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TMR Cancer

Efficacy and safety of Kang'ai injection adjunct with TP chemotherapy for the treatment of non-small cell lung cancer: a systematic review and meta-analysis of randomized controlled trials

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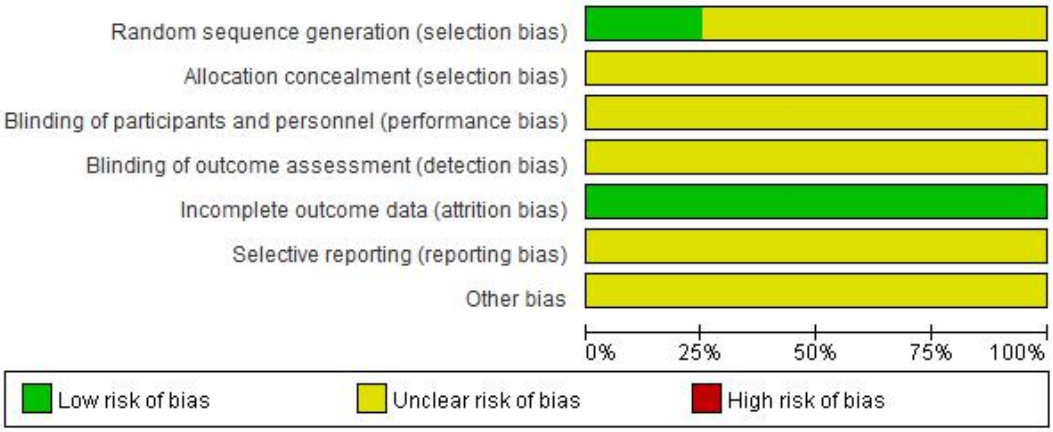
Highlights

Lung cancer has become one of the most common and frequent malignant tumors. Non-small cell lung cancer accounts for about 80% of all lung cancers, and about 75% of patients are in the advanced stage when they are discovered. Chemotherapy occupies an important position in the treatment of non-small cell lung cancer, but while chemotherapy brings curative effects, there are serious side effects. Therefore, looking for a drug that can enhance the efficacy of chemotherapy and reduce the side effects of chemotherapy is currently the treatment of lung cancer. One of the research hotspots. Traditional Chinese medicine shows unique advantages in the treatment of lung cancer. Combined with chemotherapy can effectively reduce the side effects of patients, improve the quality of life, and prolong survival.



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Abstract

Background: Combination therapy with traditional Chinese medicine and chemotherapy was proposed as a therapeutic strategy for non-small cell lung cancer patients. Therefore, we performed a systematic review and meta-analysis of randomized controlled trials to assess effects of this combination therapy on non-small cell lung cancer. To evaluate the efficacy and safety of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of non-small cell lung cancer. **Methods:** A randomized controlled study of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the databases of China National Knowledge Infrastructure Database, WanFang Database, VIP Database, Sino-Med Database, PUBMED, EMBASE and Cochrane library was searched by computer. The literatures published from the database establishment to July 1, 2020 were included in the search scope. After 2 evaluators independently evaluated and cross checked the quality of the study, Revman 5.3 was used to meta analyze the clinical effect of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy on patients with non-small cell lung cancer. **Results:** A total of 1,370 lung cancer patients were included in 20 RCTs. The results of meta-analysis showed that there were significant differences between the 2 groups in clinical efficacy (RR = 1.32, 95% CI (1.20, 1.44)), quality of life (RR = 1.44, 95% CI (1.32, 1.57)), immune function (MD = 0.53, 95% CI (0.23–0.83)), adverse reactions (RR = 0.49, 95% CI (0.41, 0.58)). **Conclusion:** The Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy is effective and safe in the treatment of non-small cell lung cancer, and has great prospects for further development. However, the quality of evidence was very low-to-moderate. Considering the poor quality of evidence, we are not very confident in the results. We look forward to more research and update results in the future and improve the evidence quality.

Key words: Kang'ai injection, Non-small cell lung cancer, Traditional Chinese medicine, Chemotherapy, Clinical research, Meta analysis

Author contributions:

Chen-Chen Zhao, Chuan-Xin Liu and Xian-Bin Kong contributed to conceive and design the project; Ying-Jie Jia and Tong Wu contributed to perform the review; Wen-Tai Pang contributed to analyze the data; Jie Zhou was responsible for quality control of the study.

***Abbreviations*:**

NSCLC, non-small cell lung cancer; TCM, traditional Chinese medicine; RCTs, randomized controlled trials; CNKI, China National Knowledge Infrastructure Database; OR, odds ratios; CI, confidence intervals; MD, mean differences; CR, complete response; PR, partial response.

***Competing interests*:**

The authors declare that they have no conflict of interest.

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Background

Lung cancer is a kind of lung cancer originated from trachea, bronchus mucosa or gland. It has become the most common and frequent cancer. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancer patients. About 75% of the patients have been found in the middle and late stage, and the 5-year survival rate is very low. According to the latest global cancer statistics 2019, lung cancer is the highest incidence rate of malignancy in the world [1], which is one of the main causes of cancer deaths. In China, the incidence of lung cancer is also not optimistic, and the overall incidence rate is the first [2]. At present, platinum based combination chemotherapy is still the standard first-line treatment for lung cancer [3–4]. However, chemotherapy is often accompanied by serious toxic and side effects [5]. Therefore, it is one of the hotspots of lung cancer treatment to find a drug that can not only enhance the efficacy of chemotherapy, but also reduce the side effects of chemotherapy.

