Original Article

Efficacy and safety of Kanglaite injection combined with first-line platinum-based chemotherapy in patients with advanced NSCLC: a systematic review and meta-analysis of 32 RCTs

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Background: As a Chinese medicine injections, Kanglaite injection (KLT) is a complementary or alternative therapy for first-line platinum-based chemotherapy. However, the effect that certain factors, including the dose of KLT, chemotherapy cycles, evaluation criteria, or supportive treatment, have on the efficacy of the objective response rate (ORR), median survival time (MST), and adverse reactions is still unknown.

Methods: Eight databases were systematically searched from the inception dates to December 1, 2019, using the keywords Kanglaite, chemotherapy, and non small cell lung carcinoma to identify randomized clinical trials (RCTs). Analyses were performed using Review Manager 5.3 and Stata 15.1.

Results: There were 32 randomized controlled trials, involving 2,577 participants, that fulfilled the inclusion criteria. Compared with first-line platinum-based chemotherapy alone, KLT combined with chemotherapy could increase the ORR [risk ratio (RR), 1.41 (95% CI: 1.28 to 1.56); absolute risk difference (ARD), 0.13 (95% CI: 0.1 to 0.17)], decrease the risk ratio of adverse reactions [nausea and vomiting: RR, 0.58 (95% CI: 0.42 to 0.81); ARD, –0.17 (95% CI: –0.26 to –0.08); leukopenia: RR, 0.61 (95% CI: 0.44 to 0.86); ARD, –0.16 (95% CI: –0.24 to –0.08)], prolong MST, and increase disease control rate and Karnofsky performance status. According to the subgroup analyses, KLT combined with cisplatin or paraplatin plus paclitaxel (TP) failed to demonstrate a significant association with the ORR. And when lacking the use of supportive treatment, this combination would not decrease the RR of both adverse reactions compared with chemotherapy alone.

Conclusions: KLT plus first-line platinum-based chemotherapy, except when chemotherapy regimens were TP, increased efficacy and quality of life in patients with advanced NSCLC. We are unsure whether this combination offers a low risk of adverse reactions. Additional high-quality RCTs are warranted to assess the effects of the combined therapy further.

Keywords: Kanglaite injection; first-line chemotherapy; non-small cell lung carcinoma (NSCLC); efficacy; meta-analysis

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Introduction

Lung cancer is the most commonly diagnosed cancer. According to global cancer statistics, lung cancer was the leading cancer-related death in 2018 (1), with 80% of these cases being non-small cell lung carcinomas (NSCLC). Even with this well-known mortality, over 50% of NSCLC present with advanced local invasion and metastasis during hospital admission diagnosis, meaning they have missed the opportunity for surgical intervention. Despite the promising emergence of molecular targeted therapy and immunotherapy, platinum-based chemotherapy is still the cornerstone of NSCLC treatment, especially for advanced stages III and IV of the disease (2). First-line platinum-based chemotherapy, including cisplatin or paraplatin plus vinorelbine, paclitaxel, gemcitabine, docetaxel, or pemetrexed (3), is widely used in advanced NSCLC. However, adverse reactions, including nausea and leukopenia, are frequently reported (4,5).

In traditional Chinese medicine (TCM) basic theory, lung cancer is nearly equivalent to the domains of "mass" or "phlegm and dampness", which is acknowledged to be one of the basic pathogeneses. Kanglaite injection (KLT) (Z10970091, China Food and Drug Administration) is extracted from the seeds of the Chinese medicinal herb (CMH) Coix lacryma-jobi, whose anticancer effect thought treating the dampness with bland and treat "mass" in traditional Chinese medicine theory. Past studies have suggested that KLT is a micro-emulsion for intravenous use that demonstrates antitumor efficacy, improves the quality of life (QOL), and reduces toxicity (6,7). However, the outcome of its combination with different chemotherapy regimens and the long-term synergistic efficacy is still unclear. Moreover, CMH is often considered to have serious adverse reactions (8), and the Chinese government has announced a post-marketing review of TCM injections in the following 5 to 10 years (9). Finally, the exact effect and survival rate after the application of KLT are also a concern.

This systematic review and meta-analysis were performed to compare KLT plus first-line platinum-based chemotherapy with first-line platinum-based chemotherapy alone in patients with advanced NSCLC by the using tumor response and adverse reactions as outcome measures. We present the following article following the PRISMA 2009 reporting checklist (available at http://dx.doi.org/10.21037/apm-20-616).

Methods

This article follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA guidelines), and the study is registered with PROSPERO (CRD 42019142414). As a systematic review and meta-analysis, Ethical approval was not required as materials of this study had been published.

Data sources

Two reviewers (Juan Li and Hong-Zheng Li) independently searched for and extracted information from randomized clinical trials (RCTs) related to KLT-assisted treatment of NSCLC. RCTs were searched for in Chinese and English databases, including the PubMed, Cochrane Library, EMBASE, Web of Science (ISI), Chinese National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-Text Database (VIP), CBM, and Wanfang databases. The searches were restricted to original publications from the time of establishment to December 1, 2019. A combination of the following keywords was used: "lung cancer", "lung carcinoma", "non-small cell lung cancer", "non-small lung carcinoma", "NSCLC", "Kanglaite", "KLT", and "Coix Seed Oil". All retrievals were implemented using the Medical Subject Headings (MeSH) and free word. Finally, all related systematic reviews (SRs) and meta-analyses were evaluated, and studies meeting the inclusion criteria were selected from the references. As an example, the electronic strategy for PubMed can be seen in *Figure S1*.

Search strategies and selection criteria

Trials were selected on the following inclusion criteria: (I) the trial was an RCT. (II) The patients were diagnosed with NSCLC stages III to IV, according to histopathological and cytological diagnostic criteria. (III) The experimental group had undergone KLT (Z10970091, China Food and Drug Administration) plus first-line platinum-based chemotherapy, and the control group had undergone first-line platinum-based chemotherapy. First-line platinum-based chemotherapy refers to cisplatin or paraplatin plus vinorelbine, paclitaxel, gemcitabine, docetaxel or pemetrexed (NP, TP, GP, DP, and AP, respectively). (IV) Patients did not receive any radiotherapy, other chemotherapy, or Chinese herbs during this study. (V) The

outcome needed to include at least an objective response rate (ORR) or adverse reactions (nausea and vomiting, leukopenia). Exclusion criteria were (I) duplicates (797 studies); (II) unrelated studies including other treatments (56 studies); (III) non-RCTs including case-control studies and series case reports (23 studies); (IV) abstracts and reviews without specific data and unrelated SRs (59 studies), and (V) studies with no ORR or adverse reaction (nausea and vomiting) data (17 studies).

Data extraction and quality assessment

Two researchers (Juan Li and Guang-Hui Zhu) independently extracted the following information from each study: the lead author; the publication time; the demographic characteristics; the sample size; the usage of KLT and the types of first-line platinum-based chemotherapy; the evaluation criteria of clinical efficacy; and whether supportive treatment including anti-nausea drugs, granulocyte colony-stimulating factor (G-CSF) were administered. Furthermore, outcomes including the ORR, leukopenia, nausea and vomiting, median survival time (MST), disease control rate (DCR), and Karnofsky performance status (KPS) were examined. The data were obtained directly from the articles. A third reviewer resolved any disagreements (Jie Li).

The methodological quality of the included RCTs was assessed independently by two researchers (Hong-Zheng Li and Guang-Hui Zhu) on the Cochrane risk-of-bias criteria (10) using the following parameters to evaluate the bias risk: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (whether the baseline is comparable). Subsequently, the trials were assessed and categorized into three levels: low risk (all items were "yes"), high risk (at least one item was "no"), and unclear risk (at least one item was "unclear").

Main outcomes

We measured the tumor response using the ORR. According to the World Health Organization (WHO) guidelines for solid tumor responses (11) or Response Evaluation Criteria in Solid Tumors (RECIST) (12), indicators were complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), with ORR being equal to CR plus PR. Adverse reactions (adverse drug events or adverse drug reactions) were pooled, including nausea and vomiting, and leukopenia.

Secondary outcomes

The long-term synergistic efficacy of this combination was considered MST. Also, the secondary outcomes included DCR and QOL. QOL was considered improved if the KPS score increased by 10 points or higher after treatment (13). DCR was calculated as CR plus PR and SD.

Statistical analysis

Two reviewers performed the meta-analysis (Juan Li and Guang-Hui Zhu) using Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and Stata 15.1. The relative risk (RR) and 95% confidence intervals (CI) were calculated. Statistical heterogeneity of the results across trials was assessed by a Chi-square based Q-statistic test, and the consistency was calculated by I^2. If the homogeneity ($P \geq 0.1$, $I^2 \leq 50\%$) was not rejected, the fixed-effects model (FEM) was used to calculate the summary RR and the 95% CI. Alternatively, the results were calculated by the random-effects model (REM). We performed a subgroup analysis according to different doses of KLT, types of first-line platinum-based chemotherapy, the cycle of chemotherapy, and evaluation criteria, which revealed their influence on tumor responses.

Furthermore, we performed a subgroup analysis regarding using supportive treatment for adverse reactions. Publication bias was evaluated using funnel plots if more than 10 included studies were included. Subgroup analyses were performed following the doses of KLT, the type, and cycle of chemotherapy, supportive treatment, and evaluation criteria to reveal the clinical heterogeneity and its influence on the endpoint.

Results

The literature search identified 188 studies and excluded 68 after careful screening of titles and abstracts. The full text of the 120 remaining studies was assessed for eligibility, and 88 were excluded because they were reviews, did not contain eligible comparators, did not report outcomes of interest, were case series, or for other reasons (*Figure 1*). Finally, 32 articles comprising 2,577 patients met the inclusion criteria

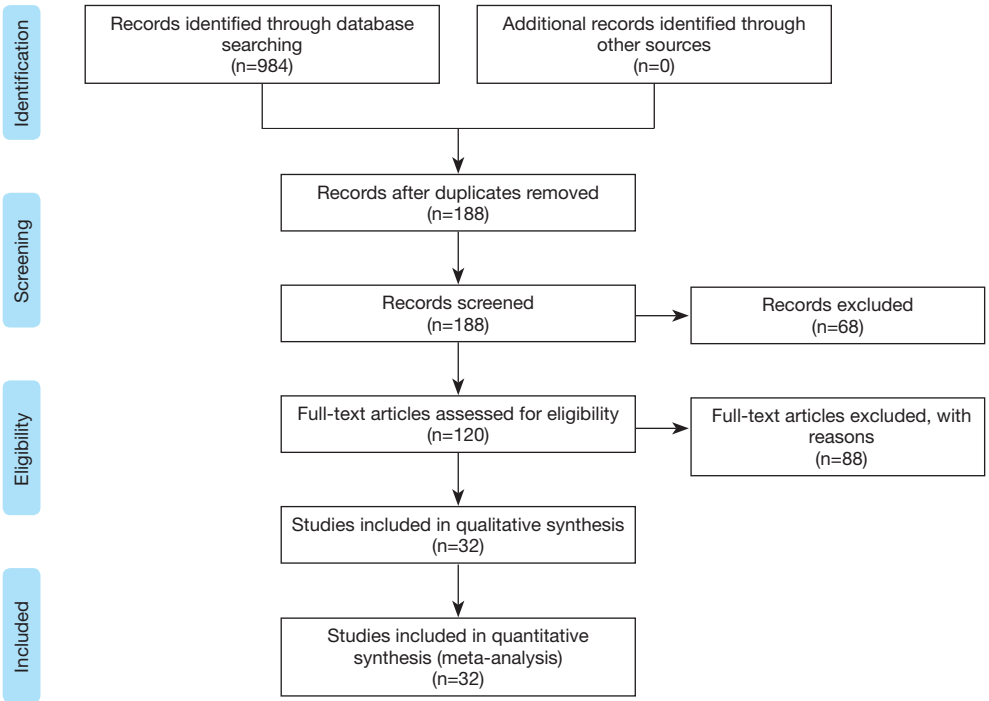

Figure 1 Articles retrieved and assessed for eligibility.

and were retrieved for quantitative synthesis, with all the records being studied in China (*Table 1*).

