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Review Article

Meta-analysis of the clinical effect of Kanglaite injection-assisted gemcitabine plus cisplatin regimen on non-small cell lung cancer

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Abstract: Objective: To systematically evaluate the clinical effect of Kanglaite (KLT) injection-assisted gemcitabine plus cisplatin (GP) regimen on non-small cell lung cancer (NSCLC). Methods: The CNKI, WanFang, VIP, Chinese Biomedical Database, PubMed, Embase and Cochrane Library databases were searched to collect the randomized controlled trials (RCTs), which evaluated the clinical effect of KLT combined with GP chemotherapy on NSCLC, published as of February 15, 2023. These articles were screened, extracted and evaluated. Revman 5.3 and STATA 17 were used for analysis, where the odds ratio (OR) was used as the statistic for the binary variables, and the mean difference (MD) was used as the statistic for the continuous variables. Results: After selection, this meta-analysis included 27 RCTs and 2,579 patients. Comparing with GP chemotherapy, KLT combined with GP regimen enhanced the total response rate (*OR*=1.76, 95% *CI*: 1.49-2.06, *P*<0.00001), improved the Karnofsky (KPS) score (*OR*=2.03, 95% *CI*: 1.55-2.66, *P*<0.00001), decreased the adverse reactions, including gastrointestinal reactions (*OR*=0.41, 95% *CI*: 0.33-0.51, *P*<0.00001), leucopenia (*OR*=0.45, 95% *CI*: 0.35-0.58, *P*<0.00001), anemia (*OR*=0.47, 95% *CI*: 0.32-0.67, *P*<0.0001) and liver function damage (*OR*=0.52, 95% *CI*: 0.38-0.73, *P*<0.0001), as well as elevated immune level, including $CD3^+$ (*MD*=8.51, 95% *CI*: 7.63-9.39, *P*<0.00001), $CD4^+$ (*MD*=5.68, 95% *CI*: 5.08-6.27, *P*<0.00001) and $CD4^+/CD8^+$ (*MD*=0.41, 95% *CI*: 0.38-0.44, *P*<0.00001). Conclusions: Current evidence shows that the combination regimen of KLT with GP has shown promising results in increasing the response rate, improving the KPS score, enhancing the immune level, and reducing the incidence of adverse reactions in NSCLC patients. However, this conclusion needs to be further verified due to limitations such as the limited number of articles included in this paper and the variability in research methodology and quality among the included studies.

Keywords: Kanglaite injection, gemcitabine, cisplatin, non-small cell lung cancer, therapeutic effect, meta-analysis

Introduction

The incidence and mortality of lung cancer have been increasing at a rapid pace [1]. Lung cancer patients usually have no obvious clinical symptoms at an early stage, so that most of the patients are diagnosed at an advanced phase [2]. Non-small cell lung cancer (NSCLC) is usually insidious, and about 80% of the patients are prone to regional metastasis or distant diffusion [3]. Most of the treatment for NSCLC is targeted therapy and chemotherapy [4]. Targeted therapy has shown significant response in patients with specific gene expression profiles, but only about 10% of NSCLC patients are sensitive to targeted therapy. As the major treatment, chemotherapy can effectively manage the symptoms of NSCLC patients and prolong their survival, especially for patients without specific gene expression profiles, making it a crucial treatment approach [5]. Gemcitabine plus Cisplatin (GP) chemotherapy regimen is a commonly used clinical treatment approach, in which gemcitabine and cisplatin are combined to inhibit tumor cell proliferation and achieve therapeutic goals in patients with NSCLC. Gemcitabine is a water-soluble analogue of deoxycytidine that interferes with DNA synthesis and repair in tumor cells by inhibiting the activity of ribonucleotide reductase. Cisplatin is a metal complex of platinum that acts as an alkylating agent with DNA as its primary target. It acts on both intra- and inter-strand chains of DNA to form DPP-DNA complexes, interfering

with DNA replication, or binding to nuclear and cytoplasmic proteins [5]. The combination of the two drugs has a good synergistic effect. However, repeated use of high concentration of chemotherapy drugs can cause cytotoxicity in patients [6]. It is imperative to explore treatment measures that are not only effective in clinical outcomes but also have minimal side effects.

According to statistics, about 52% of patients in China choose chemotherapy combined with traditional Chinese medicine to treat NSCLC to get better curative effect [7]. Kanglaite injection (KLT) is a kind of Chinese medicine developed independently in China. KLT is produced by extracting the active ingredient (mainly coix lactone) from coix seed [8], showing strong killing and inhibitory effects on tumor cells. Studies confirmed that the combination of KLT plus chemotherapy regimen demonstrates superior efficacy with manageable adverse reactions [9]. However, the quality of existing research is uneven, with different focuses. This paper systematically evaluated the clinical effect of KLT combined with GP chemotherapy on NSCLC, aiming to offer reliable guidance for its application in NSCLC treatment.

Material and methods

Inclusion and exclusion criteria

Inclusion criteria: (1) Study design: randomized controlled trials (RCTs); (2) Population: NSCLC patients confirmed by pathology; (3) Interventions: the research group received KLT plus GP chemotherapy; (4) Comparison: the control group received GP regimen only; (5) Outcome measures: articles with one of the following measures were included. ① The total clinical response rate: Complete remission (CR): after treatment, all target lesions disappeared; Partial remission (PR): after treatment, the sum of the two perpendicular dimensions of the target lesion decreased by over 30%; Progressive disease (PD): after treatment, new lesions appeared or the length and diameter of baseline lesions increased by 20% or more; Stable disease (SD): after treatment, the length of baseline lesions did not meet the criteria for PD or PR. The effective rate = cases with (CR + PR)/total number of cases. ② KPS score improvement rate: This reflects the quality of life of patients. An increase in KPS score of greater than 10 points was considered indicative of improvement. ③ Adverse reactions: Gastrointestinal reactions, leukopenia, anemia and liver function damage of grade I to grade IV. Adverse reaction rate = number of adverse reactions/total number of cases. ④ Immune function: The level of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$.

Exclusion criteria: (1) Repeated articles; (2) Articles from which data cannot be extracted or merged; (3) Articles including patients with severe cardio-cerebrovascular or psychiatric diseases; (4) Review, conference papers, animal/cell experiments.

