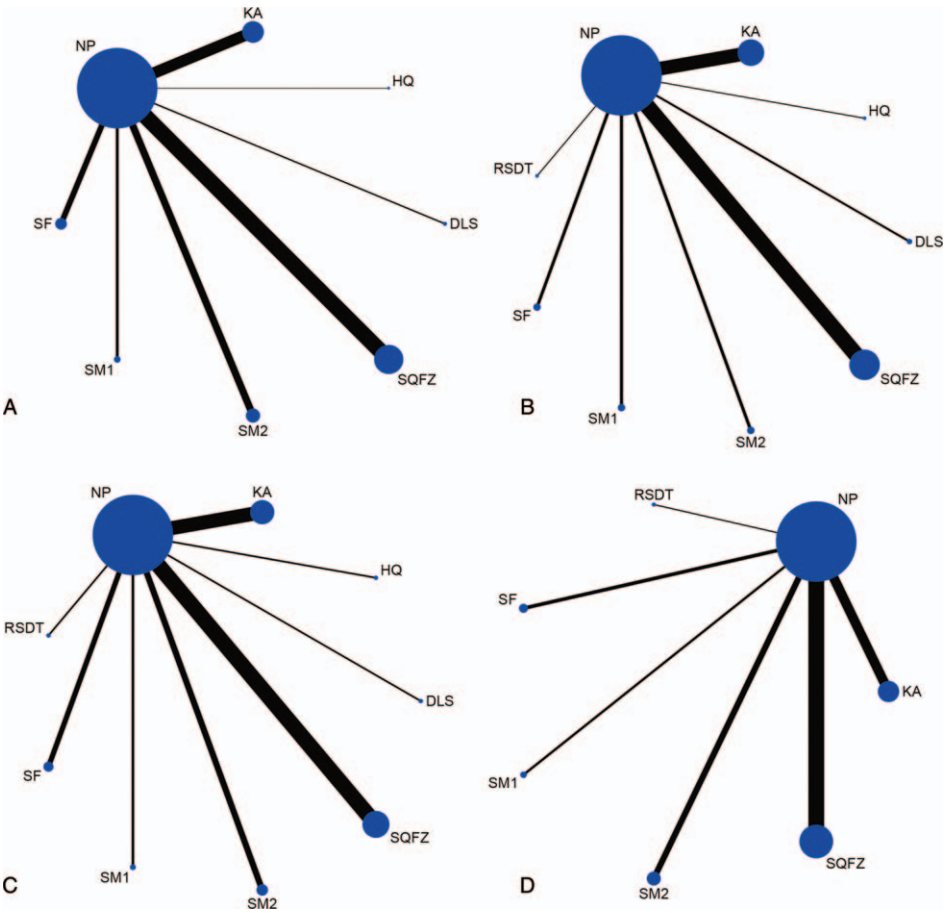

Figure 1. Network graphs of outcomes. (A) the clinical effectiveness rate; (B) performance status; (C) leukopenia; (D) nausea and vomiting. DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

Zheng) resolved the conflicts. In general, the overall quality of the studies in this review can be considered moderate. A summary of the risk of bias for each contained in RCT is shown in Figure 2.

3.2. Outcomes

3.2.1. Efficacy outcomes. In total, 63 RCTs with 7 types of CHIs contributed to the evidence network of the clinical effectiveness rate. According to the results of NMA illustrated in Table 2, Kangai + NP regimen, Shenqifuzheng + NP regimen, Shenfu + NP regimen and Shenmai + NP regimen were better than the NP regimen alone in terms of the clinical effectiveness rate. These results were statistically significant, ORs and 95% CIs were 1.33 (1.07,1.66), 0.69 (0.56,0.84), 0.64 (0.45,0.91) and 0.57 (0.42,0.79) respectively. Nevertheless, the differences