In recent years, traditional Chinese medicine (TCM) has gradually shown its unique advantages in the treatment of lung cancer [6–7]. TCM combined with radiotherapy and chemotherapy has become an effective method for the treatment of lung cancer, which can effectively prolong the survival period and improve the quality of life [8–10]. TCM has gradually shown its unique advantages in the treatment of lung cancer. Combined with surgery, radiotherapy and chemotherapy, it has become an effective method for the treatment of lung cancer, which can effectively reduce the side effects, improve the quality of life and prolong the survival period. Modern research shows that Huangqi (*Astragali radix*), Renshen (*Ginseng radix et rhizoma*) and Kushen (*Sophorae flavescentis radix*) [11–15], as the main components of the Chinese patent medicine Kang'ai injection, have good anti-tumor activity, and have better protection and stimulation on the hematopoietic function of human bone marrow, without any toxic and side effects, and have become more commonly used anti-tumor drugs in clinical.

At present, the clinical trials of the Chinese patent medicine Kang'ai injection combined with chemotherapy in the treatment of lung cancer are increasing, but the small sample trial is the main one, and some of them have methodological problems, so the clinical reference value of the conclusions is limited. The purpose of this study is to further improve and update the clinical data by collecting the randomized controlled trials (RCTs) of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC at home and abroad, and to use the method of meta analysis for systematic evaluation, so as to provide evidence-based basis for the clinical efficacy and safety of the Chinese patent medicine Kang'ai injection, and then provide reference for the clinical treatment of NSCLC.

Methods

Registration

Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16], our manuscript has been registered with PROSPERO (No. CRD42020176917) which was available online at https://www.crd.york.ac.uk/prospero/CRD42020176917.

Literature strategy

A systematic literature search was conducted (from inception to July 1, 2020) using 3 international electronic databases (PUBMED, EMBASE and Cochrane library) and 4 Chinese literature databases (China National Knowledge Infrastructure, WanFang, Sino-Med, and VIP). We identified relevant literature using the following search terms: (non-small cell lung cancer OR NSCLC) AND (Chinese herbal medicines OR CHMs OR traditional Chinese medicine OR TCM) AND (chemotherapy OR taxol). We manually searched references to detect additional articles without language or publication restriction.

Eligibility criteria

Types of studies. All the RCTs reporting the application of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy for the treatment of NSCLC were included. Studies irrelevant to RCTs or trials that participants, control measures, interventions, and outcomes did not meet the criteria were excluded.

Types of Patients. Patients with NSCLC confirmed by pathology or cytology, whose western medicine diagnosis standard and clinical stage conform to National Comprehensive Cancer Network guidelines and expert consensus [3–4].

Types of interventions. The treatment group is the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy, the control group is TP chemotherapy, the chemotherapy scheme of the treatment group and the control group needs to be completely consistent, and the chemotherapy course and drug dosage are unlimited.

Types of outcome measures. Mainly referring to the criteria for evaluating the efficacy of solid tumors (recist1.1): the efficacy indicators are divided into complete response (CR) for the disappearance of all target lesions, the short diameter of all pathological lymph nodes (including target nodes and non target nodes) must be reduced to less than 10 mm; the sum of the diameter of target lesions for partial response (PR)

is reduced by at least 30% compared with the baseline level; and the reduction of target lesions for stable disease. In addition to the minimum of the sum of the diameters of all the target lesions measured in the whole experimental study, the relative increase of the diameter and the relative increase of the diameter is at least 20% (if the baseline measurement is the minimum, the baseline value is the reference). An absolute increase of at least 5 mm in diameter and must be met (the presence of one or more new lesions is also considered progressive disease). The effective rate was calculated as CR + PR/total cases × 100%. Quality of life score (Karnofsky score): for improvement, score increase ≥ 10 points; for decrease, score decrease ≥ 10 points; for stability, score increase or decrease < 10 points. The improvement of immune function was detected by flow cytometry, mainly by CD3, $CD4^+$, $CD4^+/CD8^+$ and other indicators of cellular immune function. According to the classification standard of toxic and side effects of anticancer drugs formulated by who, it is divided into 0–IV degrees.

Data extraction

Two experienced investigators (Zhao and Kong) independently browsed through the titles and abstracts of literature for removing irrelevant articles (pharmacokinetic studies, animal or laboratory studies, and general reviews) and duplication. Subsequently, studies that met inclusion criteria were retrieved for full-text evaluation. Abstracted data were extracted with a standardized form, including study characteristics (study design, author name, and publication year), patient characteristics (age, gender, and clinical staging), and a specific description of the experiment and control group (intervention, outcomes, and duration). Divided opinions would be resolved by consensus and further discussion with a third reviewer.

Quality assessment of studies

The bias risk assessment tool recommended by the *Cochrane Handbook for Systematic Review of Interventions* [17] was applied to evaluate the methodological quality of RCTs through the following 6 domains: random sequence of generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data addressed, selective reporting, and other bias [17, 18]. The evaluation results were divided into 3 categories: high risk of bias, low risk of bias, and unclear risk of bias.

Statistical analysis

All included studies were analyzed with Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for dichotomous data, while mean differences (MD), standardized mean differences, and 95% CI were calculated for continuous data. Heterogeneity was statistically assessed using the chi-squared test and the I^2 statistic, and $I^2 > 50\%$ indicated obvious heterogeneity among trials. The analysis was carried out by the use of a random Theffect model if $P < 0.1$ or $I^2 > 50\%$ but a fixedeffect model if $P \geq 0.1$ or $I^2 \leq 50\%$. Descriptive approaches would be adopted if the data were insufficient. Funnel plots were employed to evaluate the potential publication bias for primary outcomes if more than 10 studies were included for a meta-analysis [19].

Results

Search results

The process of study selection and identification is shown in PRISMA flow diagram. A total of 565 Chinese literatures and 4 English literatures potentially relevant studies were initially screened in the electronic databases based on our literature searching strategy. After removing 457 duplicates, 112 studies were identified for further analysis. Through screening the titles and abstracts, 83 studies were excluded. A total of 29 full-text studies were retrieved for further assessment. Finally, 20 full-text studies [20–39] were then assessed for eligibility (Figure 1).

Study characteristics

Table 1 shows the details of the included studies. Of these trials, all of them were published in China. They were first published in 2008 and latest in 2017. A total of 1,370 patients with NSCLC were included in 20 studies, with a course of 2–4 cycles, including 688 in the the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy group and 682 in the TP chemotherapy group (Table 1).