Characteristics of eligible studies

The experimental group comprised 291 cases of KLT plus first-line platinum-based chemotherapy, while the control group comprised 1,286 cases of first-line platinum-based chemotherapy alone. There were 1,436, and 989 males and females included respectively, with age ranging between 32 and 80 years. The dosage of KLT was 60 to 300 mL/day, and the treatment time was 3 to 4 weeks/cycle, with 1 to 4 cycles of intravenous injection. According to the WHO guidelines for solid tumor responses (11) or RECIST (12), tumor responses were evaluated in 32 studies (14-29) involving 2,577 patients (30-45). Nausea and vomiting were evaluated in 9 studies (14,19,22,29,37,38,42,43,45) involving 692 patients, and leukopenia was evaluated in 11 studies (17,19,21,22,26,29,37-39,42,45) involving 901 patients. According to the WHO standards (11) or National Cancer Institute Common Toxicity Criteria (NCI-CTC) (46), 4 studies for nausea and 5 studies for leukopenia were included.

Methodological quality

All studies mentioned randomization, with only 17 studies (14,16,17,20,22,23,26-28,30,33-36,39,43,45) reporting the details of the randomized methods, and none reporting the details of concealed allocations. One study (38) revealed the blinding methods but not the details regarding the blinding of patients or assessors. Additionally, one study (33) revealed that all the participants were aware of the treatment in advance, which did not affect the outcome.

Fourteen participants withdrew from three studies (27,36,41), with five presenting acute/subacute toxicity, five participants were treated with another treatment, and four participants withdrew for personal or economic reasons. Furthermore, seven studies lacked outcome data (19,20,24,34,35,40,44). Three studies selectively reported acute/subacute toxicity (34,40,44), with one reporting KPS (33). The methodological bias risk of all included studies is presented in *Table 2* and *Figure 2*.

ORR

The reporting of ORR occurred in 32 studies (14-29)

Table 1 Characteristics of included studies

First author, year	NSCLC (III–IV)			Inventions			Scale (A)	Scale (B)	Supportive treatment	Outcome	
	E/C	M/F	Age	Treatment		Control				Main outcome	Secondary outcomes
				E	KLT (D/C)						
Bao 2019, (14)	31/31	38/24	39–72	GP + KLT	200 mL/2	GP	WHO	Unclear	No	⑤③	⑤
Chen 2018, (15)	30/30	Unclear	35–65	GP + KLT	200 mL/1	GP	RECIST	Unclear	Yes		⑤
Chen 2016, (16)	44/44	47/41	55–78	GP + KLT	?/4	GP	RECIST	Unclear	No		⑤
Chen 2018, (17)	51/51	59/43	57–79	GP + KLT	200 mL/4	GP	WHO	Unclear	No	⑤②	⑤
Chen 2003, (18)	28/27	33/22	33–80	NP + KLT	200 mL/2	NP	WHO	Unclear	No		⑤⑥
Guan 2009, (19)	12/12	11/12	36–72	GP + KLT	300 mL/2	GP	WHO	NCI-CTC	Yes	④②③	④⑤
He 2017, (20)	54/54	81/27	38–80	DP + KLT	100 mL/3	DP	WHO	Unclear	Yes		
Huang 2010, (21)	35/35	44/26	59–78	GP + KLT	200 mL/2	GP	WHO	WHO	No	⑤②	⑤⑥
Jia 2018, (22)	31/31	34/28	43–74	DP + KLT	200 mL/2	DP	WHO	Unclear	Yes	⑤②③	⑤
Li 2017, (23)	41/41	43/39	55–75	GP + KLT	?/4	GP	RECIST	Unclear	No		⑤
Li 2012, (24)	38/40	49/29	70–77	TP + KLT	100 mL/3	TP	RECIST	Unclear	No		⑤⑥
Li 2016, (25)	39/39	43/35	35–72	NP + KLT	200 mL/2	NP	WHO	WHO	Yes		⑤
Liang 2018, (26)	40/40	44/36	Unclear	NP + KLT	100 mL/2	NP	WHO	Unclear	Yes	⑤②	⑤
Liang 2014, (27)	23/20	Unclear	60–75	GP + KLT	100 mL/2	GP	WHO	Unclear	No		⑤⑥
Liu 2019, (28)	63/63	79/47	50–77	GP + KLT	200 mL/2	GP	RECIST	Unclear	Yes	①	④⑤⑥
Liu 2011, (29)	35/35	44/26	59–74	GP + KLT	200 mL/2	GP	RECIST	WHO	Yes	⑤②③	⑤⑥
Liu 2016, (30)	55/55	62/48	45–79	NP + KLT	200 mL/4	NP	RECIST	Unclear	No		⑤
Liu 2015, (31)	43/43	55/31	42–74	GP + KLT	200 mL/4	GP	RECIST	SFDA	Yes		⑤⑥
Long 2017, (32)	42/40	52/30	47–70	GP + KLT	200 mL/3	GP	RECIST	WHO	No		⑤
Mu 2018, (33)	47/47	56/38	45–76	DC + KLT	200 mL/2	DP	RECIST	Unclear	No		⑤
Sun 2012, (34)	35/35	41/29	37–75	GP + KLT	200 mL/4	GP	WHO	WHO	No		⑤
Wang 2018, (35)	42/42	45/39	55–78	DP + KLT	100 mL/4	DP	RECIST	Unclear	Yes		
Wang 2016, (36)	24/25	39/13	55–70	AP + KLT	200 mL/2	AP	RECIST	WHO	Yes		⑤
Wang 2014, (37)	43/43	58/28	43–79	GP + KLT	200 mL/1	GP	RECIST	WHO	Yes	⑤②③	⑤⑥
Wang 2017, (38)	36/36	32/40	Unclear	GP + KLT	60 mL/4	GP	WHO	Unclear	No	⑤②③	⑤⑥
Yan 2018, (39)	49/49	63/35	38–76	GP + KLT	200 mL/4	GP	RECIST	Unclear	Yes	⑤②	⑤
Yang 2016, (40)	35/35	33/37	Unclear	TP + KLT	100 mL/3	TP	RECIST	Unclear	No		⑤
Yang 2003, (41)	25/26	Unclear	36–68	NP + KLT	200 mL/3	NP	WHO	Unclear	No		⑤⑥
Yao 2017, (42)	70/67	78/59	Unclear	GP + KLT	200 mL/2	GP	RECIST	WHO	No	⑤②③	⑤
Ye 2017, (43)	40/40	54/26	55–74	GP + KLT	200 mL/2	GP	RECIST	Unclear	No	⑤③	⑤
Yu 2015, (44)	60/60	67/53	Unclear	TP + KLT	100 mL/3	TP	WHO	Unclear	Yes		⑤
Zhang 2019, (45)	50/50	52/48	Unclear	GP + KLT	?/3	GP	RECIST	Unclear	No	④②③	④⑤

NSCLC, non-small cell lung cancer; E/C, experimental group (Kanglaite injection plus first-line platinum-based chemotherapy)/control group (first-line platinum-based chemotherapy); M/F, male/female; KLT (D/C), dose/cycles; GP, cisplatin or paraplatin and gemcitabine; NP, cisplatin or paraplatin and vinorelbine; TP, cisplatin or paraplatin and paclitaxel; DP, cisplatin or paraplatin and docetaxel; AP, cisplatin or paraplatin and pemetrexed; scale. A, evaluation criteria of tumor response; scale. B, evaluation criteria of adverse reactions; RECIST, response evaluation criteria in solid tumors; NCI-CTC, National Cancer Institute Common Toxicity Criteria. ① , ORR = CR + PR; ② , leukopenia; ③ , nausea and vomiting; ④ , median survival time; ⑤ , DCR = CR + PR + SD; ⑥ , Karnofsky performance status (KPS).

Table 2 Risk of bias summary: the review authors' judgments about each risk-of-bias item for each included randomized control trial

First author, year	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective reporting	Other bias
			Participants and personnel	Outcome assessment			
Bao 2019	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Chen 2018	Random draw	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Chen 2016	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	Low risk
Chen 2018	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Chen 2003	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	Unclear
Guan 2009	Unclear	Unclear	Unclear	Unclear	Incomplete	Low risk	High risk
He 2017	Simple randomization	Unclear	Unclear	Unclear	Incomplete	Low risk	Low risk
Huang 2010	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Jia 2018	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	Low risk
Li 2017	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Li 2012	Unclear	Unclear	Unclear	Unclear	Incomplete	High risk	High risk
Li 2016	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	Unclear
Liang 2018	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Liang 2014	Simple randomization	Unclear	Unclear	Unclear	Incomplete	Low risk	High risk
Liu 2019	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Liu 2011	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Liu 2016	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	Low risk
Liu 2015	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Long 2017	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Mu 2018	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Sun 2012	Simple randomization	Unclear	Unclear	Unclear	Incomplete	High risk	Unclear
Wang 2018	Simple randomization	Unclear	Unclear	Unclear	Incomplete	Low risk	Unclear
Wang 2016	Simple randomization	Unclear	Unclear	Unclear	Incomplete	Low risk	Unclear
Wang 2014	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	Low risk
Wang 2017	Unclear	Unclear	Yes	Unclear	Complete	Low risk	High risk
Yan 2018	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Yang 2016	Unclear	Unclear	Unclear	Unclear	Incomplete	High risk	High risk
Yang 2003	Unclear	Unclear	Unclear	Unclear	Incomplete	Low risk	High risk
Yao 2017	Unclear	Unclear	Unclear	Unclear	Complete	Low risk	Low risk
Ye 2017	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk
Yu 2015	Unclear	Unclear	Unclear	Unclear	Incomplete	High risk	High risk
Zhang 2019	Simple randomization	Unclear	Unclear	Unclear	Complete	Low risk	High risk