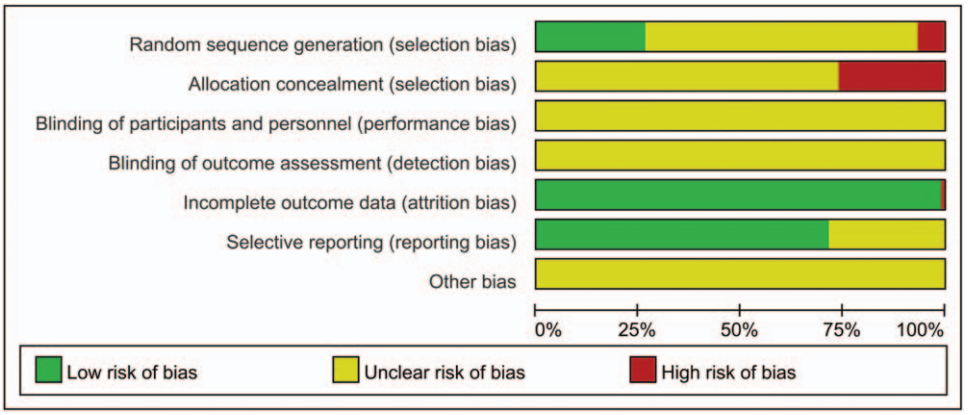

Figure 2. Risk of bias graph.

Table 2

Results (OR, 95% CIs) of network meta-analysis for the clinical effective rate (upper right) and the improvement of performance status (lower left quarter).

SQFZ	1.20 (0.82,1.75)	0.88 (0.52,1.50)	1.07 (0.72,1.59)	–	**0.69 (0.56,0.84)**	0.92 (0.68,1.23)	0.70 (0.23,2.14)	0.88 (0.47,1.64)
0.89 (0.34,2.30)	SM2	0.74 (0.41,1.33)	0.89 (0.55,1.43)	–	**0.57 (0.42,0.79)**	0.76 (0.52,1.13)	0.59 (0.19,1.84)	0.73 (0.37,1.44)
0.78 (0.29,2.09)	0.88 (0.25,3.13)	SM1	1.21 (0.66,2.20)	–	0.78 (0.48,1.27)	1.04 (0.60,1.77)	0.80 (0.24,2.64)	0.99 (0.46,2.14)
0.87 (0.36,2.09)	0.97 (0.30,3.21)	1.10 (0.33,3.72)	SF	–	**0.64 (0.45,0.91)**	0.86 (0.57,1.29)	0.66 (0.21,2.08)	0.82 (0.41,1.63)
0.70 (0.18,2.71)	0.79 (0.16,3.80)	0.90 (0.18,4.38)	0.81 (0.18,3.74)	RSDT	–	–	–	–
2.74 (1.91,3.93)	**3.09 (1.28,7.44)**	**3.49 (1.41,8.68)**	**3.16 (1.42,7.06)**	**3.90 (1.06,14.35)**	NP	**1.33 (1.07,1.66)**	1.02 (0.34,3.06)	1.27 (0.71,2.30)
1.04 (0.61,1.77)	1.17 (0.45,3.07)	1.33 (0.49,3.57)	1.20 (0.49,2.93)	1.48 (0.38,5.76)	**0.38 (0.26,0.56)**	KA	0.77 (0.25,2.35)	0.96 (0.51,1.80)
1.16 (0.22,6.17)	1.30 (0.20,8.34)	1.48 (0.23,9.58)	1.34 (0.22,8.25)	1.65 (0.20,13.32)	0.42 (0.08,2.16)	1.11 (0.21,5.96)	HQ	1.24 (0.36,4.32)
0.65 (0.25,1.65)	0.73 (0.21,2.50)	0.82 (0.23,2.89)	0.74 (0.23,2.43)	0.92 (0.19,4.39)	**0.24 (0.10,0.56)**	0.62 (0.24,1.60)	0.56 (0.09,3.55)	DLS

CIs = confidence intervals, DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, OR = odds ratio, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

between different CHIs were not statistically significant. According to the calculated probabilities of Figure 3A and Table 4, Shenmai (84.7%), Shenfu (70.0%), and Shenqifuzheng (61.6%) yielded higher probabilities of improving clinical effectiveness rate among CHIs groups. The ranks of the examined CHIs, based on the clinical effectiveness rate calculating from SUCRA, were shown as follows: Shenmai > Shenfu > Shenqifuzheng > Kangai > Delisheng > Shengmai > Huangqi.