Risk of bias assessment

Of the 20 studies included in the bias risk assessment included in the study, 5 studies adopted the correct random method [22, 25, 27, 33, 36], which is low risk, 13 studies only mentioned the specific random method [20–21, 24, 26, 28, 30–32, 34–35, 37–39], and 2 studies did not mention whether it is random [23, 29], which is unclearrisk. All 20 studies did not mention the method of assignment concealment and blindness, which is unclearrisk. None of the 20 studies were able to obtain the experimental design, so they were all rated as unclearrisk in terms of selective reporting. No incomplete data was found in 20 studies, so they were rated lowrisk (Figure 2, 3 and Appendix material 1).

Effects of interventions

Clinical efficacy. Twenty studies [20–39] the clinical efficacy of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC was reported. Through

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heterogeneity test and analysis, the homogeneity between the included studies was better (I^2 = 0%, P = 0.97), and the fixed effect model was selected. The results showed that (RR = 1.32, 95% CI (1.20, 1.44), Z = 6.10, P < 0.00001), indicating that the clinical efficacy of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy was better than that of TP chemotherapy,

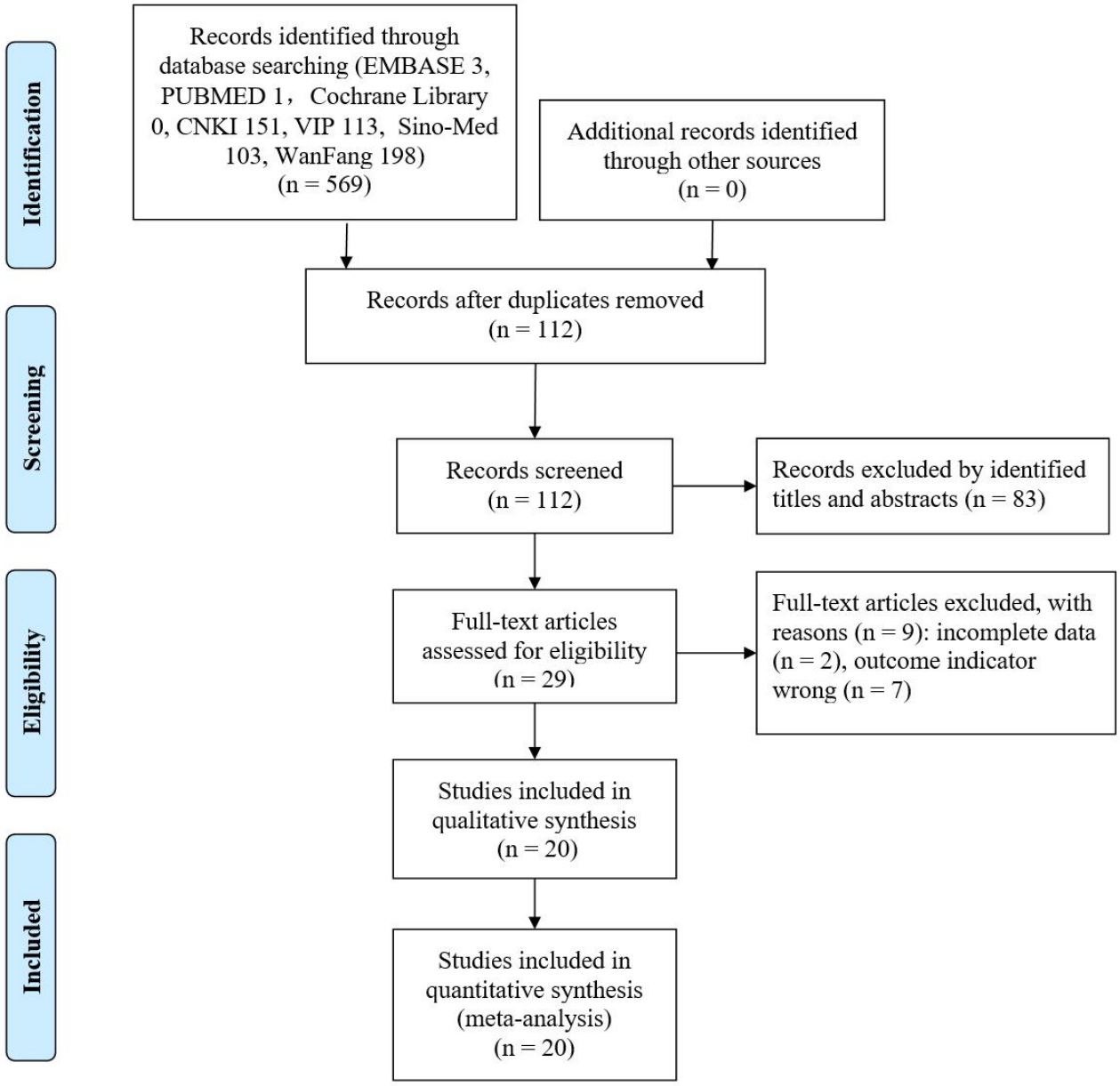

Figure 1 Flow diagram of study selection process

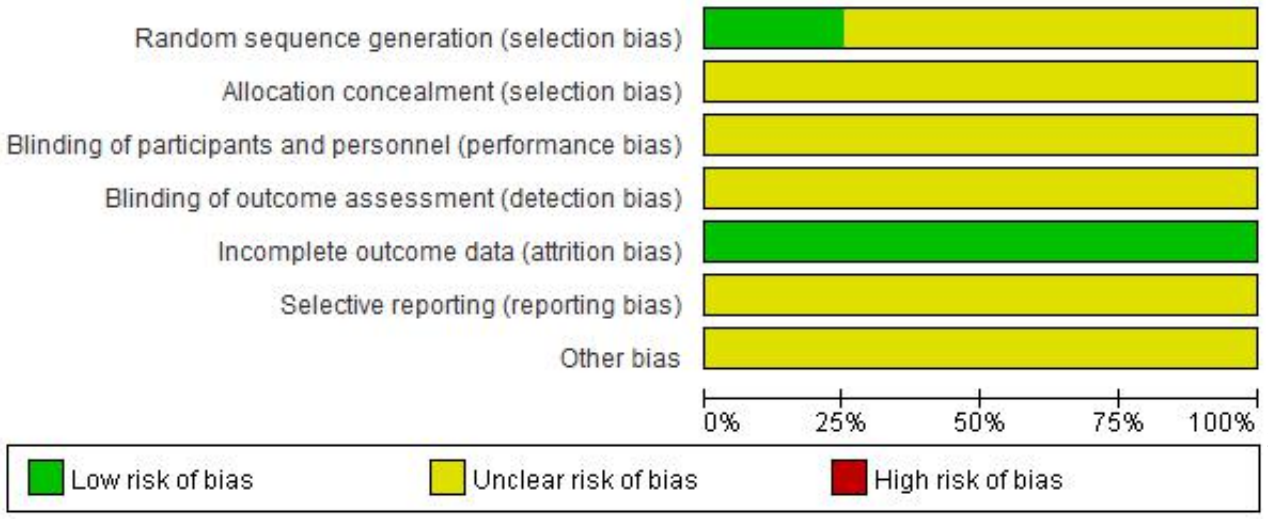

Figure 2 Risk of bias graph

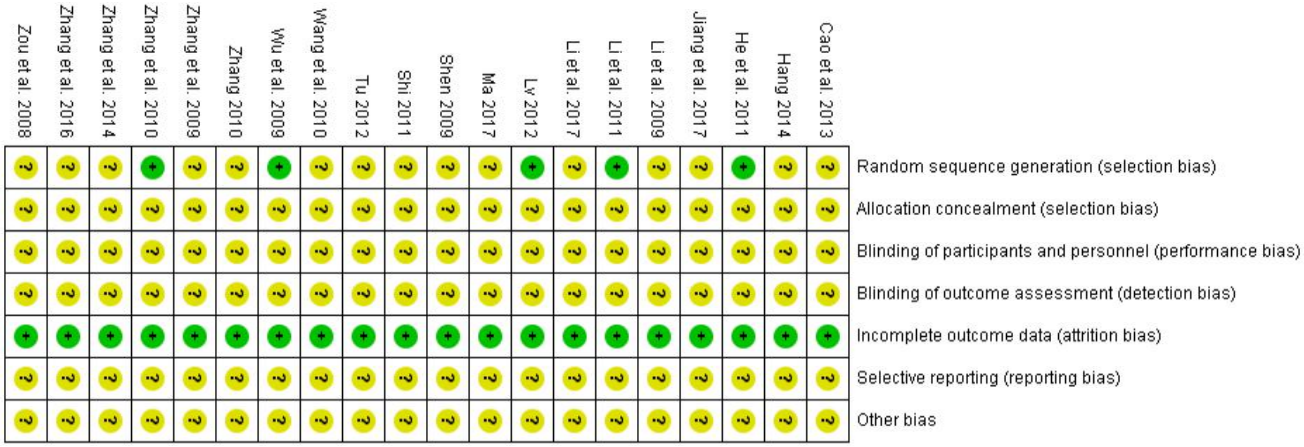