Literature retrieval strategy

The CNKI, WanFang, VIP, Chinese Biomedical Database, PubMed, Embase and Cochrane Library databases were searched to collect RCTs, which applied KLT combined with GP chemotherapy to treat NSCLC, published as of February 15, 2023. The key words included Kanglaite, Gemcitabine, Cisplatin, GP, Carcinoma and Non-Small Cell Lung Cancer. Taking PubMed as an example, the search formula was "((((“kang-lai-te”[Supplementary Concept]) and (“Gemcitabine”[Mesh])) and (((((“Cisplatin”[Mesh]) or (cis-Platinum[Title/Abstract])) or (cis Platinum[Title/Abstract])) or (cis-Diamminedichloroplatinum[Title/Abstract])) or (cis-Diamminedichloroplatinum[Title/Abstract]))) and ((((((((((“Carcinoma, Non-Small-Cell Lung”[Mesh]) or (Carcinoma, Non-Small Cell Lung[Title/Abstract])) or (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) or (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) or (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) or (Non-Small-Cell Lung Carcinomas[Title/Abstract])) or (Non-Small-Cell Lung Carcinoma[Title/Abstract])) or (Non-Small Cell Lung Carcinoma[Title/Abstract])) or (Carcinoma, Non-Small Cell Lung[Title/Abstract])) or (Non-Small Cell Lung Carcinoma[Title/Abstract])) or (Non-Small Cell Lung Cancer[Title/Abstract])) or (Non-Small Cell Lung Cancer[Title/Abstract]))) and (“Randomized Controlled Trial”[Publication Type])".

Literature screening and data extraction

After eliminating the duplicate documents, two researchers independently read the titles and abstracts of the remaining articles, and excluded those that were deemed irrelevant or non-clinical trials. Disputes were resolved by a third

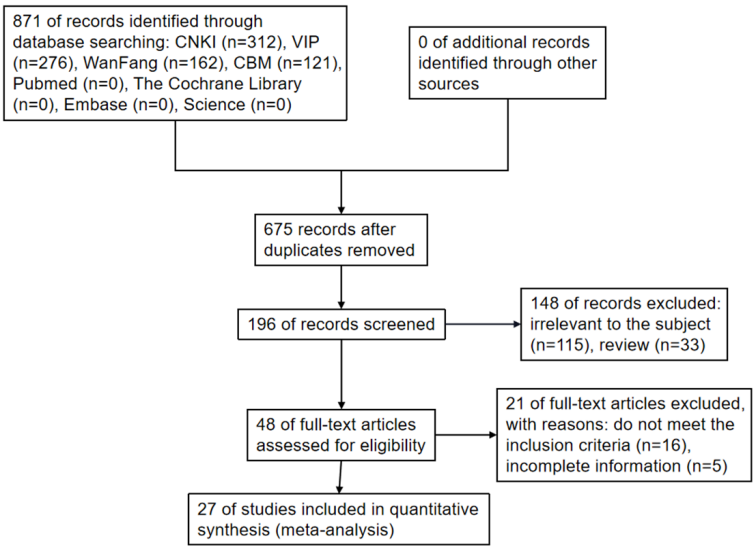

Figure 1. Literature screening process.

researcher. The rest of the articles were included after reading the full text. Important data were extracted, including TNM, course of treatment, treatment measures and outcome indicators.

Quality evaluation

The items of quality evaluation included (1) generation of random sequence (selective bias), (2) distribution concealment (selective bias), (3) implementation of blind method for researchers and subjects (implementation bias), (4) results Implementation of evaluator blind method (measurement bias), (5) integrity of result data (wear bias), (6) report bias, and (7) bias from other sources.

Primary and secondary measures

Primary measure: The total clinical response rate.

Secondary measures: KPS score improvement rate, adverse reactions (gastrointestinal reaction, leukopenia, anemia and liver function damage of grade I to grade IV), and immune function ($CD3^+$, $CD4^+$, $CD4^+/CD8^+$).

Statistical analysis

RevMan 5.3 and STATA 17 software was used for meta-analysis. The odds ratio (OR) was used as the statistic for the binary variables, and the mean difference (MD) was used as the statistic for the continuous variables, with 95% confidence interval (95% *CI*) provided. The heterogeneity among the included research results was analyzed by Q test. If the heterogeneity between the research results was low ($P>0.1$ and $I^2<50\%$), the fixed effect (FE) model was adopted; otherwise, the random effect (RE) model was used. A funnel map was drawn to assess whether there was publication bias. The sub-group analysis was performed if there was a big heterogeneity. The egger test for the publication bias was performed in STATA 17. $P<0.05$ indicates a statistically significant difference.

Writing of the meta-analysis

Writing of the meta-analysis followed the PRISMA guidelines.

Results

Literature screening process and basic characteristics of the included research

As shown in **Figure 1**, there were 871 relevant articles at the time of initial searching. After screening, 27 articles were included, with a total of 2,579 patients with NSCLS included. The number of cases, TNM stage, course of treatment and primary outcome of the included studies are shown in **Table 1**.

Quality evaluation

The selection bias of 23 studies was considered "low risk" since they described specific random classification methods, with 19 studies using the random number table method and 4 studies using the paper bag method. The others did not describe the random classification method, so they were evaluated as "unclear". In terms of blind method, 10 studies didn't mention the implementation of blind method, so they were evaluated as "unclear". Seven studies, which didn't explain the hidden distribution, were evaluated as "unclear". In addition, 18 studies did not have cases of lost visits/withdrawals, and 20 studies did not selectively report the results of the study, which were evaluated as "low risk" correspondingly. For other

Table 1. Grouping and patient information in each study

Study Year	Cases (n)		TNM stage	Course of treatment (days)	Primary outcome
	Experimental group	Control group			
Che 2012 [10]	49	49	III-IV	7 days * 4 times	A B C D F
Chen 2016 [11]	44	44	III-IV	21 days * 4 times	A G H I
Chen 2018 [12]	30	30	IIIB-IV	21 days	A C D F
Chen 2018 (2) [13]	51	51	III-IV	21 days * 4 times	A C D F
Dai 2019 [14]	41	41	-	7 days * 3 times	A
Guan 2010 [15]	35	30	IIIB-IV	21 days * 2 times	A B D G H I
Gui 2020 [16]	60	60	III-IV	21 days * 3 times	A C D E F G H I
Han 2018 [17]	99	101	III-IV	21 days * 2 times	A B C D E F G H I
Hang 2017 [18]	70	67	IIIB-IV	21 days * 2 times	A C E G H I
Li 2017 [19]	41	41	III-IV	21 days * 2 times	A
Liang 2014 [20]	23	20	IIIB-IV	21 days * 2 times	A B C D E F
Liu 2015 [21]	43	43	IIIB-IV	21 days * 4 times	A B C
Liu 2017 [22]	34	35	IIIB-IV	21 days * 3 times	A B G H I
Liu 2019 [23]	63	63	IIIB-IV	21 days * 2 times	A B
Long 2017 [24]	42	40	IIIB-IV	21 days * 3 times	A C F
Lu 2016 [25]	62	62	III-IV	21 days * 3 times	A B
Mao 2014 [26]	63	63	III-IV	21 days * 2 times	A
Ning 2018 [27]	34	34	-	21 days * 3 times	A C D F G H I
Sun 2012 [28]	35	35	III-IV	21 days * 4 times	A
Sun 2021 [29]	66	72	-	21 days * 2 times	A C D E G H I
Wang 2014 [30]	43	43	IIIB-IV	21 days	A B C D E G H I
Yan 2018 [31]	49	49	III-IV	21 days * 4 times	A C D F
Ye 2019 [32]	40	40	III-IV	21 days * 2 times	A C G H I
Zhai 2013 [33]	30	18	IIIB-IV	28 days * 2 times	A C D
Zhang 2021 [34]	48	48	III-IV	21 days	A C D E F
Zheng 2020 [35]	62	58	-	21 days	A C D
Zhu 2016 [36]	43	42	III-IV	21 days * 2 times	A C D E F G H I