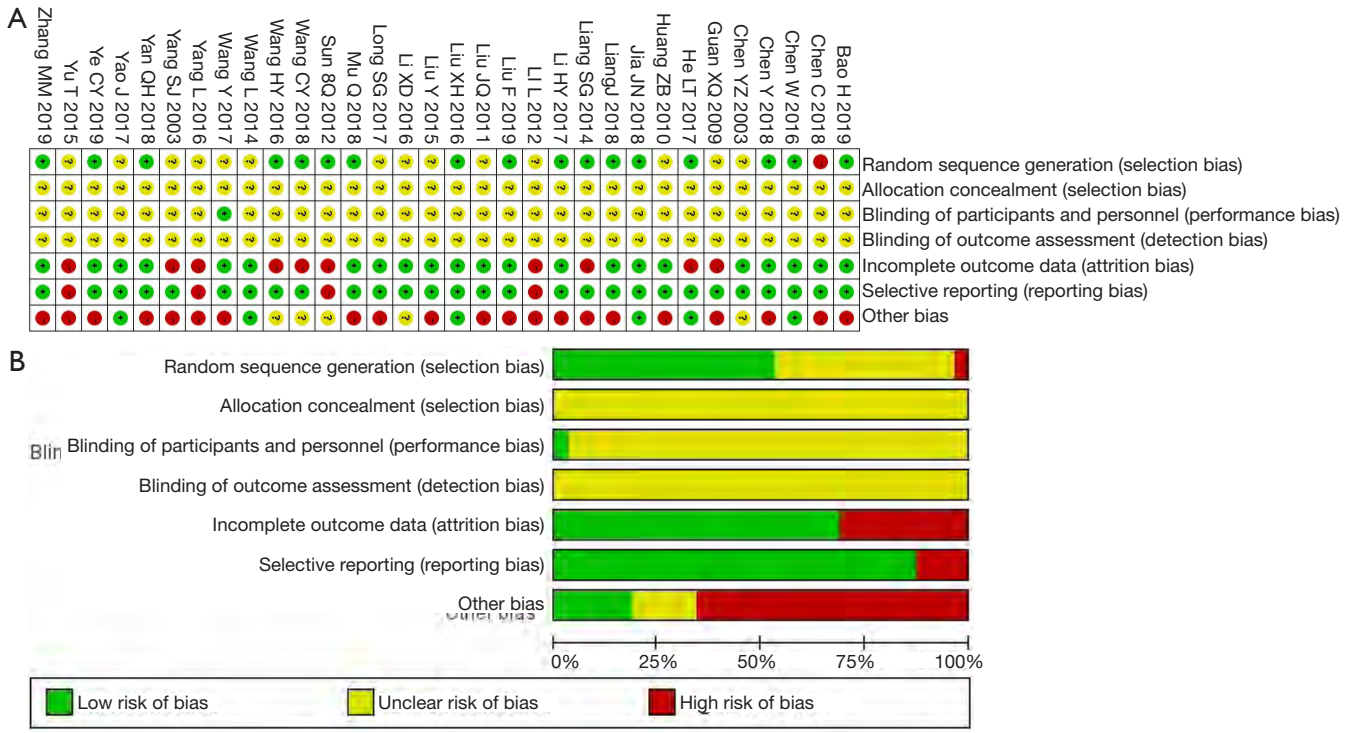

Figure 2 Risk of methodological bias. (A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

comprising 2,577 cases (30-45) (*Figure 3*). Pearson's Chi-square test and I^2 test indicated the absence of statistical heterogeneity among studies (I^2=0%). The ORR in the meta-analysis demonstrated statistical differences between KLT plus first-line platinum-based chemotherapy and first-line platinum-based chemotherapy alone (RR =1.41, 95% CI: 1.28 to 1.56, ARD =0.13, 95% CI: 0.1. to 0.17, and P<0.00001) by FEM.

Adverse reactions

A high heterogeneity was observed among studies regarding nausea and vomiting (I^2=64%) (*Figure 4*) and leukopenia (I^2=77%) (*Figure 5*). The meta-analysis revealed that KLT plus first-line platinum-based chemotherapy involved a lower risk of nausea and vomiting (RR =0.58, 95% CI: 0.42 to 0.81, ARD =–0.17, 95% CI: –0.26 to –0.08, and P=0.001) and leukopenia (RR =0.61, 95% CI: 0.44 to 0.86, ARD =–0.16, 95% CI: –0.24 to –0.08, and P=0.004) than the first-line platinum-based chemotherapy alone using REM. Furthermore, all differences were statistically significant.

Effects on secondary outcomes

For secondary outcomes, 3 studies with 243 cases (19,28,45) mentioned the average value of MST (*Figure 6*, *Table 3*), while 10 studies with 899 cases (18,21,24,27,29-31,37,38,41) reported the KPS scale evaluated by QOL (*Figure 7*). DCR was reported in 31 studies with 2,493 cases (*Figure 8*). Minimal heterogeneity was observed among studies in MST (I^2=0%), KPS (I^2=0%), and DCR (I^2=2%). Meta-analysis demonstrated that MST (HR =0.37, 95% CI: 0.12 to 0.62), QOL (RR =1.82, 95% CI: 1.51 to 2.19, ARD =0.23, 95% CI: 0.16 to 0.29), and DCR (RR =1.16, 95% CI: 1.11 to 1.22, ARD =0.11, 95% CI: 0.08 to 0.15) indicated statistical differences between the two groups by FEM.

Subgroup analysis

Subgroup analysis of ORR

Subgroup analysis was performed to reveal the influence of different doses, types of first-line platinum-based chemotherapy, cycles of chemotherapy, and evaluation

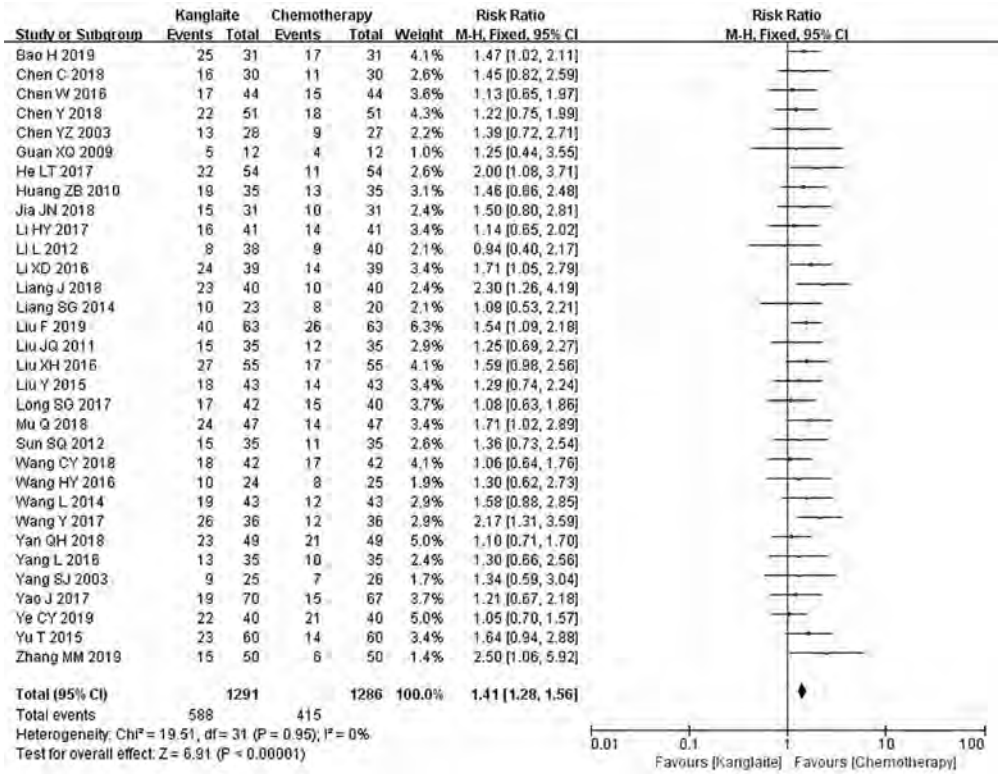

Figure 3 The analysis of ORR between two groups. ORR, objective response rate.

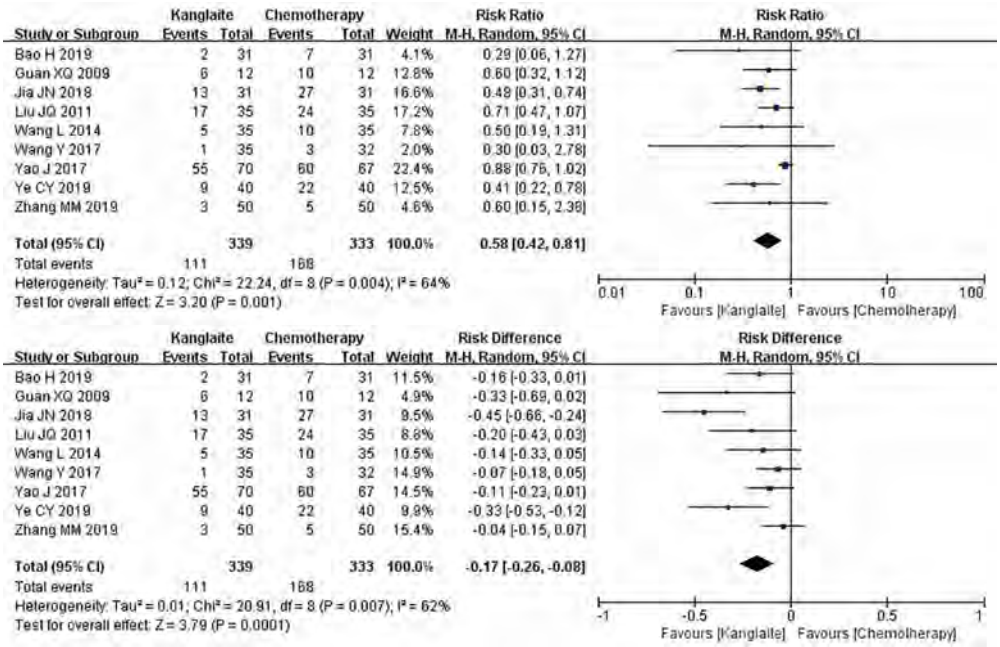

Figure 4 The analysis of nausea and vomiting between two groups.

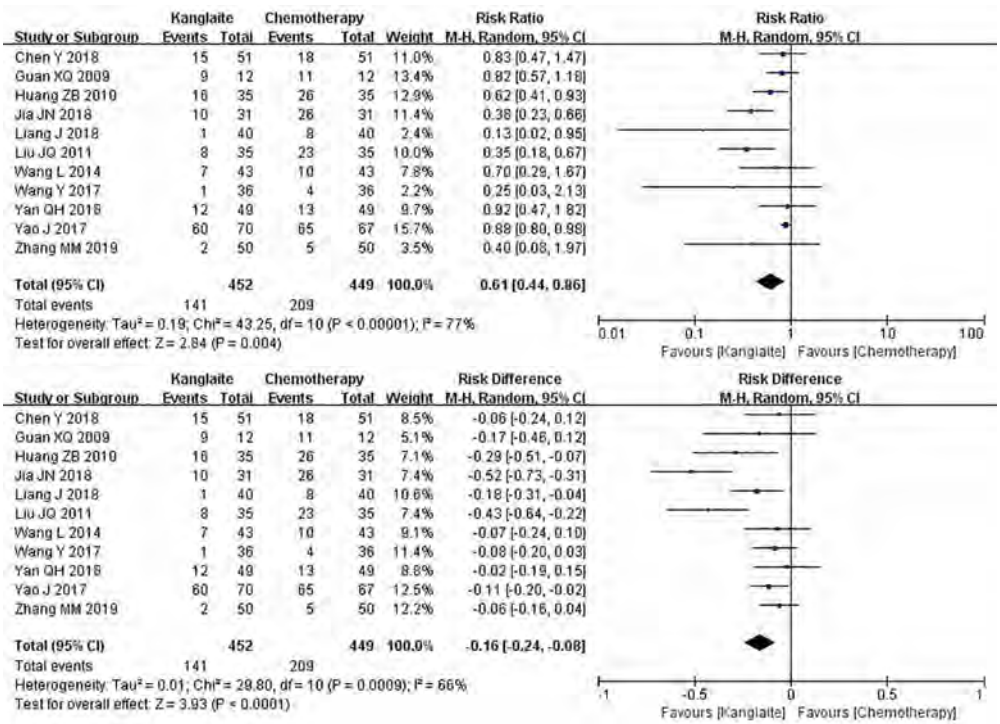

Figure 5 The analysis of leukopenia between two groups.