Figure 3 Risk of bias summary

Table 1 Baseline characteristics of included studies

Study	Sample size (T/C)	Age (years)	Male/female ratio	Clinical staging	Intervention (T)	Intervention (C)	Duration course (cycles)	Outcomes
Cao et al. 2013 [20]	38/38	38–73	54/22	III-IV	KAI + TP	TP	4	①③④⑤
Hang 2014 [21]	28/28	67–75	38/18	III-IV	KAI + TP	TP	2	①②③
He et al. 2011 [22]	31/30	51–76	47/14	III-IV	KAI + TP	TP	2	①③
Jiang et al. 2017 [23]	50/50	55–76	81/19	III-IV	KAI + TP	TP	2	①③
Li et al. 2009 [24]	28/28	36–70	32/24	IIIB-IV	KAI + TP	TP	2	①②③
Li et al. 2011 [25]	30/30	50–79	43/17	III-IV	KAI + TP	TP	3	①②③⑤
Li et al. 2017 [26]	30/30	35–70	38/22	IIIB-IV	KAI + TP	TP	2	①②③
Lv 2012 [27]	60/60	62–86	72/48	III-IV	KAI + TP	TP	2	①②③
Ma 2017 [28]	40/42	46–77	53/29	III-IV	KAI + TP	TP	4	①③④⑤
Shen 2009 [39]	30/30	35–75	39/21	IIIB-IV	KAI + TP	TP	2	①②③
Shi 2011 [30]	29/29	34–70	36/22	IIIB-IV	KAI + TP	TP	2	①②③
Tu 2012 [31]	32/31	70–85	40/23	III-IV	KAI + TP	TP	2	①②③
Wang et al. 2010 [32]	32/32	30–76	46/18	III-IV	KAI + TP	TP	4	①②③⑤
Wu et al. 2009 [33]	28/28	36–76	43/13	IIIB-IV	KAI + TP	TP	2	①②③
Zhang 2010 [34]	15/15	43–73	17/13	III-IV	KAI + TP	TP	2	①②③⑤
Zhang et al. 2009 [35]	60/60	29–75	76/44	III-IV	KAI + TP	TP	2	①②③④⑤
Zhang et al. 2010 [36]	30/30	51–78	45/15	III-IV	KAI + TP	TP	2	①②③
Zhang et al. 2014 [37]	30/25	45–84	43/12	III-IV	KAI + TP	TP	2	①②③
Zhang et al. 2016 [38]	41/41	50–79	50/32	III-IV	KAI + TP	TP	4	①③
Zou et al. 2008 [39]	26/25	31–77	39/12	IIIB-IV	KAI + TP	TP	2	①②④⑤

and the difference was uniform (Figure 4).