Note: A. Total response rate; B. Karnofsky (KPS) score improvement rate; C. Gastrointestinal reactions; D. Leucopenia; E. Anemia; F. Liver function damage; G. $CD3^+$; H. $CD4^+$; I. $CD4^+/CD8^+$.

biased sources, due to insufficient information in the original study, 6 studies were evaluated as "unclear". See **Figures 2** and **3**. The evaluation indicated that there was some bias in the included publications. Sub-groups analysis was needed if there was a big heterogeneity in the outcome comparison.

Meta-analysis results

Total clinical response rate: As shown in **Figure 4**, FE model was adopted to evaluate the total clinical response rate in 27 studies. It was found that KLT combined with GP enhanced the response rate compared with GP (*OR*=1.76, 95% *CI*: 1.49-2.06, *P*<0.00001).

KPS score improvement rate: As shown in **Figure 5**, FE model was adopted to analyze the improvement rate of KPS score in 9 studies. It was found that KLT combined with GP improved the KPS score of patients compared with GP alone (*OR*=2.03, 95% *CI*: 1.55-2.66, *P*<0.00001).

Adverse reaction rate: Gastrointestinal reactions: FE model was adopted to evaluate gastrointestinal reactions in 18 studies. It was found that the gastrointestinal reaction rate in the patients receiving KLT plus GP was lower than that in the patients receiving GP (*OR*=0.41, 95% *CI*: 0.33-0.51, *P*<0.00001). See **Figure 6**.

Leucopenia: FE model was adopted to evaluate leucopenia in 15 studies. It was found that KLT plus GP can effectively reduce the incidence of leukopenia compared with GP (*OR*=0.45, 95% *CI*: 0.35-0.58, *P*<0.00001). See **Figure 7**.

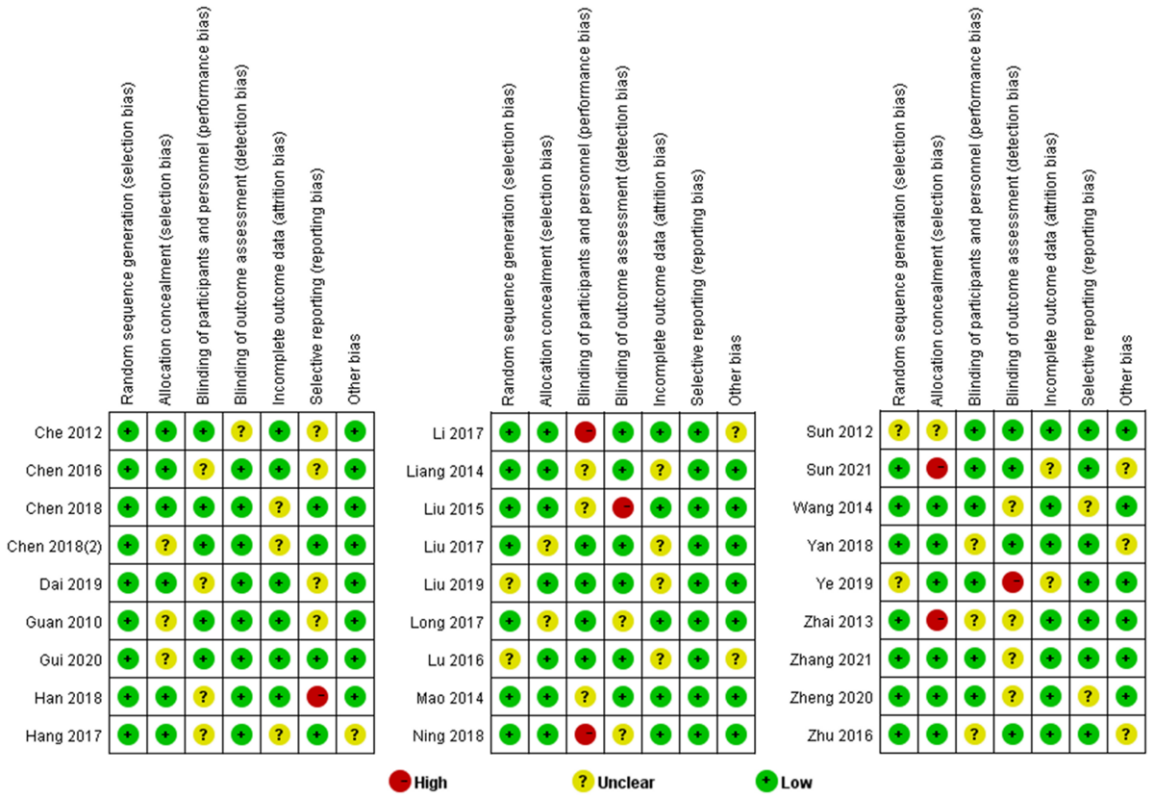

Figure 2. The scale for assessing the report quality of clinical trials.

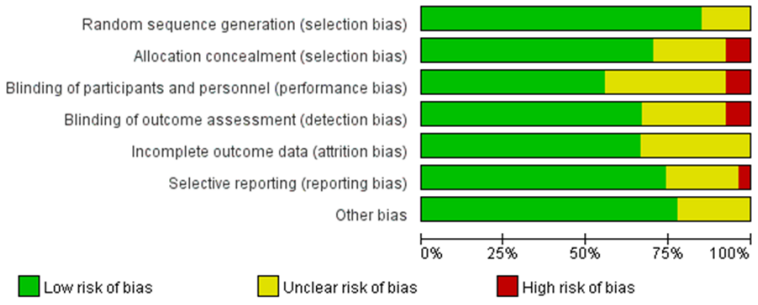

Figure 3. Summary chart of the risk bias assessment for the 27 studies.

Anemia: Eight studies were eligible to compare the anemia rate between two groups. Meta-analysis of FE model showed that KLT combined with GP chemotherapy can effectively reduce the incidence of anemia as compared with GP (*OR*=0.47, 95% *CI*: 0.32-0.67, *P*< 0.0001). See **Figure 8**.