A total of 41 RCTs, including 8 types of CHIs, reported PS information. The results demonstrated that receiving Renshenduotang + NP regimen, Shengmai + NP regimen, Shenfu + NP regimen, Shenmai + NP regimen, Shenqifuzheng + NP regimen, Kangai + NP regimen and Delisheng + NP regimen were associated with a substantial improvement in PS versus receiving the NP regimen alone; these between-group differences were statistically significant, with ORs and 95% CIs of 3.90 (1.06, 14.35), 3.49 (1.41, 8.68), 3.16 (1.42, 7.06), 3.09 (1.28, 7.44), 2.74 (1.91, 3.93), 0.38 (0.26,0.56), and 0.24 (0.10, 0.56), respectively (Table 2). According to the calculated probabilities, Delisheng (74.3%), Renshenduotang (66.2%), and Shengmai (62.8%) seemed to be the optimal choices for improving PS (Fig. 3B and Table 4). Based on SUCRA from the calculated probabilities of

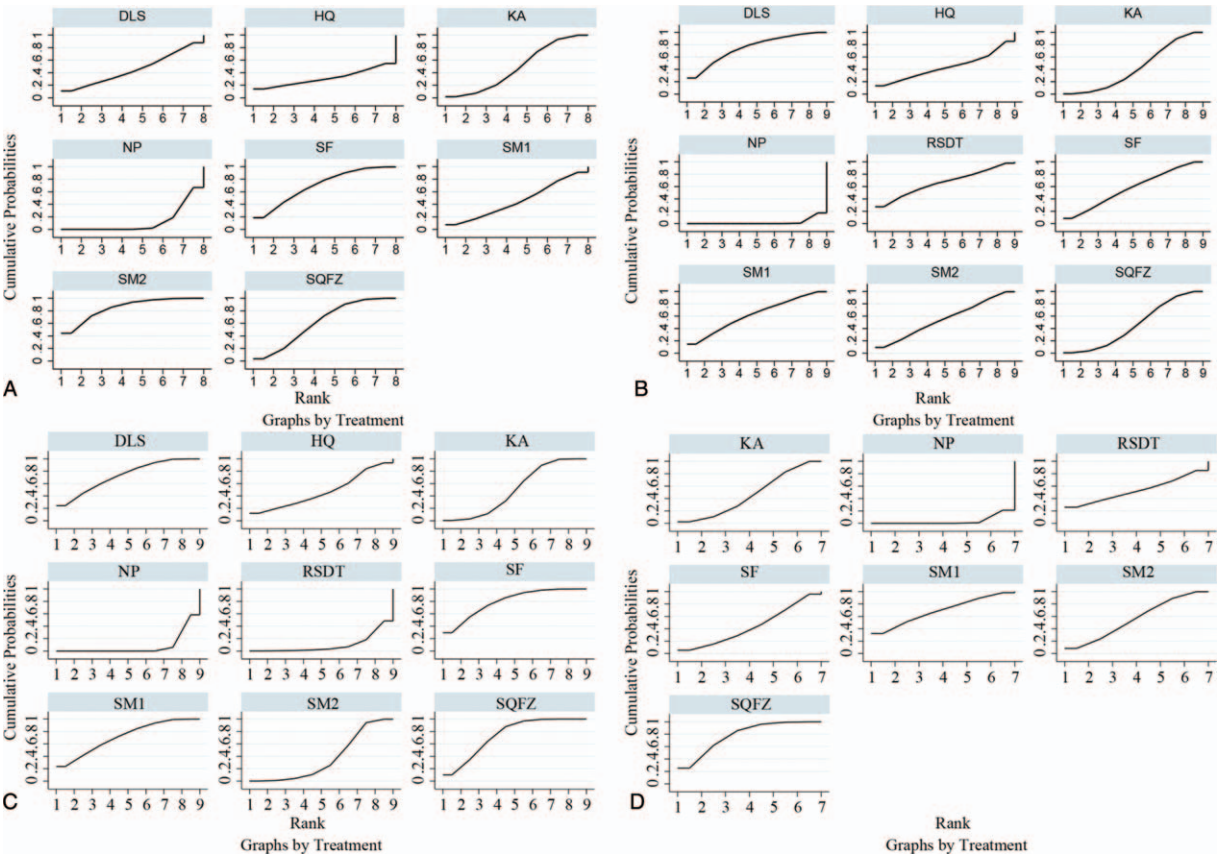

Figure 3. Rank of the cumulative probabilities for outcomes. (A) the clinical effectiveness rate; (B) performance status; (C) leukopenia; (D) nausea and vomiting. DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

Table 3

Results (OR, 95%CIs) of network meta-analysis for nausea and vomiting (upper right) and leucopenia (lower left quarter).

SQFZ	1.34 (0.63,2.86)	1.06 (0.35,3.24)	1.59 (0.64,3.97)	1.38 (0.27,7.18)	**3.20 (2.11,4.86)**	1.50 (0.77,2.93)	–	–