Clinical efficacy subgroup analysis. Twenty studies [20–39] reported the clinical efficacy of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC patients. According to the different duration courses, a subgroup analysis was performed. In the 2 cycle treatment groups, the difference was statistically significant (RR = 1.32, 95% CI (1.19, 1.47), $P < 0.00001$). In the 3 cycle treatment groups, there was only one study, no P value statistics were done (RR = 1.15, 95% CI (0.67, 1.99)). In the 4 cycle treatment groups, the difference was statistically significant (RR = 1.32, 95% CI (1.12, 1.56), P =0.001) (Figure 5).

Life quality. Fifteen studies on quality of life [21, 24–27, 29–37, 39] the quality of life of patients with NSCLC treated with the Chinese patent medicine Kang'ai injection and TP chemotherapy was reported.

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The heterogeneity test analysis showed that the homogeneity of the included studies was good (I^2 = 47%, P = 0.02). The fixed effect model was selected. The results showed that (RR = 1.44, 95% CI (1.32, 1.57), Z = 8.22, P < 0.00001). The quality of life of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy was better than that of TP chemotherapy, and the difference was statistically

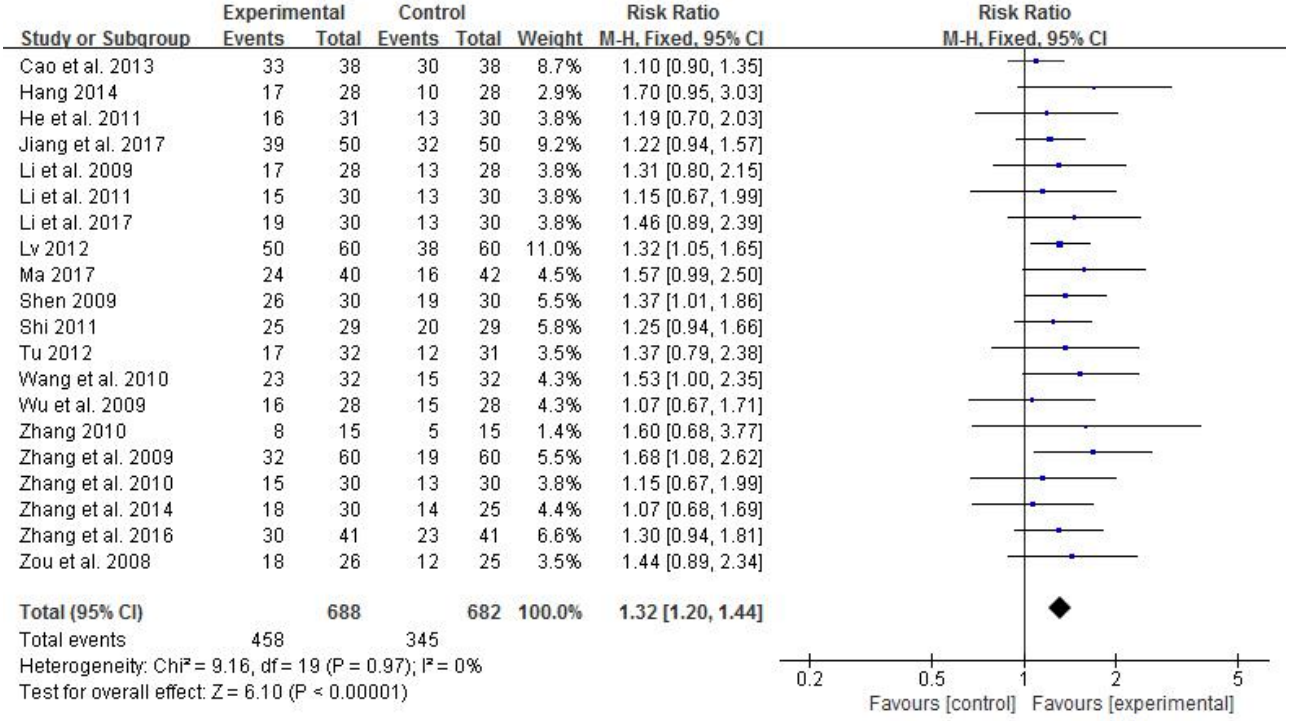

Figure 4 Forest plot for total effective rate between treatment group and control group