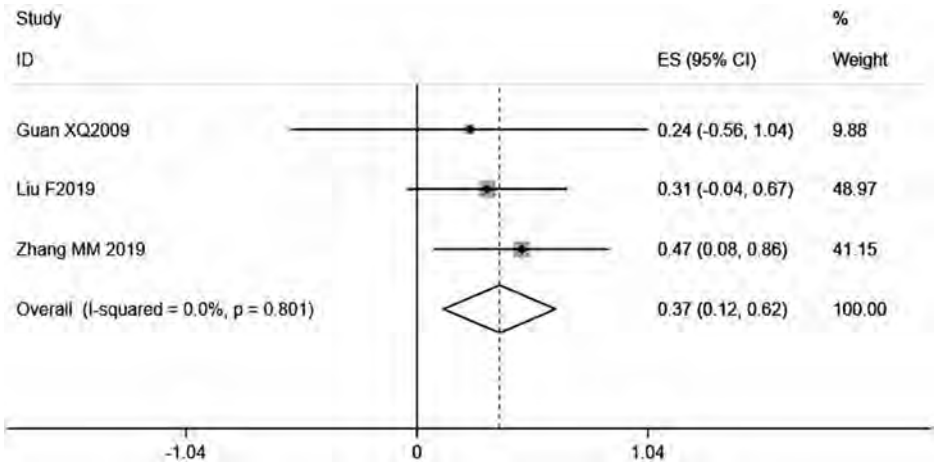

Figure 6 The analysis of MST between two groups. MST, median survival time.

Table 3 Characteristics of studies with median survival time

First author, year	NSCLC (III–IV)			MST		1-year survival rate		ES (95% conf. interval)
	E/C	M/F	Age	Treatment	Control	Treatment	Control	
Guan 2009, (19)	12/12	11/12	36–72	18.1 months	14.3 months	Not reported	Not reported	0.236 (–0.564, 1.036)
Liu 2019, (28)	63/63	79/47	50–77	43.7 weeks	31.9 weeks	50.8%	34.9%	0.315 (–0.045, 0.674)
Zhang 2019, (45)	50/50	52/48	Unclear	13.65 months	8.54 months	48%	24%	0.469 (0.077, 0.861)

NSCLC, non-small cell lung cancer; MST, median survival time.

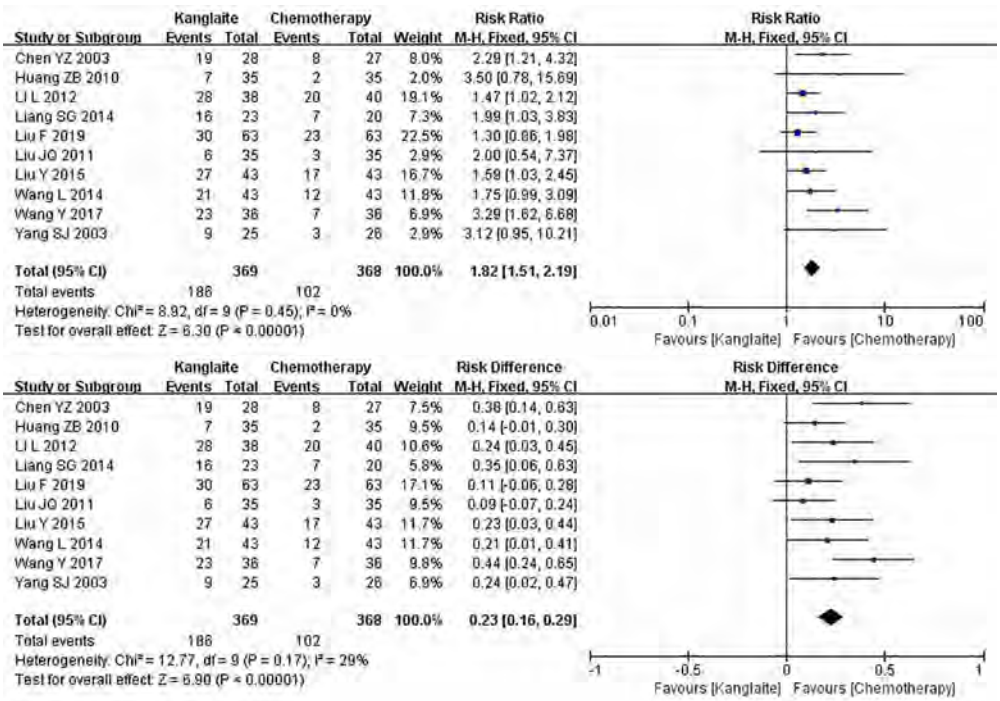

Figure 7 The analysis of KPS between two groups. KPS, Karnofsky performance status.

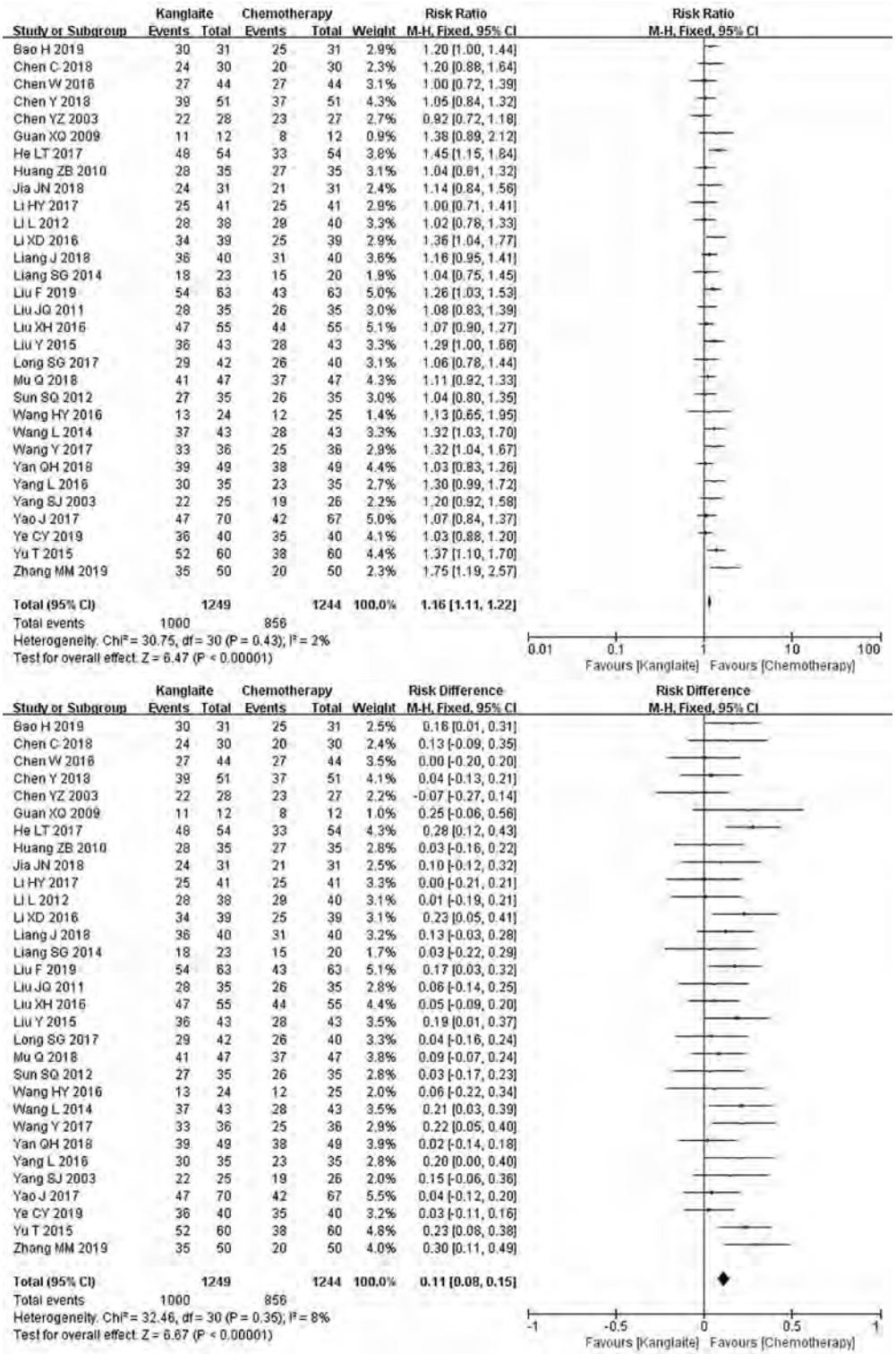

Figure 8 The analysis of DCR between two groups. DCR, disease control rate.

Table 4 Subgroup analysis of ORR for each variable

Variable	No. of trials	No. of participants		Fracture, RR (95% CI)	P value[a]
		ORR: CR + PR	Total		
Kanglaite dose					0.32
200 mL	20	677	1628	1.37 (1.22, 1.54)	
Other[b]	9	243	679	1.55 (1.26, 1.90)	
Type of first-line platinum-based chemotherapy					0.59
GP	19	624	1538	1.34 (1.19, 1.52)	
NP	5	153	374	1.68 (1.30, 2.18)	
DP	4	131	348	1.52 (1.15, 2.01)	
TP	3	77	268	1.35 (0.92, 1.98)	
AP	1	18	49	1.30 (0.62, 2.73)	
Cycle of chemotherapy					0.67
2-cycle	14	445	1030	1.45 (1.25, 1.67)	
Other[c]	18	558	1547	1.38 (1.21, 1.58)	
Evaluation criteria					0.25
WHO	15	457	1063	1.50 (1.30, 1.73)	
RECIST	17	546	1514	1.34 (1.17, 1.53)	

[a]P value: heterogeneity between subgroups; [b]other: includes Kanglaite doses about 60, 100 and 300 mL; [c]other: includes chemotherapy cycles about 1-cycle, 3-cycle, 4-cycle. ORR, objective response rate; CR, complete response; PR, partial response; GP, cisplatin or paraplatin and gemcitabine; NP, cisplatin or paraplatin and vinorelbine; TP, cisplatin or paraplatin and paclitaxel; DP, cisplatin or paraplatin and docetaxel; AP, cisplatin or paraplatin and pemetrexed.

criteria on the ORR (*Table 4* and *Figure S2A*,*B*,*C*,*D*). Drug doses included 200 mL on the KLT medicine instruction (47) and other doses. Subgroup analysis indicated that both doses increased the ORR. Types of first-line platinum-based chemotherapy included cisplatin or paraplatin plus vinorelbine, paclitaxel, gemcitabine, docetaxel, or pemetrexed (NP, TP, GP, DP, and AP). Subgroup analysis demonstrated that only KLT plus GP, NP, and DP could increase the ORR. The differences between TP (P=0.12) and AP (P=0.49) were not statistically significant. The chemotherapy cycles included 2 cycles and more, and both cycles could increase the ORR. Tumor responses were evaluated using WHO or RECIST criteria. Subgroup analysis showed that KLT plus first-line platinum-based chemotherapy could increase the ORR using the WHO or RECIST criteria.