0.60 (0.34,1.07)	SM2	0.79 (0.24,2.66)	1.19 (0.43,3.32)	1.03 (0.19,5.72)	**2.39 (1.27,4.49)**	1.12 (0.49,2.55)	–	–
1.00 (0.44,2.27)	1.66 (0.68,4.08)	SM1	1.50 (0.40,5.58)	1.30 (0.19,8.68)	**3.01 (1.07,8.45)**	1.41 (0.44,4.50)	–	–
1.11 (0.56,2.23)	1.85 (0.85,4.05)	1.11 (0.42,2.96)	SF	0.87 (0.15,5.19)	2.01 (0.89,4.53)	0.94 (0.36,2.48)	–	–
0.29 (0.10,0.81)	0.48 (0.16,1.43)	**0.29 (0.08,0.99)**	**0.26 (0.08,0.82)**	RSDT	2.31 (0.47,11.36)	1.09 (0.20,5.81)	–	–
0.30 (0.22,0.42)	**0.50 (0.31,0.82)**	**0.30 (0.14,0.65)**	**0.27 (0.15,0.50)**	1.05 (0.40,2.81)	NP	**0.47 (0.28,0.79)**	–	–
0.75 (0.48,1.18)	1.25 (0.70,2.22)	0.75 (0.33,1.71)	0.67 (0.33,1.35)	2.61 (0.93,7.34)	**2.47 (1.78,3.44)**	KA	–	–
0.66 (0.19,2.31)	1.10 (0.30,4.05)	0.66 (0.16,2.76)	0.60 (0.15,2.31)	2.31 (0.49,10.95)	2.19 (0.66,7.33)	0.89 (0.25,3.09)	HQ	–
1.01 (0.45,2.28)	1.68 (0.69,4.11)	1.01 (0.35,2.94)	0.91 (0.35,2.40)	**3.53 (1.03,12.11)**	**3.35 (1.59,7.06)**	1.35 (0.60,3.06)	1.53 (0.37,6.31)	DLS

CIs = confidence intervals, DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, OR = odds ratio, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

PS, the examined CHIs were ranked as follows: Delisheng > Renshenduotang > Shengmai > Shenfu > Shenmai > Shenqifuzheng > Kangai > Huangqi. The SUCRA values of each CHIs group of outcomes are listed in Table 4.

