Systematic Review and Meta-Analysis

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Evidence of Astragalus injection combined platinum-based chemotherapy in advanced nonsmall cell lung cancer patients

A systematic review and meta-analysis

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Abstract

Background: Platinum-based chemotherapy is one of the standard treatments for advanced nonsmall cell lung cancer (NSCLC). Despite on an effective treatment for advanced NSCLC patients, its high toxicity and limited clinical effects have raised big concerns. Astragalus injection (AGI) has been commonly employed as an adjutant chemotherapy drug for NSCLC in China. This review was conducted to evaluate the beneficial of AGI in combination with platinum-based chemotherapy in advanced NSCLC.

Methods: We collected all studies about AGI plus platinum-based chemotherapy for advanced NSCLC in the PubMed, EMBASE, China National Knowledge Infrastructure Database, the Cochrane Library, Wanfang Database, China Biological Medicine Database, and Chinese Scientific Journal Database established on July 2018 without language restriction. Cochrane handbook was applied to assess the quality of included trials. Stata (version 12.0) and RevMan (version 5.3) were employed for data analysis. The quality of the evidence was assessed with the GRADE approach.

Results: Nineteen randomized controlled trials (RCTs) including 1635 patients were included to determine the effectiveness and safety of AGI combined with platinum-based chemotherapy in the treatment of NSCLC. The result of meta-analysis indicated that comparing with chemotherapy alone, AGI combined chemotherapy could significantly improve the objective response rate (relative risk [RR] = 1.19, 95% confidence interval [CI] [1.06, 1.33], $P = .002$), the Karnofsky performance status (RR = 2.28, 95% CI [1.63, 3.18], $P < .00001$), and 1-year survival rate (RR = 1.40, 95% CI [1.16, 1.70], $P = .0005$), meanwhile increase the percentages of $CD3^+$ (weighted mean differences [WMD] = 11.98, 95% CI [8.0, 15.96], $P < .00001$), $CD4^+$ (WMD = 2.98, 95% CI [0.45, 5.52], $P = .02$), $CD4^+/CD8^+$ (WMD = 0.33, 95% CI [0.20, 0.46], $P < .00001$), and NK cells (WMD = 9.5, 95% CI [7.25, 11.76], $P < .00001$), decrease the incidence of leukopenia (RR = 0.52, 95% CI [0.44, 0.61], $P < .00001$), platelet toxicity (RR = 0.62, 95% CI [0.50, 0.76], $P < .00001$), and vomiting (RR = 0.72, 95% CI [0.60, 0.87], $P = .0006$). Based on the system evaluation results, the GRADE system recommendation grading method was adopted to evaluate the evidence quality. The results showed that the level of evidence was low.

Conclusions: The AGI apparently has attenuation and synergistic efficacy to platinum-based chemotherapy patients. However, considering the limits of articles included in the present researches, the recommendation is likely to be weak. High-quality RCTs are urgently used to generate conclusive results.

Abbreviations: AGI = Astragalus injection, CI = confidence interval, KPS = Karnofsky performance status, NSCLC = nonsmall cell lung cancer, ORR = objective response rate, RCT = randomized controlled trial, RR = relative risk, TCM = Traditional Chinese Medicine, WMD = weighted mean differences.

Keywords: Astragalus injection, chemotherapy, meta-analysis, nonsmall cell lung cancer

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] More than one-third of newly diagnosed lung cancers occurred in China, representing a high pressure on the patients, families, society, and authorities.[2] Nonsmall cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of the cases.[3] However, diagnosis often occurs late, which means approximately two-thirds of patients have lost the opportunities to radical surgery. Epidermal growth factor receptor (EGFR) mutations now guide the clinical use of EGFR-targeted therapy in advanced NSCLC. Conversely, in the absence of such mutations, the probability of a patient achieving an objective response is very limited. Hence, platinum-based chemotherapy, as primary antineoplastic therapy, occupies the dominant position, especially for individuals with NSCLC in the absence of such mutations. Although an effective treatment for advanced NSCLC patients, chemotherapy can also cause significant toxicity, which may lead withdrawal of some patients to profit by chemotherapy. Interventions for managing majority of these side effects are limited and there is an urgent need to settle this effectiveness gap.