Liver function damage: Eleven studies were eligible for the comparison of liver function damage rate between the two groups. Meta-analysis of FE model showed that the liver function damage rate was decreased greatly in the patients receiving KLT plus GP (*OR*=0.52, 95% *CI*: 0.38-0.73, *P*<0.0001). See **Figure 9**.

Immune function

$CD3^+$ level: Eleven studies were eligible for the analysis of the $CD3^+$ level after treatment between the two groups. As shown in **Figure 10**, KLT plus GP effectively increased $CD3^+$ level as compared with GP (*MD*=8.51, 95% *CI*: 7.63-9.39, *P*<0.00001), but there was a large heterogeneity (I^2=80%). Further, a subgroup analysis based on the TNM stage was performed, where the patients in 5 publications were in III-IV stage, the patients in 4 articles were in IIIB-IV stage, and the TNM stage of patients in two publications were unknown. In the subgroup of III-IV stage, the results showed that I^2=38% (*MD*=5.17, 95% *CI*: 3.80-6.54, *P*<0.00001). In the subgroup of IIIB-IV, the result showed that

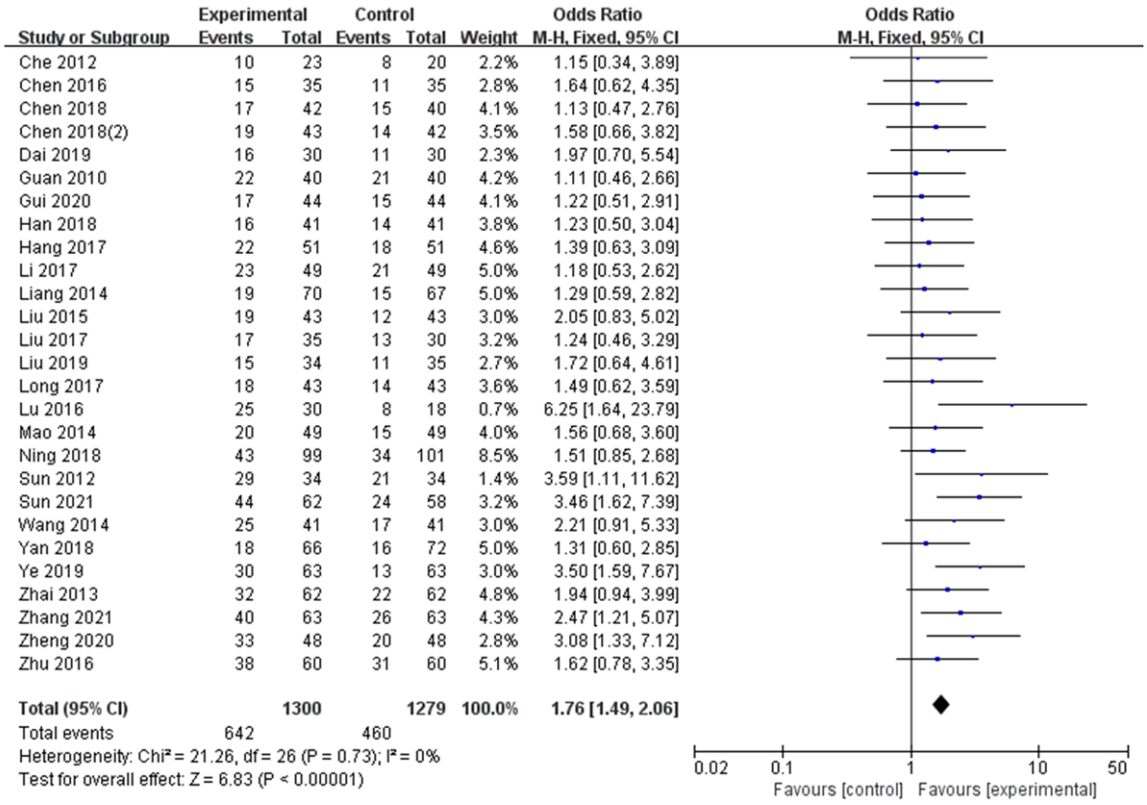

Figure 4. The comparison of total response rate between the two groups.

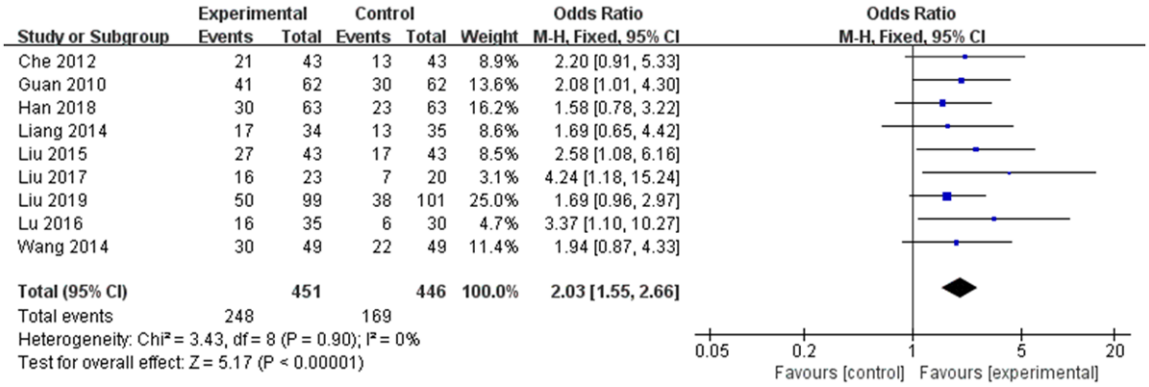

Figure 5. The comparison of KPS score improvement rate between the two groups.

I^2=0% (*MD*=11.64, 95% *CI*: 10.27-13.01, *P*< 0.00001). In the subgroup of unknown, the result showed that I^2=0% (*MD*=9.00, 95% *CI*: 6.92-11.09, *P*<0.00001).