Subgroup analysis of nausea and vomiting

Subgroup analysis was performed to reveal the influence of different doses, types of first-line platinum-based chemotherapy, cycles of chemotherapy, evaluation criteria, and supportive treatment for nausea and vomiting (*Table 5* and *Figure S3A*,*B*,*C*,*D*,*E*). The subgroup analysis failed to find any significant differences among the subgroups on the dose of KLT, chemotherapy types, chemotherapy cycles, and supportive treatment. Furthermore, the other doses (P=0.07), other cycles (P=0.24), and unclear supportive treatment (P=0.08) were not statistically significant. Additionally, high subgroup differences regarding evaluation criteria (I2=84.8%, P=0.01) were observed.

Subgroup analysis of leukopenia

The subgroup analysis failed to report any significant differences among subgroups on the dose of KLT, chemotherapy cycles, evaluation criteria, and supportive treatment for leukopenia (*Table 6* and *Figure S4A*,*B*,*C*,*D*,*E*). Additionally, other doses (P=0.28), other cycles (P=0.26), and unclear supportive treatment (P=0.09) were not statistically significant, but high subgroup differences regarding chemotherapy types (I2=66%, P=0.09) were noted.

Table 5 subgroup analysis of nausea and vomiting for each variable

Variable	No. of trials	No. of participants		Fracture, RR (95% CI)	P value[a]	I^{2a}
		Nausea and vomiting	Total			
Kanglaite dose					0.97	0%
200 ml	6	251	481	0.58 (0.39, 0.87)		
Other[b]	2	20	91	0.57 (0.31, 1.04)		
Type of first-line platinum-based chemotherapy					0.40	0%
GP	8	239	610	0.61 (0.43, 0.87)		
TP	1	40	62	0.48 (0.31, 0.74)		
Cycle of chemotherapy					0.79	0%
2-cycle	7	267	505	0.59 (0.41, 0.83)		
Other[c]	2	12	167	0.50 (0.15, 1.60)		
Evaluation criteria					0.01	84.8%
Yes	4	187	301	0.77 (0.61, 0.98)		
Unclear	5	92	371	0.45 (0.32, 0.63)		
Supportive treatment					0.78	0%
Yes	4	112	226	0.59 (0.45, 0.76)		
No	5	167	446	0.53 (0.26, 1.08)		

[a]P value, I^2: heterogeneity between subgroups; [b]other: includes Kanglaite doses about 60 and 300 mL; [c]other: includes chemotherapy cycles about 3-cycle and 4-cycle. GP, cisplatin or paraplatin and gemcitabine; NP, cisplatin or paraplatin and vinorelbine; TP, cisplatin or paraplatin and paclitaxel; DP, cisplatin or paraplatin and docetaxel; AP, cisplatin or paraplatin and pemetrexed.

Table 6 Subgroup analysis of leukopenia for each variable

Variable	No. of trials	No. of participants		Fracture, RR (95% CI)	P value[a]	I^{2a}
		Leukopenia	Total			
Kanglaite dose					0.53	0%
200 mL	7	309	625	0.64 (0.43, 0.94)		
Other[b]	3	34	176	0.34 (0.05, 2.45)		
Type of first-line platinum-based chemotherapy					0.09	66%
GP	9	305	759	0.70 (0.53, 0.93)		
Other[c]	2	45	142	0.32 (0.14, 0.75)		
Cycle of chemotherapy					0.29	9.3%
2-cycle	7	280	529	0.56 (0.35, 0.90)		
Other[d]	4	70	372	0.79 (0.52, 1.19)		
Evaluation criteria					0.52	0%
Yes	6	235	387	0.67 (0.46, 0.99)		
Unclear	5	115	514	0.55 (0.33, 0.90)		
Supportive treatment					0.32	0%
Yes	5	138	420	0.55 (0.35, 0.87)		
No	6	212	481	0.74 (0.52, 1.05)		

[a]P value, I^2: heterogeneity between subgroups; [b]other: includes Kanglaite doses about 60, 100 and 300 mL; [c]other: includes chemotherapy types about DP and NP; [d]other: includes chemotherapy cycles about 3-cycle and 4-cycle. NP, cisplatin or paraplatin and vinorelbine; DP, cisplatin or paraplatin and docetaxel.

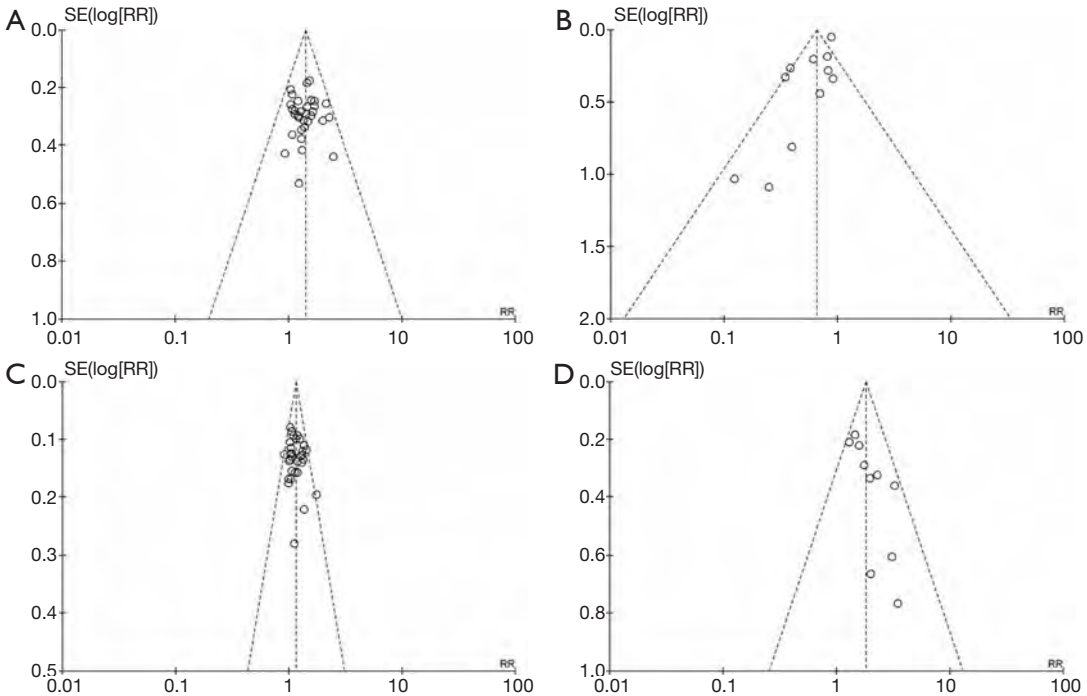

Figure 9 Publication bias analysis.

Publication bias analysis (Figure 9)

The funnel plots were symmetric in ORR, DCR, and KPS (*Figure 9A*,*C*,*D*). Furthermore, no publication bias was observed in studies that objectively reported the results. The funnel plots were asymmetric in leukopenia (*Figure 9B*). These results indicated publication bias. Leukopenia was overestimated in one study (42).

Summary of evidence

We used the Grading of Recommendations Assessment Development and Evaluation (GRADE) to report the quality of evidence for ORR, DCR, KPS, and adverse events. The quality of evidence was rated as high, moderate, low, and very low, and the results revealed a moderate or low overall quality (*Figure S5*).

Discussion

As a traditional Chinese medicine injection, KLT is widely used in clinical patients with lung, gastric, and liver cancer (48,49) as an adjunct to chemotherapy for improving the curative effect. Some studies have shown that KLT can sensitize cancer cells to chemotherapy (50,51). One network meta-analysis (52) that included three traditional Chinese medicine injections showed KLT combined with NP had the greatest efficacy in ORR, ranking first with a probability of 71%.

Summary of the results

In our study, KLT plus first-line platinum-based chemotherapy improved the ORR and decreased the risk ratio of nausea, vomiting, and leukopenia in NSCLC. We observed significant clinical heterogeneity in adverse reactions, which is consistent with previous studies (7). However, previous studies failed to explain the long-term synergistic efficacy of this combination and did not perform subgroup analysis to clarify the observed clinical heterogeneity. Our subgroup analysis indicated these results were generally consistent regardless of the dose of KLT, chemotherapy cycles, and evaluation criteria for ORR. Regarding the type of chemotherapy, there were no significant differences between KLT combined with TP or AP. We did not reach any definite conclusions about AP due to only one relevant study being available. There were three studies in the TP subgroup and showed no obvious quality problems of ORR. Ma observed that the inhibitory effect of KLT plus TP in Lewis lung cancer cell lines was not significantly different from TP (53). Previous studies have

reported KLT plus paclitaxel demonstrated no significance compared to paclitaxel in advanced malignant thymoma (54). Aside from insufficient quantity, we assumed KLT combined with GP, NP, and DP, but not TP, could increase tumor responses. We applied the KPS scale to evaluate the QOL and observed that KLT significantly increased the KPS.

Furthermore, a meta-analysis with 31 studies showed that KLT could slightly increase the DCR. Therefore, we believe KLT plus first-line platinum-based chemotherapy, excluding the TP combination, could significantly increase clinical efficacy. The results indirectly indicate KLT may have a synergistic efficacy with first-line platinum-based chemotherapy.

First-line platinum-based chemotherapy demonstrates varying degrees of blood and gastrointestinal toxicity, and we selected the most common clinical adverse reactions, including nausea, vomiting, and leukopenia, to evaluate the role of KLT in preventing adverse reactions. For nausea and vomiting, further subgroup analysis indicated that clear evaluation criteria were the source of heterogeneity. For leukopenia, further subgroup analysis showed that variability in chemotherapy type was the source of heterogeneity, and leukopenia was overestimated in one study (41). It is worth mentioning that using use of supportive treatment during KLT plus first-line platinum-based chemotherapy would not decrease the risk ratio of both adverse reactions compared with chemotherapy alone, which has not been mentioned in previous studies (48,55). However, there are many factors in clinical settings, including supportive treatment, treatment dosage, type of chemotherapy. Hence, we assumed an indefinite conclusion regarding the role of KLT in the matter.

Strengths and limitations

This is the most detailed meta-analysis focusing on the efficacy of ORR, KPS, and adverse reactions, and can thus better inform the clinical application of KLT. However, some limitations this study should be noted. First, only Chinese and English databases were searched, and some relevant studies might have been excluded due to language restrictions. Furthermore, all of the included studies were published in China, which might have led to publication bias. Secondly, only 17 studies reported the random allocation methods, but no study provided detailed information on the random allocation concealment.