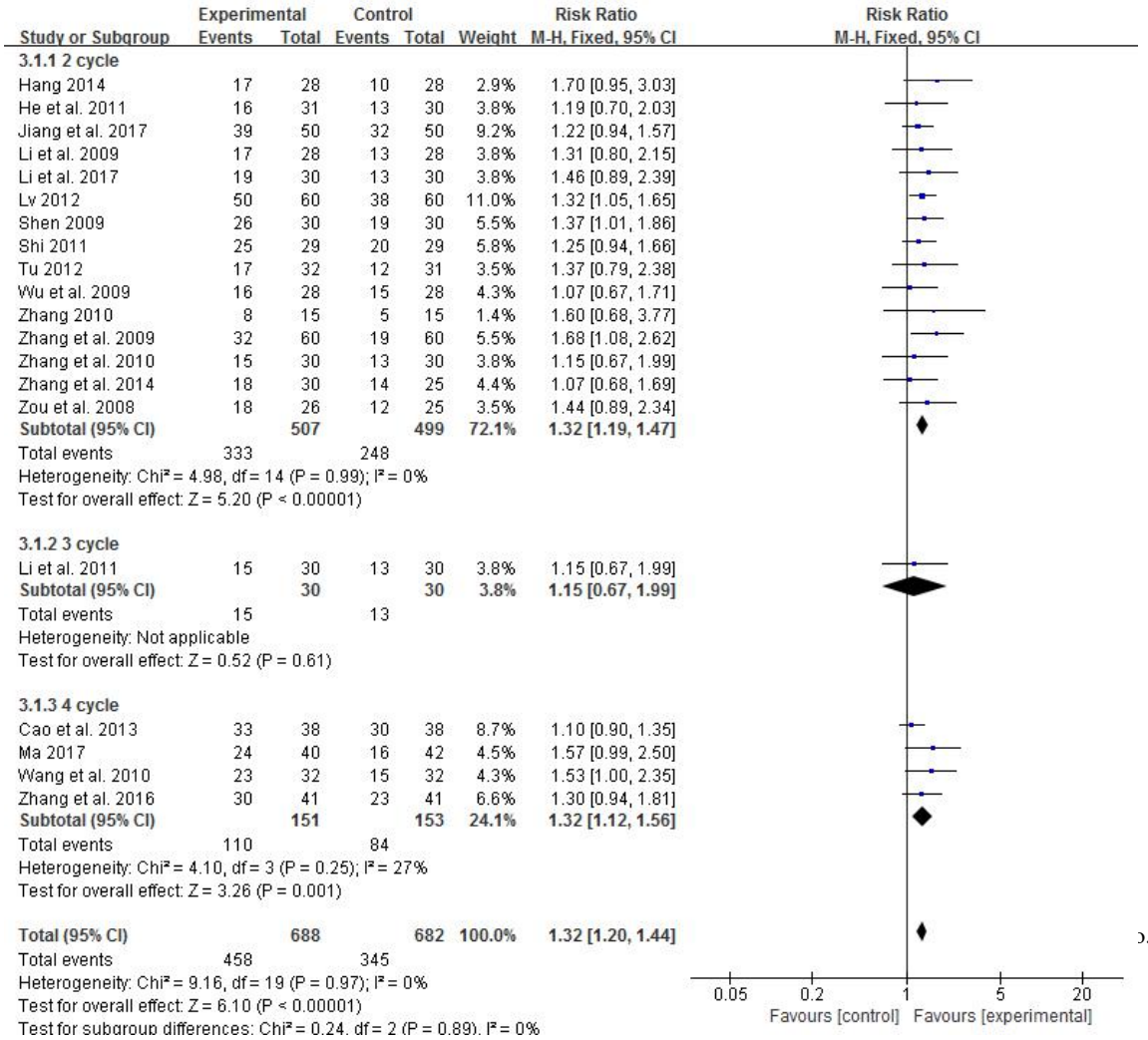

Figure 5 Forest plot for total effective rate subgroup analysis between treatment group and control group

significant (Figure 6).

Immune function. Analysis of 4 studies [20, 28, 35, 39] the immune function of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC was reported. According to the heterogeneity test and analysis, there was statistical heterogeneity between the included studies (I^2 = 92%, P = 0.0005). The random effect model was selected for meta analysis. The results showed that (MD = 0.53 (95% CI, 0.23–0.83), Z = 3.47, P < 0.00001), indicating that the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy group had better immune function. The difference was statistically significant in TP group (Figure 7).

Adverse events. Nineteen studies [20–38] reported the safety related information of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC patients, mainly involving digestive tract reaction, myelosuppression, liver and kidney function damage, hair loss, fatigue and other aspects. Digestive tract reaction and myelosuppression were more common. Adverse reactions of digestive tract were reported in 19 studies [20–38], and myelosuppression adverse reactions were reported in nineteen studies [20–38]. Through heterogeneity test and analysis: the homogeneity between the included studies was good (I^2 = 0%, P = 0.73). The fixed effect model was selected. The results showed that (RR = 0.49, 95% CI (0.41, 0.58), Z = 8.22, P < 0.00001). It showed that the incidence and degree of adverse reactions of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy were lower than that of TP chemotherapy, the difference was statistically significant, and there were fewer adverse reactions above grade III in the 2 groups. The use of TP chemotherapy is related, and it can be relieved after drug withdrawal or symptomatic treatment. No other serious adverse events were found. Therefore, Kangai injection is safe (Figure 8).

Analysis of publication bias

To evaluate the publication bias of the total clinical efficacy, life quality and adverse events of each included literature. Take log (RR) as the abscissa and Se (log (RR)) as the ordinate to draw the inverted funnel diagram. It can be seen from the diagram that the funnel diagram is asymmetric, indicating that there is publication bias (Figure 9).

Sensitivity analysis

The results of the fxed-effects and random-effects model had good consistency. Afer deleting the low quality studies with relatively high overall risk of bias, the results were still similar to the results before they were excluded, which revealed that the results of our meta-analysis were reliable and verifable.