$CD4^+$ level: As shown in **Figure 11**, FE model was adopted to evaluate the $CD4^+$ level after treatment between two groups in 11 studies. It was found that KLT plus GP effectively improved the $CD4^+$ level as compared with GP (*MD*=5.68, 95% *CI*: 5.08-6.27, *P*<0.00001), but there was a large heterogeneity (I^2=58%). Based on the course of treatment, a subgroup analysis was performed. In the subgroup of 21 days, only one publication was included, and the result showed that (*MD*=4.86, 95% *CI*: 3.94-5.78, *P*<0.00001). Five publications were included in the subgroup of 21 days * 2 courses, and the results showed that I^2=37% (*MD*=5.22, 95% *CI*: 4.18-6.26, *P*<0.00001). Three publications

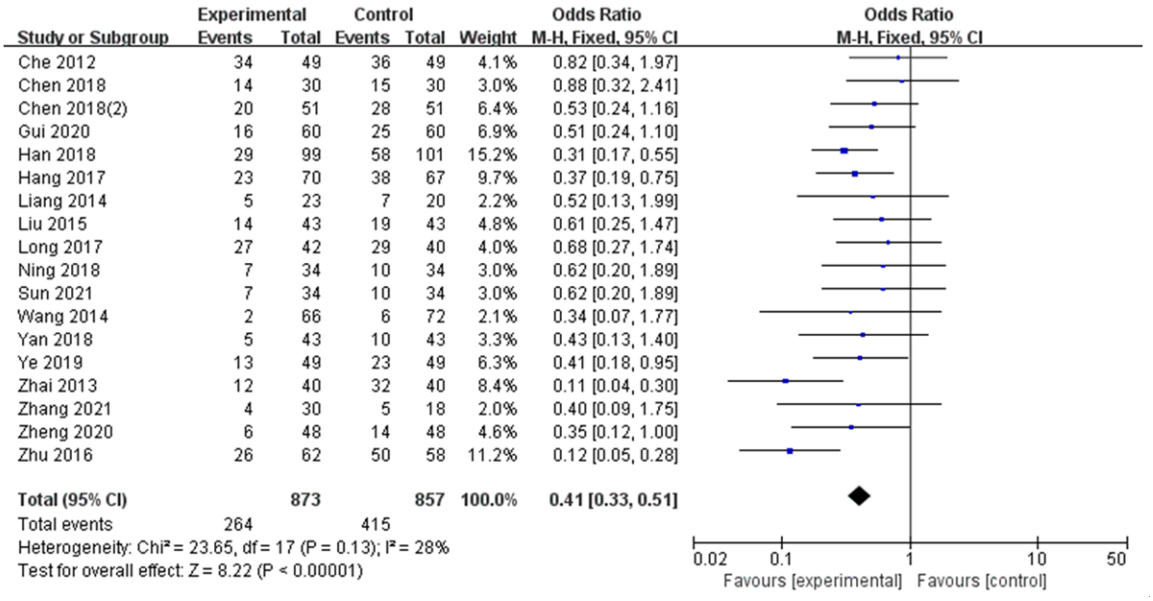

Figure 6. The comparison of gastrointestinal reaction rate between the two groups.

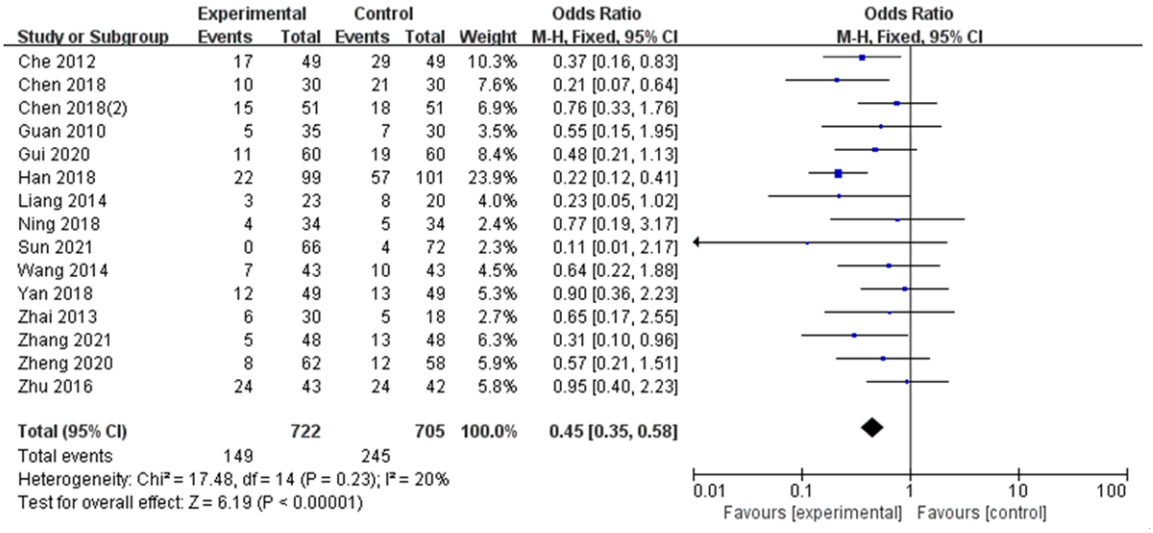

Figure 7. The comparison of leucopenia rate between the two groups.

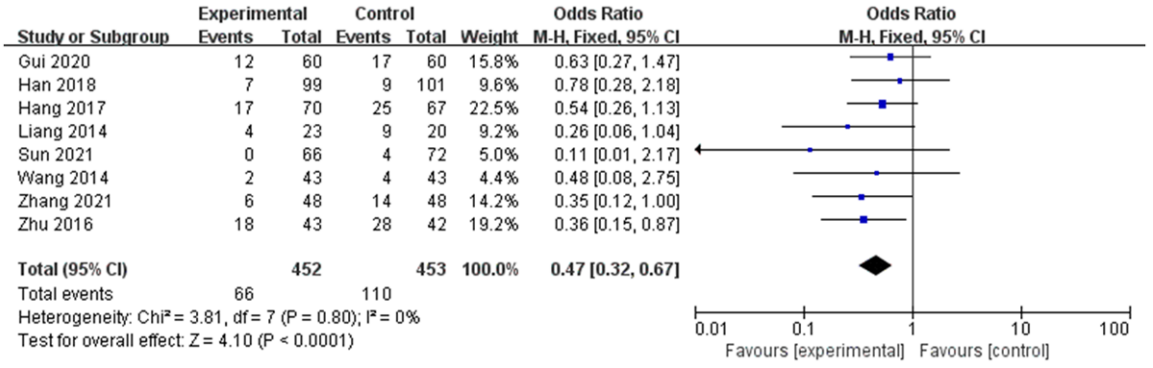

Figure 8. The comparison of anemia rate between the two groups.