3.2.2. Safety outcome. The data on leucopenia were available for 56 RCTs involving 8 types of CHIs. The results indicated a favorable trend of relieving leucopenia when Shenqifuzheng + NP regimen, Shenmai + NP regimen, Shengmai + NP regimen, Shenfu + NP regimen, Kangai + NP regimen and Delisheng + NP regimen were applied. The ORs and 95% CIs were 0.30 (0.22,0.42), 0.50 (0.31,0.82), 0.30 (0.14,0.65), 0.27 (0.15,0.50), 2.47 (1.78,3.44), and 3.35 (1.59,7.06) respectively (Table 3). The calculated probabilities demonstrated in Figure 3C and Table 4, Shenfu (79.4%), Shenqifuzheng (74.4%), and Shengmai (71.9%) seemed to better than other injections in relieving leucopenia. According to the SUCRA from the calculated probabilities for the leucopenia (Table 4), the examined CHIs were ranked as follows: Shenfu > Shenqifuzheng > Shengmai > Delisheng > Kangai > Huangqi > Shenmai > Renshenduotang.

The study including 32 RCTs, involving 6 types of CHIs provided sufficient information for nausea and vomiting: Shenqifuzheng + NP regimen, Shenmai + NP regimen, Shengmai + NP regimen, and Kangai + NP regimen were associated with a substantially relieving nausea and vomiting compared the NP regimen alone. And their ORs and 95% CIs were 3.20 (2.11, 4.86), 2.39 (1.27, 4.49), 3.01 (1.07, 8.45), and 0.47 (0.28, 0.79), respectively (Table 3). Figure 3D and Table 4 showed the calculated probabilities, Shenqifuzheng (78.4%), Shengmai (68.6%) and Shenmai (55.1%) are superior in relieving nausea and vomiting compared with other injections. Under the SUCRA from the calculated probabilities (Table 4), the examined CHIs were ranked as follows: Shenqifuzheng > Shengmai > Shenmai > Renshenduotang > Kangai > Shenfu.

3.3. Publication bias

As depicted in Figure 4, the publication bias of the included trials regarding the clinical effectiveness rate (A), PS (B), leukopenia (C), nausea and vomiting (D) were measured by funnel plots. The results illustrated that there might be potential publication bias among included RCTs. Since the visual asymmetrical funnel plot suggested the possibility of publication bias, which might influence the accuracy of the pooling result.

3.4. Cluster analysis

To estimate the optimal YQFZ CHIs combined with the efficacy and safety, we performed a cluster analysis for RCTs and described the details of the results simultaneously. The plot is based on SUCRA values of CHI groups, and each color represents a group of treatments. The groups of the upper right corner indicate superior to other CHIs in efficacy and safety. The cluster analysis demonstrated that Delisheng, Shenfu, and Shenmai injections have better therapeutic effects in the efficacy outcomes (Fig. 5A). Regarding the safety outcomes, the cluster analysis revealed that Shenqifuzheng, Shengmai and Shenfu injections might be the acceptable options for relieving ADRs (Fig. 5B). In contrast, only the NP regimen had the worst overall rank of the current result (Fig. 5A and B).

4. Discussion

In summary, the NMA results show that Shenfu injection combined with the NP regimen seems to be the best choice for

Table 4

SUCRA values of different groups for outcomes.

	The Clinical Effectiveness Rate	Performance Status	Leucopenia	Nausea and vomiting
DLS	45.6%	74.3%	71.7%	–
HQ	31.9%	42.3%	47.1%	–
KA	48.6%	43.2%	50.4%	46.9%
NP	12.5%	2.3%	8.2%	3.9%
RSDT	–	66.2%	9.9%	52.4%
SF	70.0%	57.1%	79.4%	44.8%
SM1	45.0%	62.8%	71.9%	68.6%
SM2	84.7%	55.1%	37.0%	55.1%
SQFZ	61.6	46.7%	74.4%	78.4%

DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

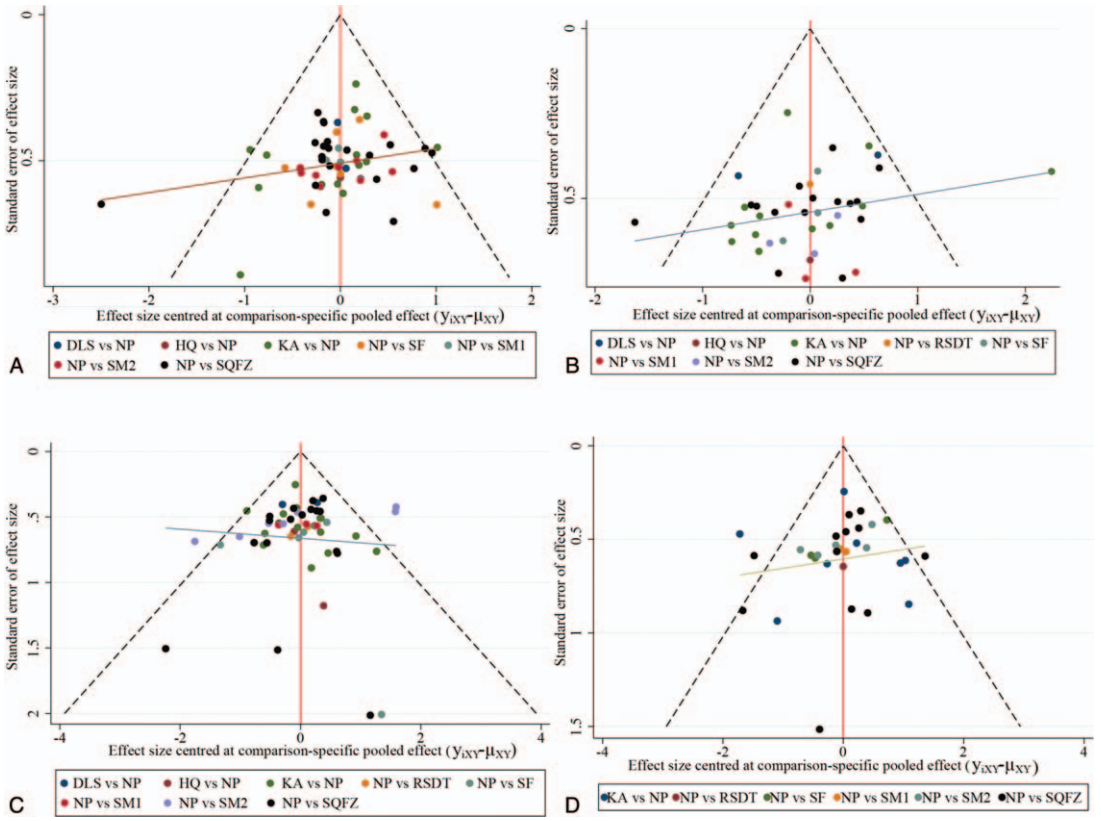

Figure 4. Funnel plot of outcomes. (A) the clinical effectiveness rate; (B) performance status; (C) leukopenia; (D) nausea and vomiting. DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

NSCLC patients in terms of efficacy and safety. However, Shenfu, Shenqifuzheng and Shenmai injection also can improve the clinical effects compared with the NP regimen alone. From the aspect of PS, the NP regimen combined with Delisheng, Renshenduotang and Shengmai injection are superior choices. Plus Shenfu, Shenqifuzheng, and Shengmai injections are preferable to receiving NP regimens alone in the field of relieving leukopenia. Besides, combine with Shenqifuzheng, Shengmai, and Shenmai injections can alleviate nausea and vomiting better than the NP regimen alone. Statistically significant differences were observed between these groups. Consider both efficacy and safety aspects, Shenfu injection is the better choice.

Chemotherapy is usually the first-choice treatment option for advanced and metastatic NSCLC patients. As one of the first-line treatments, the NP regimen can alleviate symptoms and improves the quality of life.[7–9,39] However, the symptoms of hematologic toxic, fatigue, nausea, anorexia, and vomiting caused by chemotherapy are inevitable until now. Prolonging survival times and improving tumor-related symptoms are the primary targets of palliative chemotherapy for advanced NSCLC patients.