Moreover, 14 participants withdrew from the clinical study with 5 reporting acute/subacute toxicity; this could have influenced the outcome of adverse reactions. Additionally, three studies demonstrated selective reporting concerning acute/subacute toxicity, and 1 study did so concerning KPS. Thirdly, the methods used to classify studies as high quality might have been relatively lenient, and other researchers may have selected different definitions for study quality.

Suggestions for future clinical trials

Differences in survival rates are of utmost importance to clinicians and NSCLC patients alike. We are similarly interested in the long-term synergistic efficacy of KLT plus first-line platinum-based chemotherapy, particularly as it relates to survival and deterioration rate effect. In our meta-analysis, three studies (19,28,45) mentioned MST, and the combined treatment showed a positive effect on MST compared with first-line platinum-based chemotherapy merely. We noticed that evidence concerning long-term synergistic efficacy, such as overall survival and progression-free survival, was still insufficient. Apart from that, we noticed that some studies demonstrated the survival rate using a life table to show the changes vividly, but only complete reporting may bring meaningful work to NSCLC treatment. Therefore, we appeal to clinical researchers to include short-term and long-term synergistic efficacy with the specific normative data type and regard it as a vital outcome in further research.

Conclusions

The evidence indicates KLT plus first-line platinum-based chemotherapy, except the combination with TP, may significantly improve the clinical efficacy in patients with advanced NSCLC. With supportive treatments, this combination demonstrated a lower risk of nausea, vomiting, and leukopenia, and positively affected MST and KPS. These results indicate KLT may indirectly have ameliorative and synergistic efficacy with first-line platinum-based chemotherapy. Finally, many shortcomings in clinical trial methodology resulted in an inadequate assessment of clinical efficacy and safety. We are thus eager to evaluate larger-scale RCTs or real-world studies to present an in-depth review in the near future.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-616). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. As a systematic review and meta-analysis, Ethical approval was not required as materials of this study had been published.

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Supplementary

Search	Add to builder	Query	Items found	Time
#23	Add	Search ((((Kanglaite) OR Coix Seed Oil)) AND ((non-small cell lung carcinoma[Title/Abstract]) OR NSCLC[Title/Abstract])) AND ((((((((((Randomized Controled Trials) OR Randomized Controled Trial) OR controlled clinical trial) OR placebo) OR drug therapy) OR randomly) OR trial) OR groups)) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms]))	4	06:15:09
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#20	Add	Search (animals[MeSH Terms]) NOT humans[MeSH Terms]	4632487	06:14:07
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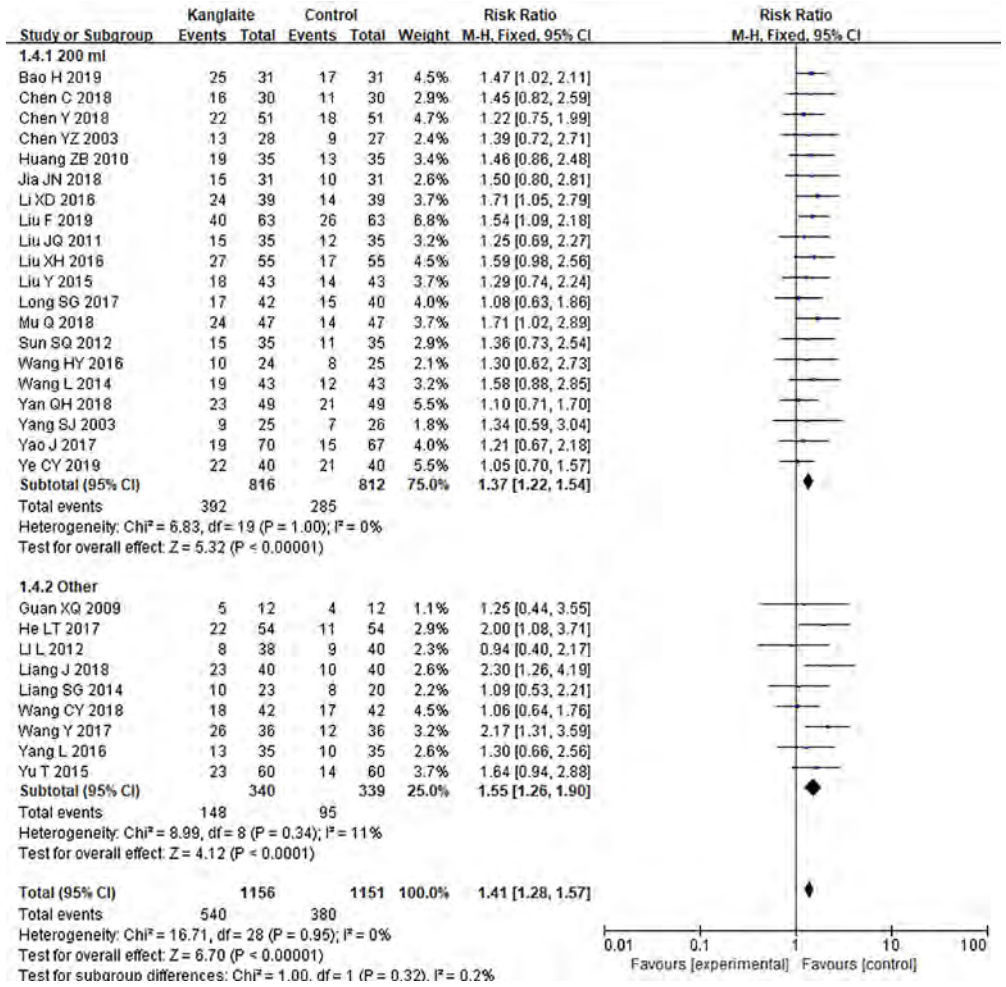
#18	Add	Search groups	2094991	06:12:30
#17	Add	Search trial	1354201	06:12:24
#16	Add	Search randomly	320848	06:12:18
#15	Add	Search drug therapy	3111089	06:12:07
#14	Add	Search placebo	222394	06:11:58
#13	Add	Search controlled clinical trial	713222	06:11:48
#12	Add	Search Randomized Controled Trial	32	06:08:42
#11	Add	Search Randomized Controled Trials	16	06:08:33
#9	Add	Search Coix Seed Oil	26	06:07:57
#8	Add	Search (non-small cell lung carcinoma[Title/Abstract]) OR NSCLC[Title/Abstract]	41561	06:07:35
#7	Add	Search Kanglaite	46	06:06:55

Figure S1 Electronic search strategy for PubMed.

A



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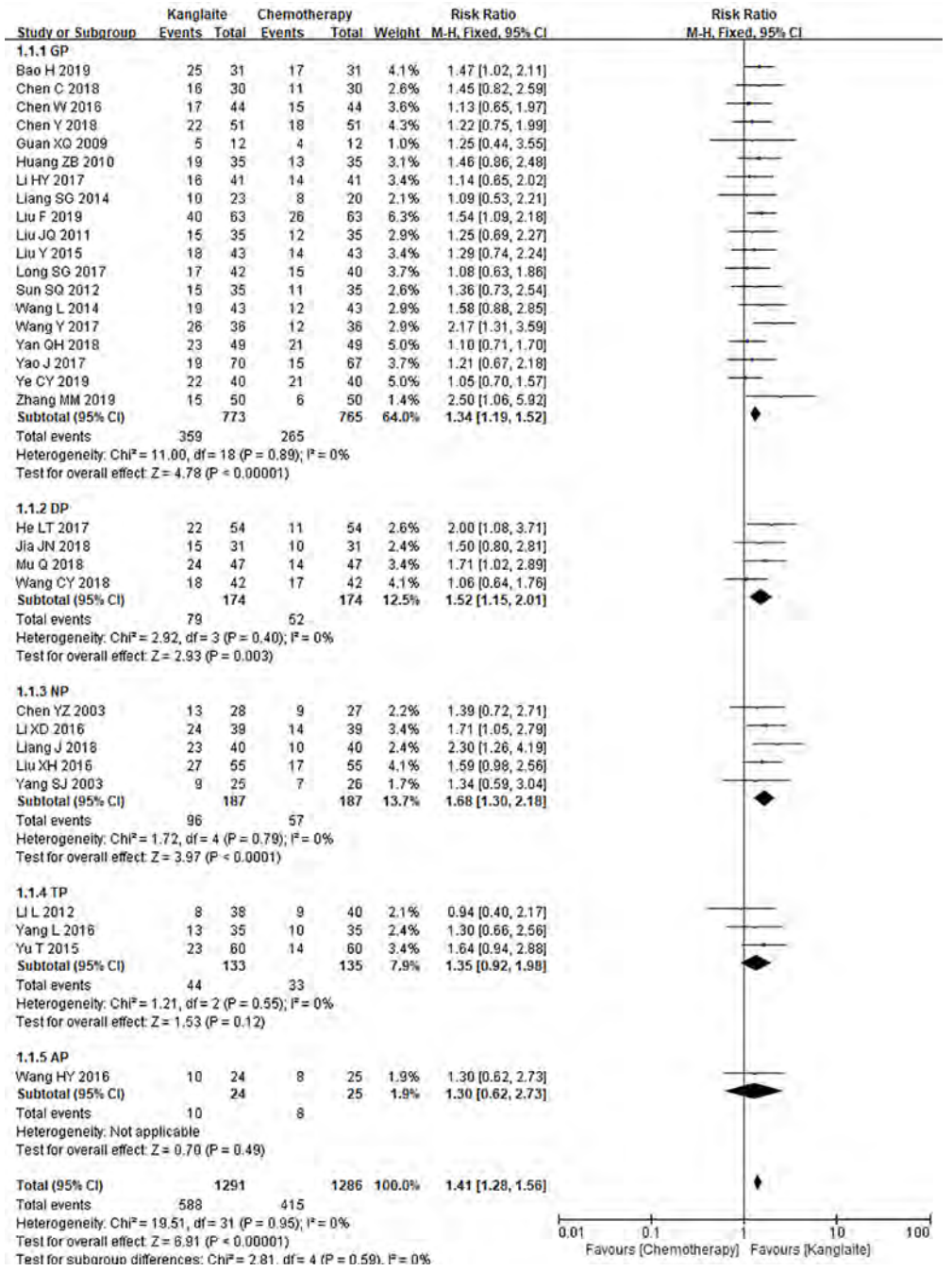