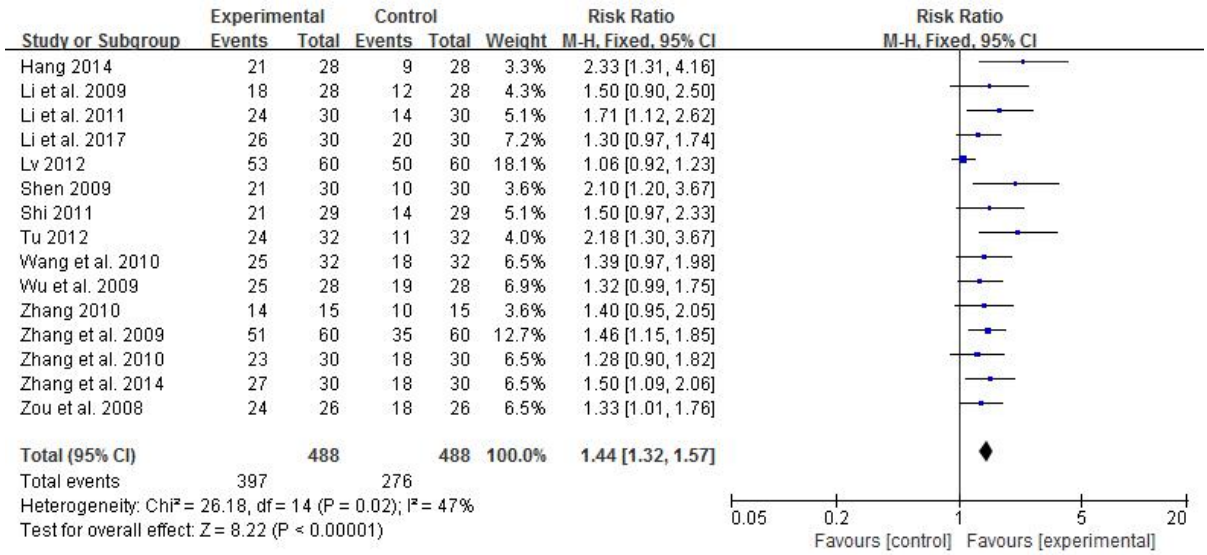

Figure 6 Forest plot for life quality between treatment group and control group

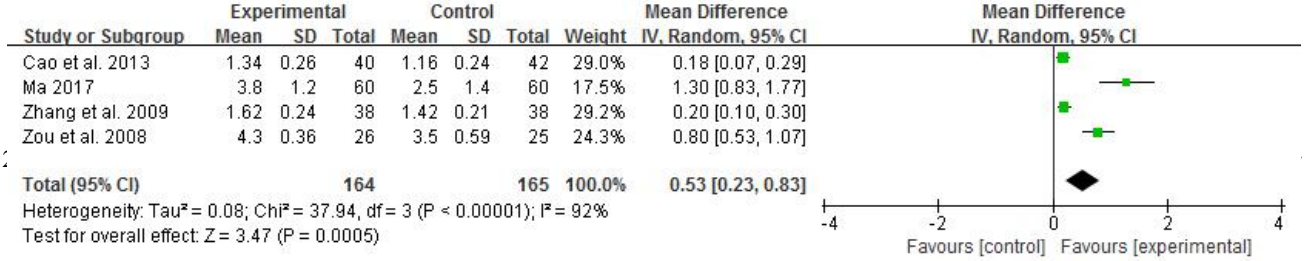

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Figure 7 Forest plot for immune function between treatment group and control group

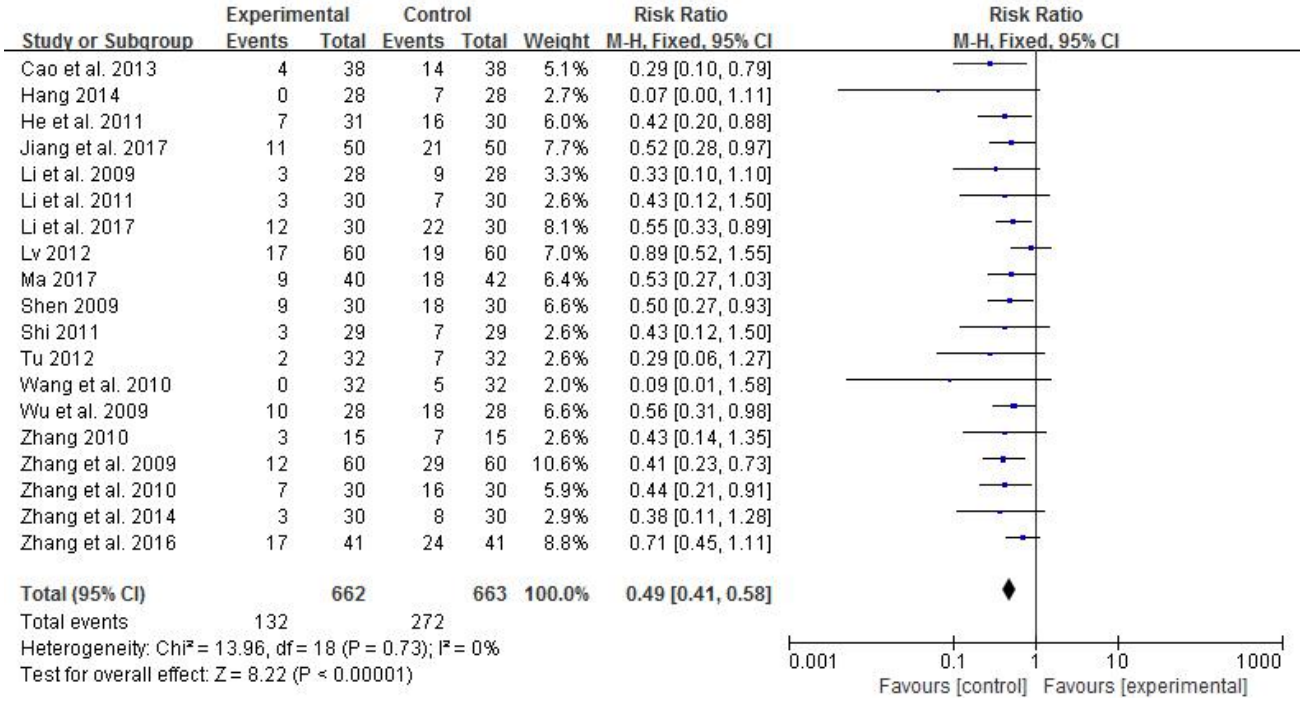

Figure 8 Forest plot for adverse reactions between treatment group and control group