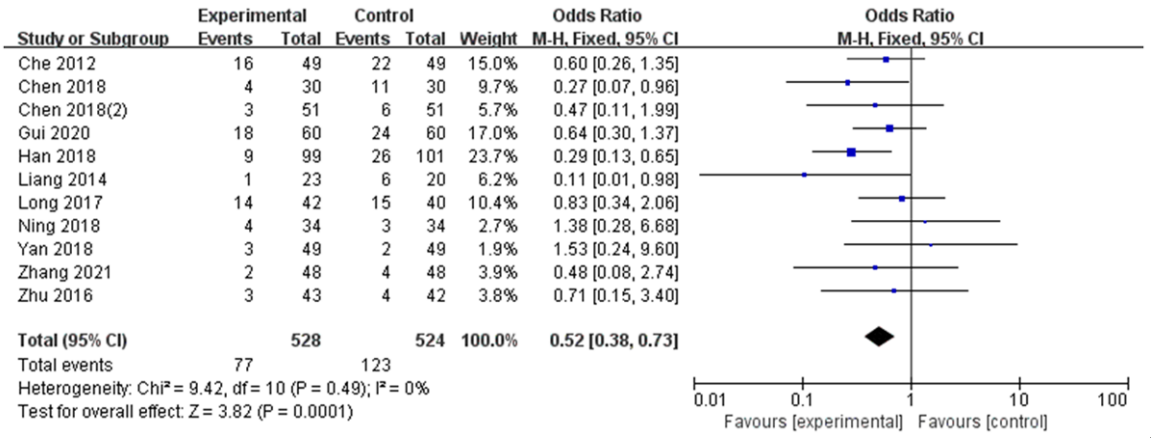

Figure 9. The comparison of liver function damage rate between the two groups.

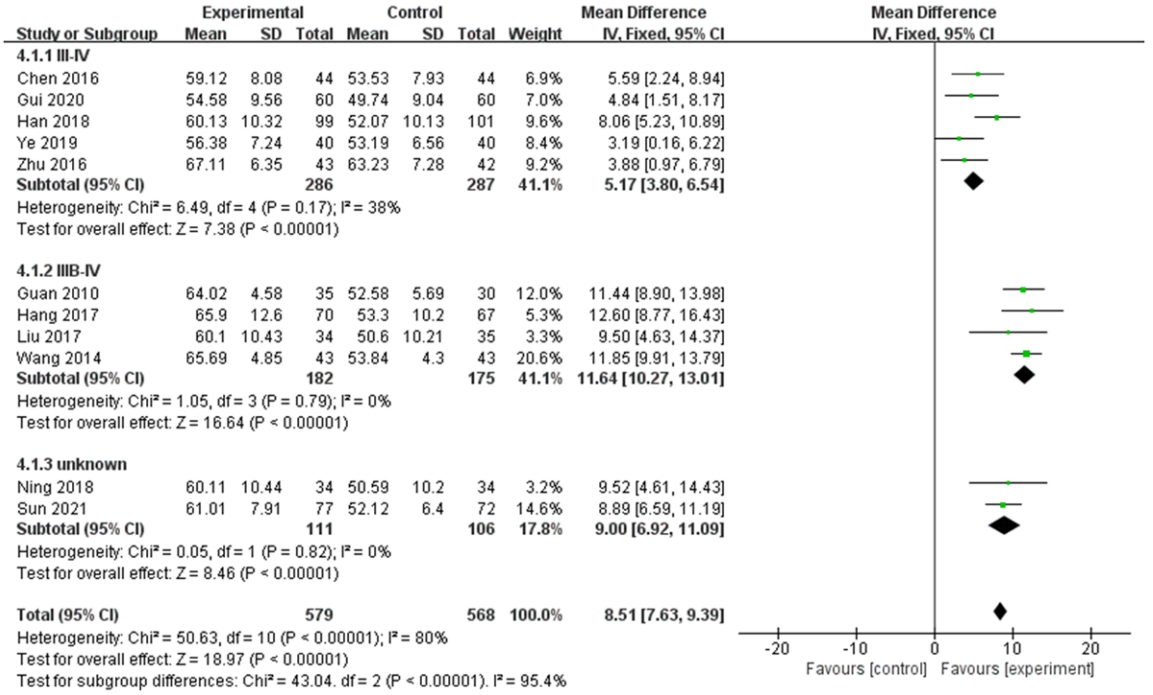

Figure 10. The subgroup analysis of $CD3^+$ level after treatment between the two groups.

were included in the subgroup of 21 days * 3 courses, and the results showed that I^2=0% (*MD*=6.68, 95% *CI*: 4.97-8.39, *P*<0.00001). Two studies were included in the subgroup of 21 days * 4 courses, and the results showed that I^2=0% (*MD*=8.46, 95% *CI*: 6.83-10.08, *P*<0.00001).

$CD4^+/CD8^+$ level: FE model was adopted for the comparison of $CD4^+/CD8^+$ level after treatment between the two groups in 11 studies. It was found that the $CD4^+/CD8^+$ level in the patients receiving KLT + GP was higher than that in the patients receiving GP after treatment (*MD*=0.41, 95% *CI*: 0.38~0.44, *P*<0.00001), but there was a large heterogeneity (I^2=92%). Based on the course of treatment, a subgroup analysis was performed. In the subgroup of 21 days, only one publication was included, and the results showed that (*MD*=0.14, 95% *CI*: -0.02-0.30, *P*=0.10). Five publications were included in the subgroup of 21 days * 2 courses, and the results showed that I^2=36% (*MD*=0.36, 95% *CI*: 0.33-0.40, *P*<0.00001).