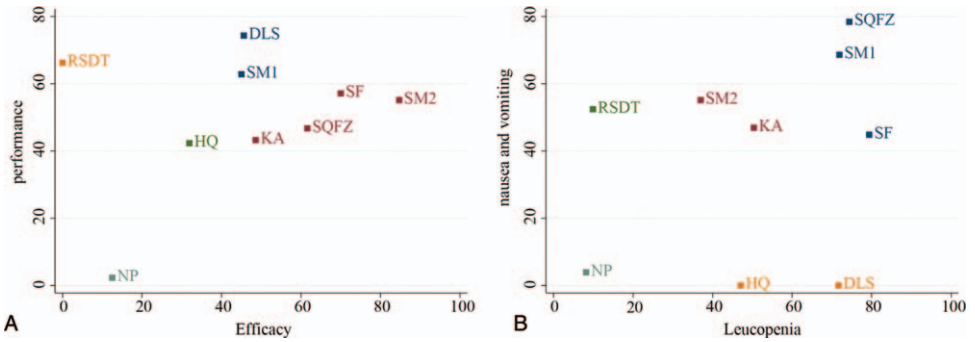

Figure 5. Cluster analysis plot of outcomes. (A) the clinical effectiveness rate (x-axis) and performance status (y-axis); (B) leukopenia (x-axis) and nausea and vomiting (y-axis). DLS = Delisheng injection, HQ = Huangqi injection, KA = Kangai injection, NP = NP regimen, RSDT = Renshenduotang injection, SF = Shenfu injection, SM1 = Shengmai injection, SM2 = Shenmai injection, SQFZ = Shenqifuzheng injection.

Research has shown that CHM has significant advantages in inhibiting tumor progression, enhancing the anti-tumor effects of chemotherapeutics, reducing toxic, and ADRs, improving hematopoietic function and enhancing immune system function of the organism.[40,41]

The active ingredients of Shenfu injection are mainly ginsenoside, aconitine and ginseng polysaccharide. Aconitine upregulates the expression of proapoptotic factors, such as Bax, cl-caspase-3, cl-caspase-9, cleaved poly(ADP-ribose) polymerase 1, and decreasing the anti-apoptotic Bcl-2 expression to induce pancreatic cancer cells apoptosis.[42] Shenmai injection is widely used for the treatment of coronary heart disease and tumors, which was mainly made of Red Ginseng and Radix Ophiopogonis.[43–45] Ginseng saponins, a major component of Shenmai injection, many studies have found that it works synergistically with chemotherapeutic drugs through a variety of cancer signaling pathways, such as NF-κB, JNK, MAPK/ERK, p53, among others.[46,47] Ginsenoside enhances the chemosensitivity of tumor tissue to cisplatin by reducing the basal level of HO-1/NQO-1 and nuclear Nrf2, thereby exerting antitumor activity. Besides, it can scavenge cisplatin-induced intracellular ROS damage to protect and kidney and liver.[48] Delisheng injection, composed of ginseng, milk vetch root, secretion bufonis, and Cantharidium, usually used to combine with chemotherapy for cancer. Evidence revealed that DeliSheng might inhibit cell invasion and migration through the NF-κB pathway.[49] Regarding Shenqifuzheng injection, the primary consisted of astragalus and codonopsis, ordinarily used to improve immune function against chronic diseases. Animal experimental results showed that Shenqifuzheng injection could increase the spleen index of nude mice induced by cyclophosphamide, promote recovery of peripheral white blood cells and marrow cells, enhanced T cell, and B cell proliferation responses, increase the activity of splenic natural killer cells and peritoneal macrophages, and restored the level of interleukin-2 in the serum. Therefore, it showed that Shenqifuzheng injection could accelerate the recovery of immunosuppression.[50] Moreover, multiple ingredients of flavonoids (a component of Shenqifuzheng injection) have been discovered to reverse the MDR of tumor cells.[51] Kangai injection, a typical anticancer injection of TCM, mainly composed of ginseng, astragali radix, and matrine. A variety of active ingredients of Kangai injection have anticancer activity, such as ginsenoside, astragaloside, matrine, oxymatrine.[52] The study showed that matrine might inhibit the migration and invasion of NSCLC cells by block PAX2 expression to interfere with the epithelial-mesenchymal transition signaling pathway.[53] Astragaloside could induce apoptosis of cancer cells through triggering DNA fracture and chromatin condensation.[54] What is more, it also could down-regulate regulatory T cells and up-regulate cytotoxic T lymphocytes to interfere with T-cell immunity. And blocking Indoleamine 2,3-dioxygenase induction to inhibit the progression of lung cancer.[55]