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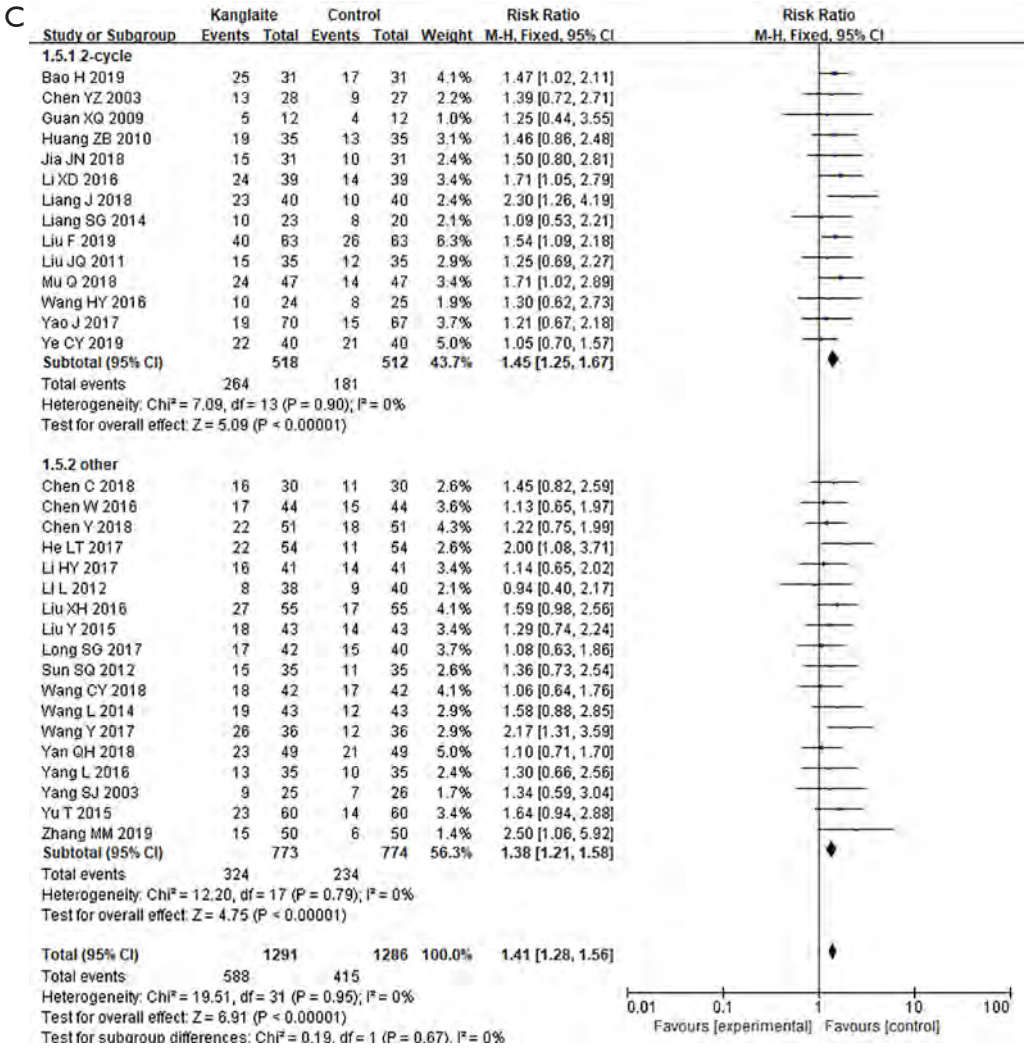

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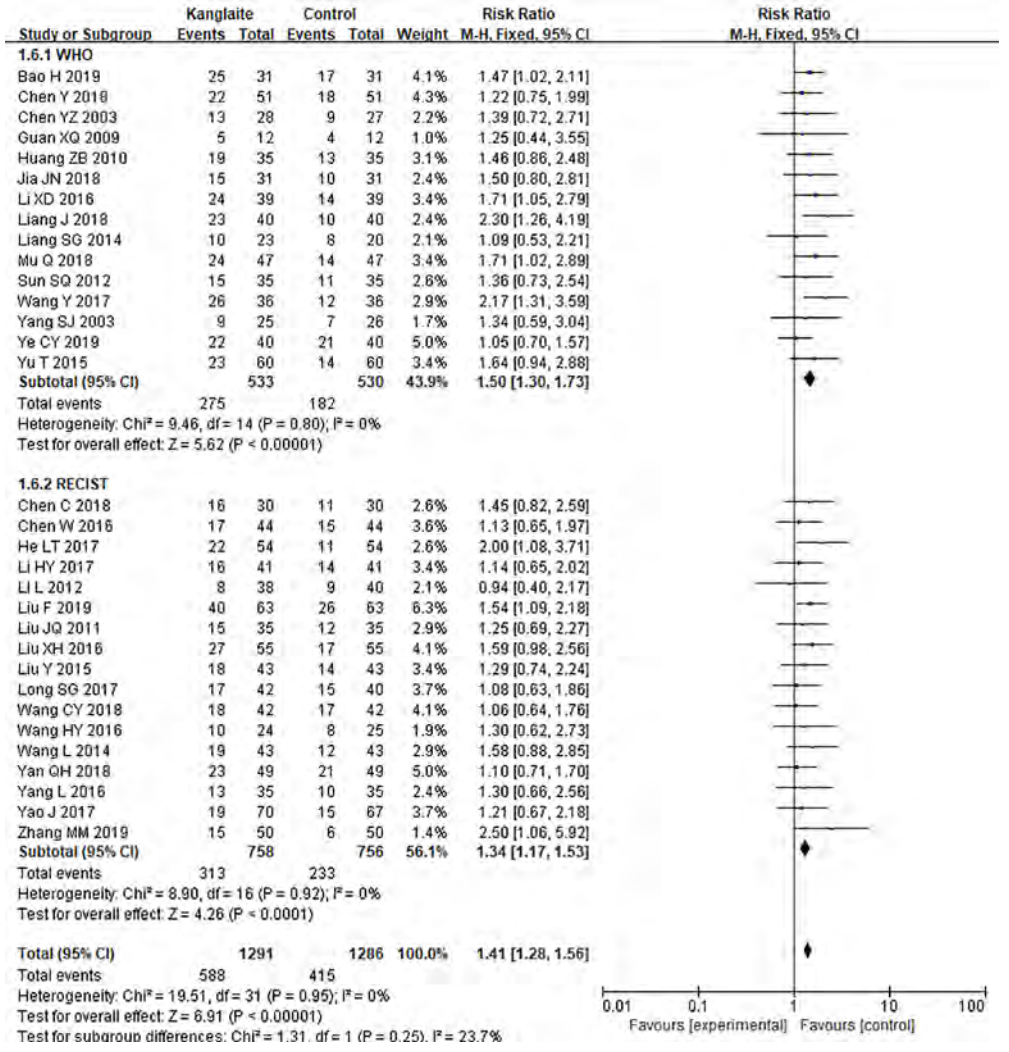


Figure S2 Subgroup analysis of ORR for each variable. (A) Subgroup analysis of ORR for Kanglaite dose; (B) subgroup analysis of ORR for type of first-line platinum-based chemotherapy; (C) subgroup analysis of ORR for cycle of chemotherapy; (D) subgroup analysis of ORR for evaluation criteria. ORR, objective response rate.