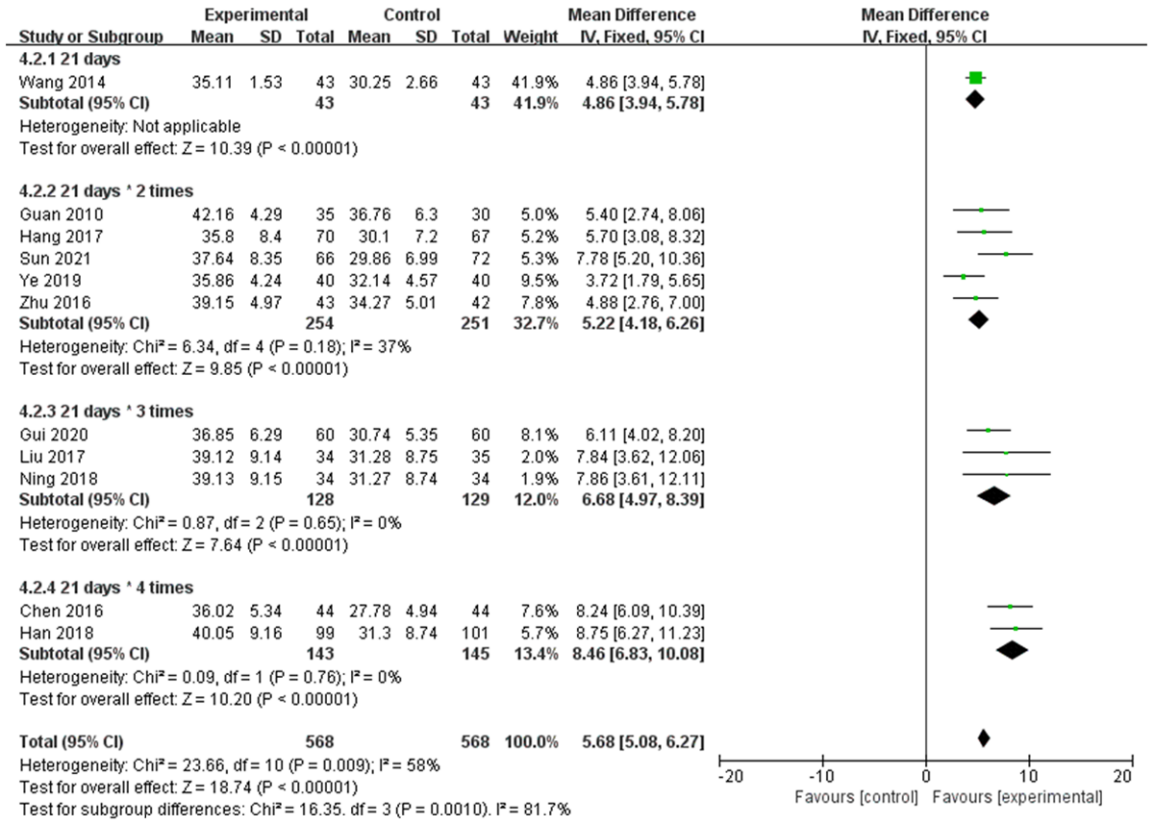

Figure 11. The subgroup analysis of $CD4^+$ level after treatment between the two groups.

Three publications were included in the subgroup of 21 days * 3 courses, and the results showed that I^2=0% (*MD*=0.94, 95% *CI*: 0.83-1.05, *P*<0.00001). Two studies were included in the subgroup of 21 days * 4 courses, and the results showed that I^2=0% (*MD*=0.46, 95% *CI*: 0.37-0.56, *P*<0.00001). See **Figure 12**.

Publication bias

A funnel chart of each outcome was drawn to evaluate the publication bias. The scattered distribution of the included studies in total response rate, KPS score improvement rate, gastrointestinal reactions, leucopenia, anemia, liver function damage, $CD3^+$, and $CD4^+$ was asymmetric, indicating publication bias (P> 0.05), which may be related to the sample size, publication year, TNM stage, or course of treatment of the included studies. For $CD4^+/CD8^+$, there was no the publication bias (P<0.05). See **Figure 13**; **Table 2**.

Discussion

NSCLC is a common clinical type of lung cancer, with high incidence rate [37]. At present, NSCLC is mainly treated by radiotherapy and chemotherapy in clinical practice. However, while killing tumor cells, the treatments also damage the hematopoietic system and immune system of the body and bone marrow, resulting in the decline of the patient's immunity and treatment compliance [38]. KLT injection is an anti-tumor traditional Chinese medicine, which can induce cell apoptosis, inhibit tumor angiogenesis, and reverse the drug resistance of tumor cells caused by chemotherapy to act in anti-tumor mechanisms [8]. As a popular anti-tumor drug in China, KLT is widely used to treat NSCLC, liver cancer, stomach cancer and other cancers. KLT is derived from plants, which can be made into microemulsions for intravenous injection. Its main active ingredient is coix seed oil. Study found that KLT could effectively kill cancer cells and improve immunity. Besides, when used in combination with chemotherapy or radiotherapy, KLT has a synergistic effect in enhancing the efficacy [9].

Here, 27 RCTs were analyzed, with a total of 2,579 patients. Our results showed that the research group receiving KLT combined with

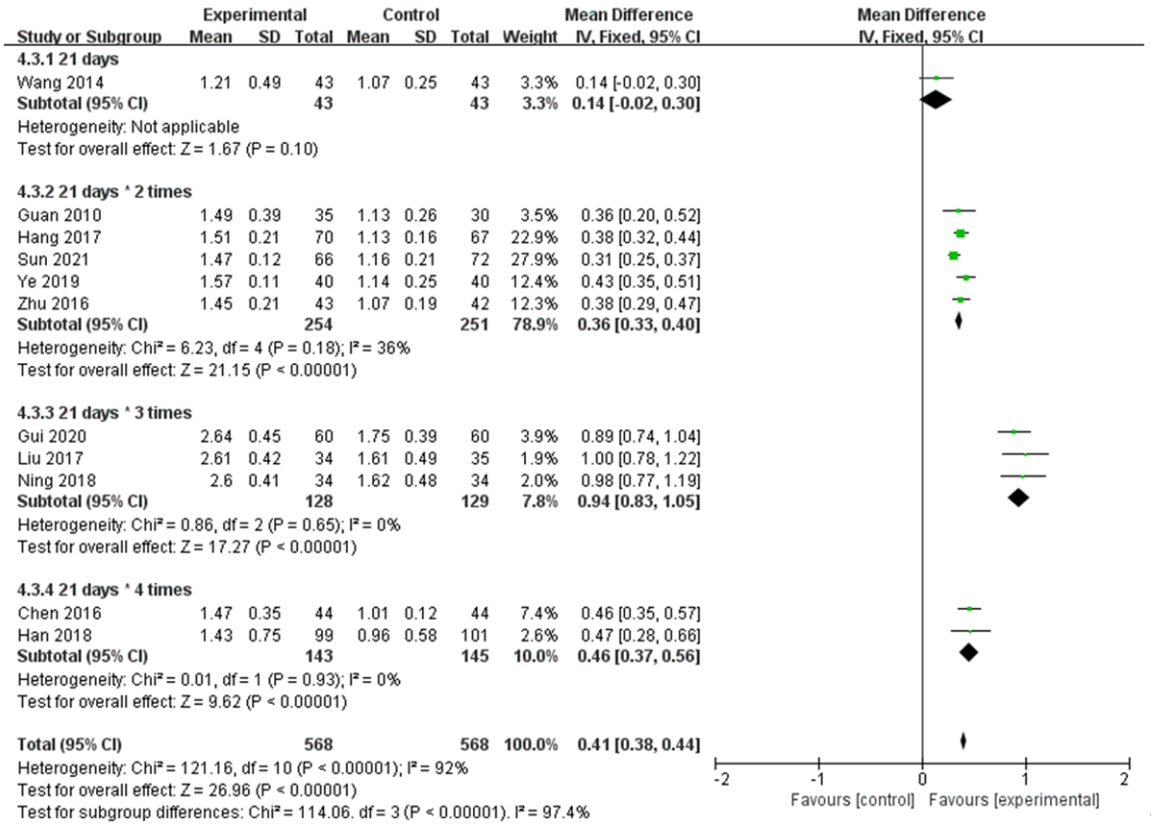

Figure 12. The subgroup analysis of $CD4^+/CD8^+$ level after treatment between the two groups.