In recent years, with the recognition of evidence-based medicine, systematic reviews and meta-analysis have been widely accepted and used to guide clinical practice.[56] At present, many pieces of research are focused on the CHIs combined with chemotherapy for treating NSCLC, there are rare reports combined with specific chemotherapy regimens. By contrast, the strengths of the moment study include the comprehensive coverage of the current and latest research findings. Furthermore, a single NP regimen was evaluated in our study to avoid potential interference caused by the different chemotherapeutic drugs in clinics. Above all, we rigorously established inclusion and exclusion criteria through a potential RCTs selection process, used reliable Bayesian NMA statistical methods to evaluate different outcomes meanwhile. The efficacy outcomes in the present study involved the clinical effectiveness rate and PS, and safety outcomes referred to leucopenia, nausea, and vomiting. The size of SUCRA was used to identify the optimal treatment for each result, and the cluster analysis was used to estimate the superior CHIs in terms of efficacy and safety.

Several limitations of the current NMA should be attention. Firstly, although the current NMA has addressed this limitation to a certain extent, there was a lack of head-to-head comparisons of different CHIs. It is necessary to draw more head-to-head comparisons between different types of CHIs to obtain more reliable conclusions. Secondly, the endpoint outcomes, such as overall survival and progression-free survival, play a crucial role in identifying and judging the therapeutic effects of cancer patients, while the majority of the included trials did not report long-term endpoint outcomes. Hence, clinical trials of tumors patients should focus on more meaningful endpoints. Thirdly, all selected trials are published in Chinese journals, only partially listed in the international databases, which reduces the universality of the results. Another apparent limitation of the present research contains the methodological quality of the RCTs. More details of the randomized method, allocation concealment and blind methods should be provided in future studies, because the methodological quality of RCTs is closely associated with the credibility of the assessments in the systematic reviews. For this reason, we suggest that clinical trials should pay attention to improving the quality of methodologies to promote the rational use of CHIs. Finally, in the original literature, although the historical types of each article were mentioned in the baseline data, the therapeutic effect of each subtype of NSCLC in the result were not analyzed. So, we cannot determine which subtype of NSCLC is more effective in combination with CHI plus NP regimen due to the limitation of original data. We advised that we should pay more considerable attention to exploring which historical type of NSCLC is more effective in the combination of CHI plus NP regimen, which will promote the scientific clinical decision making. Given the limited quality and quantity of the included studies, more rigorous RCTs are needed to verify the beneficial role of CHIs combined with chemotherapy in NSCLC patients. Despite the above limitations, our NMA provided a complete evaluation of the efficacy and safety of different YQFZ CHIs for NSCLC patients combined with the NP regimen.

5. Conclusion

In conclusion, the current evidence recommends that the combination of Shenfu injection with NP regimen is the most preferable and beneficial option for NSCLC patients in terms of efficacy and safety. Nevertheless, the results from multi-center trials and high-quality research are critical to support our findings.

Author contributions

Huiyan Luo and Wenjiang Zheng contributed equally to this work and should be regarded as co-first authors.

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Methodology: Wenjiang Zheng, Qian Yan, Fan He.
Project administration: Huiyan Luo.
Resources: Huiyan Luo, Wenjiang Zheng.
Software: Boqing Wang.
Supervision: Huiyan Luo, Wenjiang Zheng, Qian Yan, Xiongwen Wang.
Validation: Xiongwen Wang, Huiyan Luo, Wenjiang Zheng, Qian Yan.

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