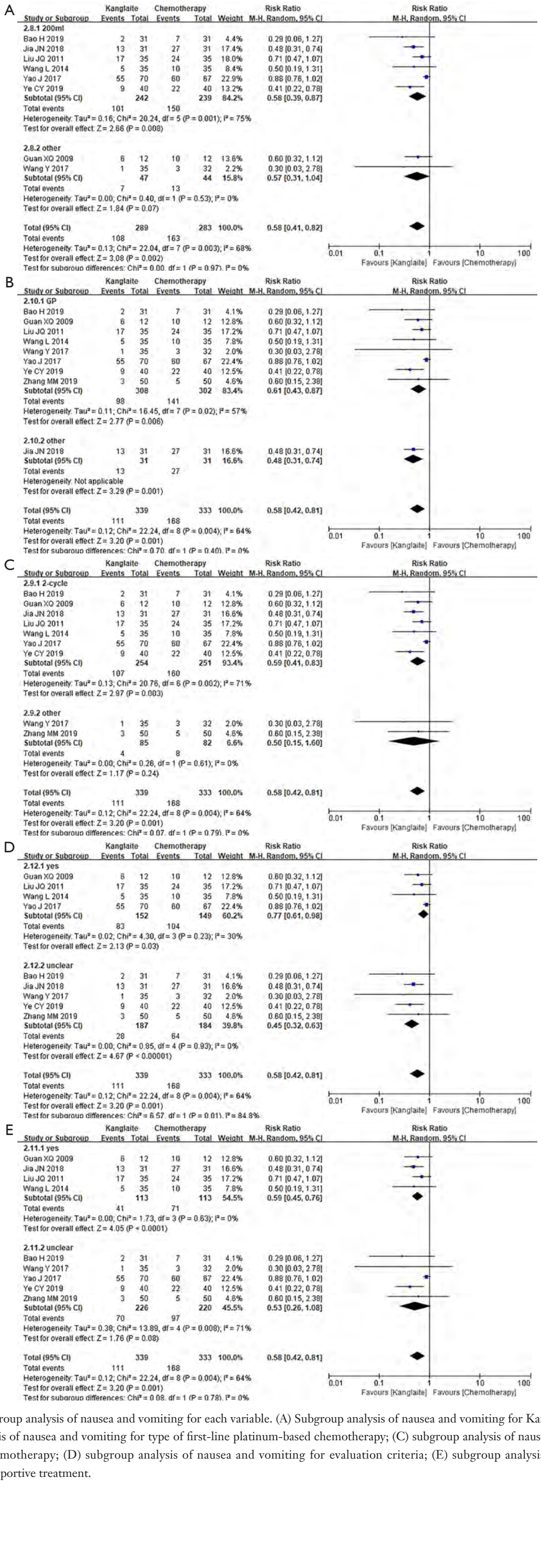
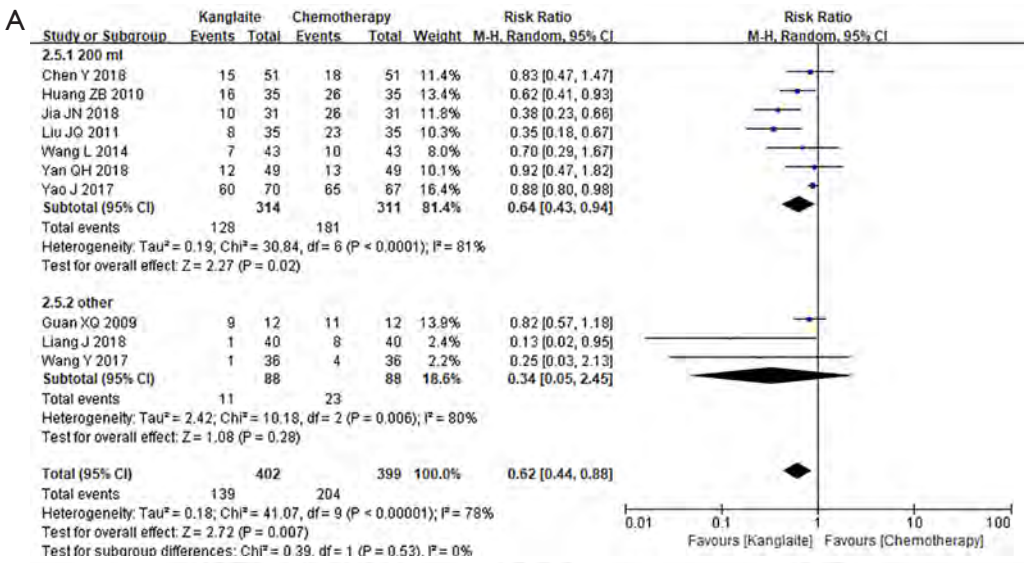
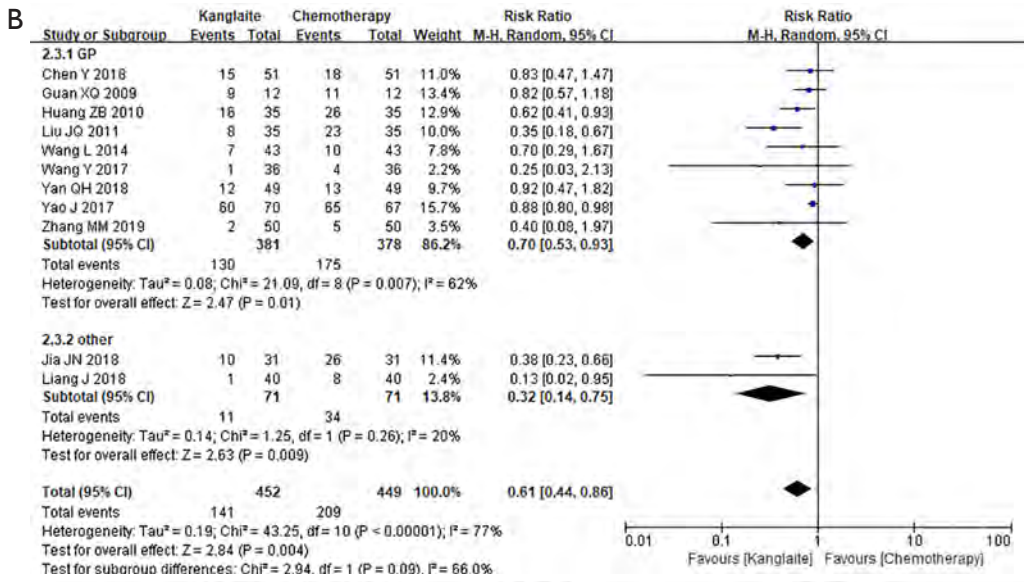
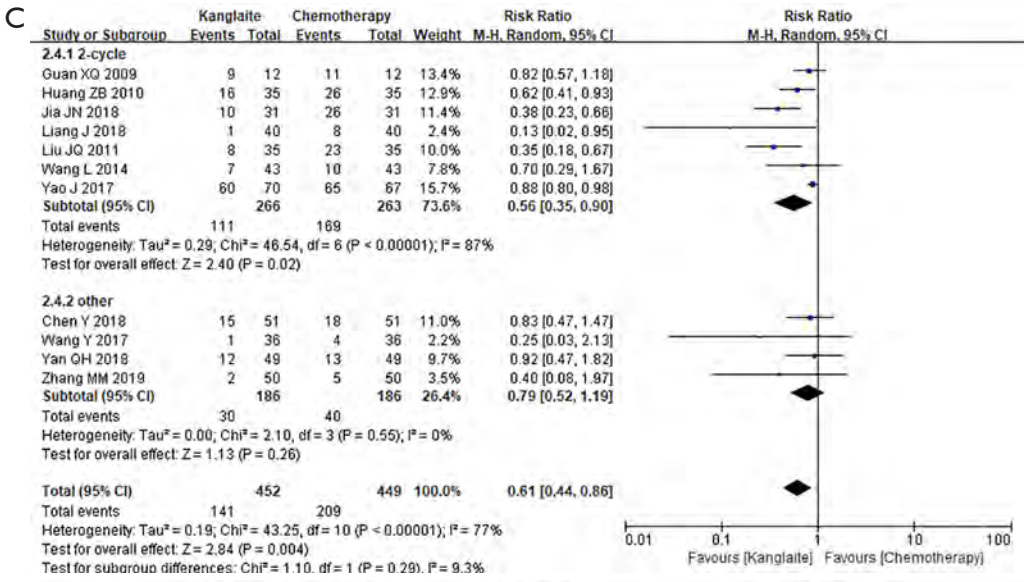
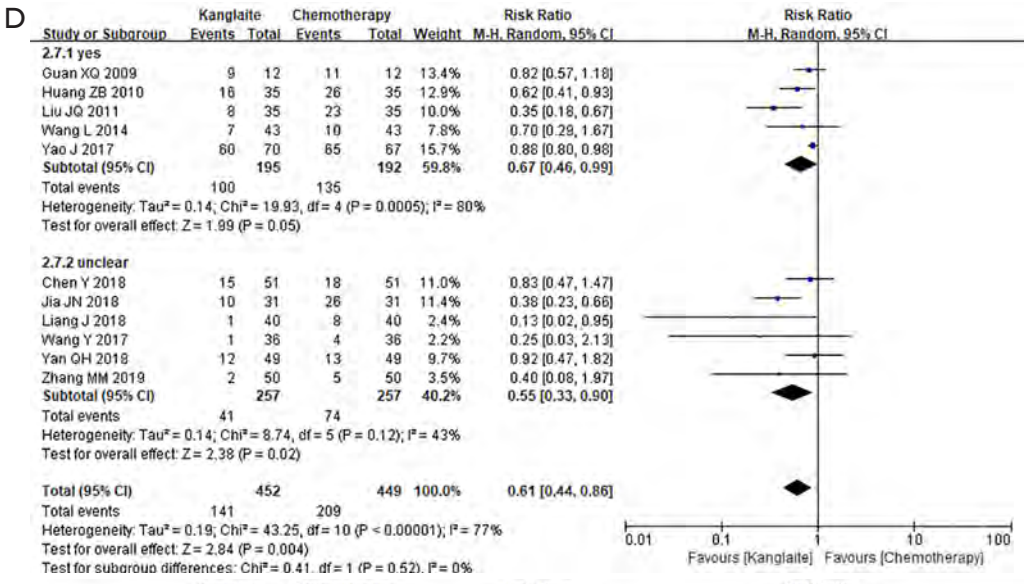


Figure S3 Subgroup analysis of nausea and vomiting for each variable. (A) Subgroup analysis of nausea and vomiting for Kanglaite dose; (B) subgroup analysis of nausea and vomiting for type of first-line platinum-based chemotherapy; (C) subgroup analysis of nausea and vomiting for cycle of chemotherapy; (D) subgroup analysis of nausea and vomiting for evaluation criteria; (E) subgroup analysis of nausea and vomiting for supportive treatment.









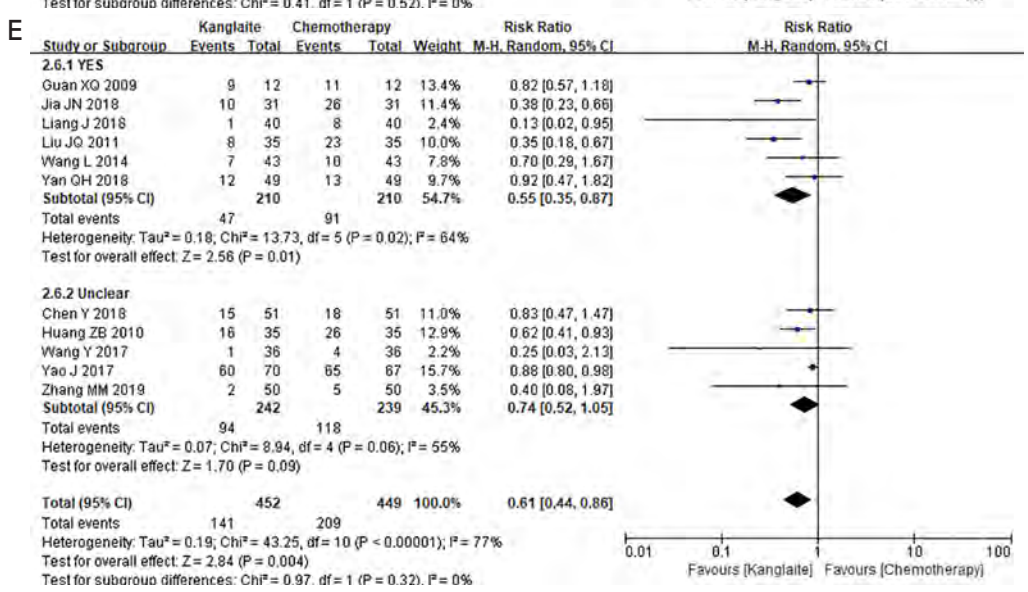


Figure S4 Subgroup analysis of leukopenia for each variable. (A) Subgroup analysis of leukopenia for Kanglaite dose; (B) subgroup analysis of leukopenia for type of first-line platinum-based chemotherapy; (C) subgroup analysis of leukopenia for cycle of chemotherapy; (D) subgroup analysis of leukopenia for evaluation criteria; (E) subgroup analysis of leukopenia for supportive treatment.

Question: Should Kanglaite combined with chemotherapy vs chemotherapy be used for NSCLC?											
Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Chemotherapy	With Kanglaite combined with chemotherapy		Risk with Chemotherapy	Risk difference with Kanglaite combined with chemotherapy (95% CI)
CR+PR (CRITICAL OUTCOME; assessed with: follow up)											
2577 (32 studies) 1 to 4 weeks	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias	415/1286 (32.3%)	588/1291 (45.5%)	RR 1.41 (1.28 to 1.56)	Study population	
										323 ORR per 1000	132 more ORR per 1000 (from 90 more to 181 more)
										Moderate	
										333 ORR per 1000	137 more ORR per 1000 (from 93 more to 186 more)
CR+PR+SD (CRITICAL OUTCOME; assessed with: follow up)											
2493 (31 studies) 1 to 4 weeks	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊖⊖ LOW[1,2] due to risk of bias	856/1244 (68.8%)	1000/1249 (80.1%)	RR 1.16 (1.11 to 1.22)	Study population	
										688 DCR per 1000	110 more DCR per 1000 (from 76 more to 151 more)
										Moderate	
										673 DCR per 1000	108 more DCR per 1000 (from 74 more to 148 more)
KPS (IMPORTANT OUTCOME; assessed with: KPS scale)											
737 (10 studies) 1 to 4 weeks	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	102/368 (27.7%)	186/369 (50.4%)	RR 1.82 (1.51 to 2.19)	Study population	
										277 KPS per 1000	227 more KPS per 1000 (from 141 more to 330 more)
										Moderate	
										673 KPS per 1000	552 more KPS per 1000 (from 343 more to 801 more)
nausea and vomiting (CRITICAL OUTCOME; assessed with: follow up)											
672 (9 studies) 1 to 4 weeks	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, imprecision	168/333 (50.5%)	111/339 (32.7%)	RR 0.58 (0.42 to 0.81)	Study population	
										505 NV per 1000	212 fewer NV per 1000 (from 96 fewer to 293 fewer)
										Low	
										400 NV per 1000	168 fewer NV per 1000 (from 76 fewer to 232 fewer)
leukopenia (CRITICAL OUTCOME; assessed with: follow up)											
901 (10 studies) 1 to 4 weeks	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	209/449 (46.5%)	141/452 (31.2%)	RR 0.61 (0.44 to 0.86)	Study population	
										465 LP per 1000	182 fewer LP per 1000 (from 65 fewer to 261 fewer)
										Moderate	
										673 LP per 1000	262 fewer LP per 1000 (from 94 fewer to 377 fewer)

[1] lack of blinding; [2] selective bias; [3] regards nausea and vomit as two different symptoms to rate

Figure S5 Summary of evidence.