GP chemotherapy regimen exhibited increased total response rate and quality of life. It may be because coix seed oil, the effective component of KLT, is a biphasic broad-spectrum anticancer substance, which can effectively inhibit cancer cells and significantly improve the body's immune function [8]. The results also indicated that the combination treatment of KLT and GP enhances the immunity as compared with GP alone. The main reason could be that KLT injection can further induce tumor necrosis factors and interleukin by increasing macrophages and inhibiting the formation of tumor cell neovascularization, so as to enhance the immunity of patients [39]. For the medication safety, the research group showed reduced incidence of gastrointestinal reactions, leukopenia, anemia and liver function damage, and the differences were statistically significant. It is suggested that the combination of KLT injection and GP regimen is safer than chemotherapy alone [40].

In this meta-analysis, there is a significant heterogeneity in the analysis results of immune function, including $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$. Based on TNM staging and treatment course, we conducted subgroup analysis on outcome indicators with significant heterogeneity. In each subgroup, heterogeneity was significantly reduced.

Although strict inclusion and exclusion criteria have been formulated in this study, there are still some limitations. (1) At present, there are few RCTs applied KLT for the treatment of NSCLC, so the sample size was small, which reduces the test efficiency. (2) The quality of methodology included in the study is different, and there is a certain bias in random method, blind method, etc. (3) There are only a few reports investigating the safety of KLT in the included studies. Therefore, the conclusions need to be verified by further research with bigger sample size. A multi-center, randomized, double-blind trial design can be used to enhance the rigor of the study by minimizing confounding factors and improving the quality of evidence.

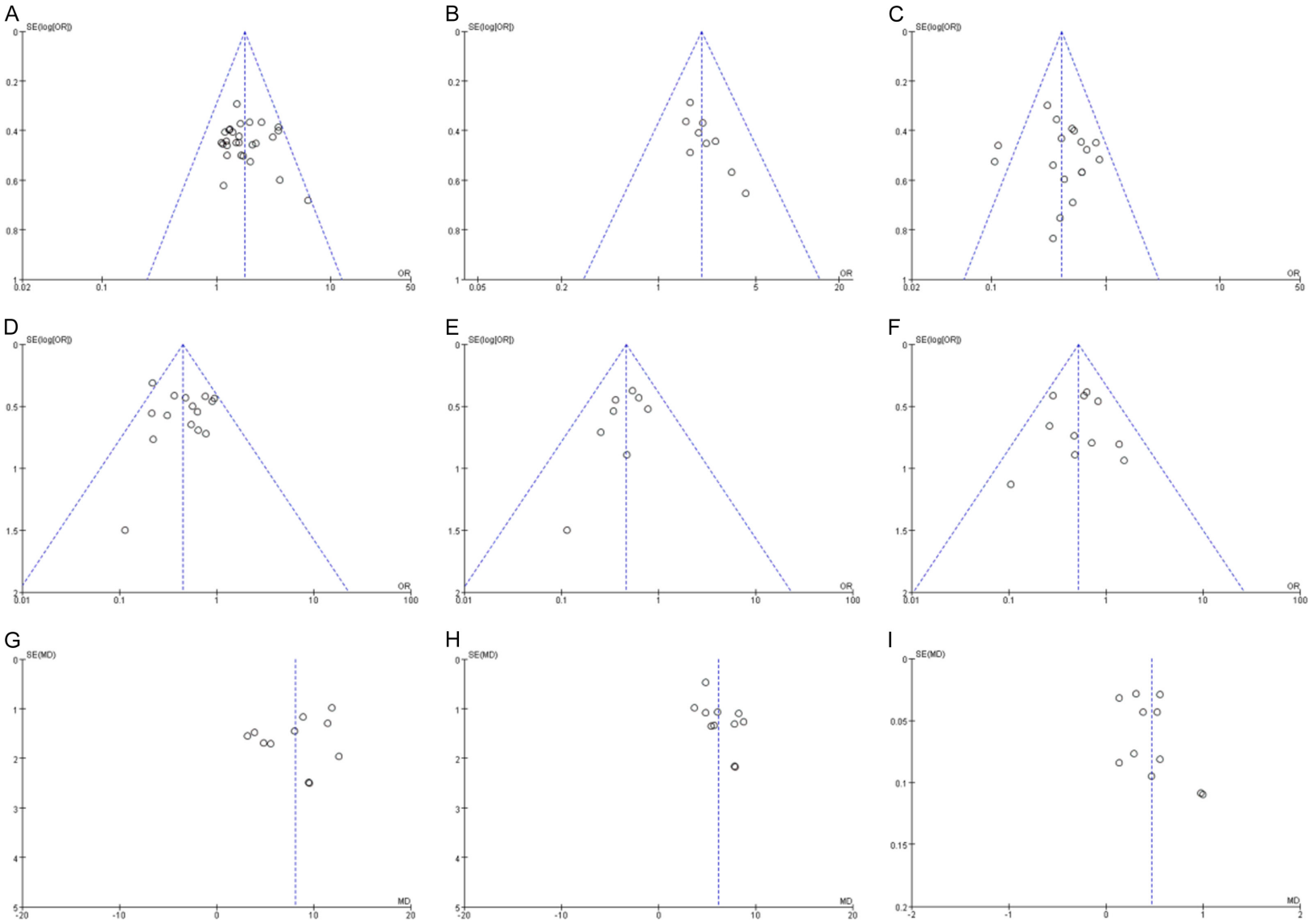

Figure 13. The funnel analysis of publication bias. (A) Total response rate, (B) KPS score improvement rate, (C) Gastrointestinal reactions, (D) Leucopenia, (E) Anemia, (F) Liver function damage, (G) $CD3^+$, (H) $CD4^+$, (I) $CD4^+/CD8^+$.

Table 2. The egger test for the publication bias

Outcomes	Coefficient	Std. err.	t	P>|t|	[95% conf. interval]
Response rate	1.024653	1.248437	0.82	0.420	-1.551995~3.6013
KPS score	1.644336	1.939308	0.85	0.429	-3.100981~6.389653
Gastrointestinal reaction	-.0832026	1.106227	-0.08	0.941	-2.441069~2.274664
Leucopenia	-.421046	1.047316	-0.40	0.695	-2.702951~1.860858
Anemia	-1.139402	1.073126	-1.06	0.337	-3.897961~1.619158
Liver function damage	-.0629638	.9558217	-0.07	0.949	-2.267093~2.141165
$CD3^+$	4.3974	5.067086	0.87	0.411	-7.287321~16.08212
$CD4^+$	4.535197	3.056957	1.48	0.176	-2.514158~11.58455
$CD4^+/CD8^+$	10.74333	2.709	3.97	0.004	4.496367~16.9903

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Disclosure of conflict of interest

None.

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