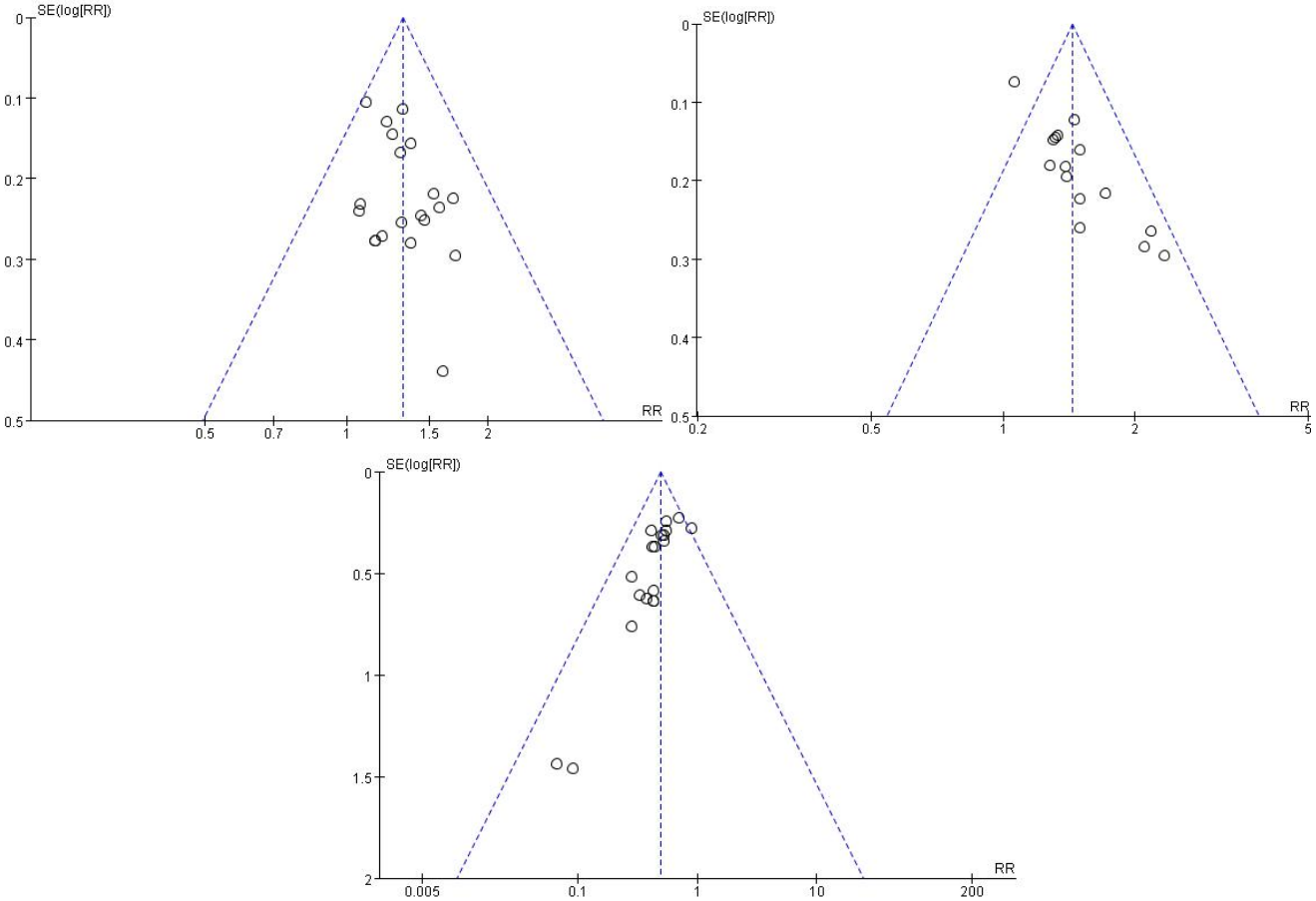

Figure 9 (a) Funnel chart of clinical efficacy. (b) Funnel chart of life quality. (c) Funnel chart of adverse

events

Discussion

It has been found that [40–42], the curative effect of TCM on a variety of malignant tumors is accurate, and it has gradually become a recognized method for the treatment of malignant tumors [43–45]. The treatment of tumor patients should be based on the overall grasp of the premise, taking into account the specimen, according to the patient's own constitution for disease identification and syndrome differentiation, which can effectively alleviate the clinical symptoms, reduce the side effects of simple western medicine treatment, prolong the survival period and improve the quality of life.

In this study, we collected all the published RCTs, and got 20 clinical studies of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC. Using the method of meta analysis, we systematically evaluated the efficacy of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC. This study shows that the clinical effect of the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy in the treatment of NSCLC patients is significantly higher than that of TP chemotherapy, and it can improve the quality of life and immune function of patients, reduce the incidence of myelosuppression and gastrointestinal reaction, suggesting that the Chinese patent medicine Kang'ai injection combined with chemotherapy can play a role in reducing toxicity and enhancing efficiency, and ensure the smooth progress of chemotherapy.

In this study, the criteria for inclusion and exclusion of literature were clearly defined, including the age of inclusion, research objects, outcome indicators and other relevant conditions, which basically controlled the selection bias of this study. However, there are some limitations in this study, for example, most of the studies are based on small sample tests, some of them have methodological problems, and the reference value of the conclusions is limited; all the included studies are positive results, and the possibility of publication bias cannot be completely ruled out, and the quality of the included studies is not high, thus affecting the reliability of the above conclusions to varying degrees; all the included literatures did not mention mentioned the blind method, did not achieve distribution concealment, did not describe the loss of interview and withdrawal in detail, and there was a certain gap from the requirements of evidence-based medicine, which led to the low reliability of the research and the quality of the literature. Based on this, in future clinical trials, the subjects should be correctly randomly divided into different groups, and different interventions should be carried out to control the different effects. To avoid bias in clinical trial design and implementation to the greatest extent, balance confounding factors, improve the effectiveness of statistical test, and then improve the scientific research.

In conclusion, although there are some deficiencies in the systematic evaluation of the literature, the results show that the Chinese patent medicine Kang'ai injection adjunct with TP chemotherapy can effectively improve the clinical efficacy of NSCLC patients, and the safety is good, with the effect of reducing toxicity and increasing efficiency, which has a certain guiding significance for the clinical treatment of lung cancer. At the same time, it is suggested that the researchers should carefully contact clinical practice and make a comprehensive judgment based on the consensus of relevant guidelines, and call for a wide range of multi center, large sample, well-designed clinical RCTs on Kangai injection adjunct with TP chemotherapy for NSCLC.

Data availability

Most of the data information is fully reflected in the article (paritcipants, age, gende, risk of bias, et al.). As a supplement, we uploaded a RevMan file (.rm5) containing the original data.

Ethical approval

This systematic review and meta-analysis was based on published original studies that were consistent with their respective ethical requirements; thus, we did not apply for an ethical review. This systematic review and meta-analysis is compliant with local laws and regulations.

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