Astragalus injection (AGI), a natural lipid-soluble plant drug extracted from Astragalus, has been widely used as an effective anticancer drug. Astragalus is one of the most popular health-promoted herbs in Traditional Chinese Medicine (TCM) with other herbs to stimulate the immune system. It is historically used to manage the deficiency of qi (vita energy). Based on traditional use and clinical experience, Astragalus is generally considered to be safely used. In clinical study, it was found that AGI combined with chemotherapy therapy had the effect of synergism and reduction of toxicity.[4] In pharmacological research, Astragalus contains various active substances such as glycosides, polysaccharides, flavone, amino acids, and flavonoids, which has the pharmacological effects of inhibiting cell proliferation, affecting tumor tissue metabolism, and enhancing body immunity.[5] However, at present no relevant articles or evaluations have been published in the English medical journals and the guidance for the combination therapy regimen is lacking. As a consequence, to precisely reveal its real synergistic efficacy and toxicity attenuation to platinum-based chemotherapy, we conducted this systematic review and meta-analysis to provide evidence of effectiveness and safety for the clinical use of AGI combined with chemotherapy in the treatment of advanced NSCLC patients in an objective manner.

2. Methods

2.1. Searching strategies

Published studies were retrieved from 7 databases, including EMBASE, PubMed, Cochrane Library, China Knowledge Resource Integrated Database, Chinese Scientific Journal Database, Chinese Biomedical Database, and Wanfang Database (from established to July 2018). The initial search was designed to find all trials using the following search strategy: ("Lung Neoplasms" [Mesh] OR "carcinoma, nonsmall cell lung" [MeSH] OR lung cancer [All Fields] OR lung cancer [All Fields] OR lung canceration [All Fields] OR lung cancerigenesis [All Fields] OR lung cancerous [All Fields] OR lung cancers [All Fields]) OR ("carcinoma" [All Fields] AND "non-small-cell" [All Fields] AND "lung" [All Fields]) OR "non-small-cell lung carcinoma" [All Fields] OR "nsclc" [All Fields]) AND ("astragalus injection" [All Fields]). No language restrictions were placed on the search.

2.2. Inclusion criteria

Included studies must meet the following criteria: the disease was diagnosed and confirmed with NSCLC by histopathological or cytological diagnostic criteria. The stage of NSCLC tumor lymph node metastasis was advanced stage (III–IV). The patients of each study were divided into at 2 arms. The intervention of 1 arm was platinum-based chemotherapy alone, whereas the intervention in the other arm was platinum-based chemotherapy plus AGI. The reported data must have at least one of following outcomes: objective tumor response (ORR); reductions in chemotherapy toxicity; Karnofsky performance score (KPS); relevant indicators of cellular immune function; and survival rate. Type of study was randomized controlled trial (RCT), regardless of language. Ethical approval was not required, as this study is a meta-analysis of published studies.

2.3. Exclusion criteria

The research would be excluded if one or more of the following conditions apply: duplicated articles; the interventions that were combined with other Chinese herbs or other TCM therapies; participants with any comorbidity; the studies without specific data or statistical data could not be used; and patients whose baseline data were significantly inconsistent.

2.4. Outcome measures

Two of the reviewers independently extracted data on ORR, reductions in chemotherapy toxicity, KPS, and relevant indicators of cellular immune function and survival rate. Outcome measures included primary and secondary indices. ORR was primary outcomes and the rest were regarded as the secondary indices of evaluation. ORR formulated by the World Health Organization (WHO) scale,[6] equals complete response + partial response. According to KPS grading system,[7] the KPS score improvement rate was calculated as the number of patients whose KPS scores increased by more than 10 points divided by the total number of patients in each treatment group. The 5-point WHO scale[6] for anticancer drug toxicity (0–4 grading system) was used to evaluate chemotherapy toxicity and the rate of severe chemotherapy toxicity was evaluated by white blood cell, platelet, and vomiting toxicity. The rate of severe chemotherapy toxicity was defined as the number of patients with any severe toxicity (WHO grade 2, 3, or 4) divided by the total number of patients in each treatment group (WHO grades 0, 1, 2, 3, and 4). The $CD3^+$ T cells, $CD4^+$ T cells, $CD4^+/CD8^+$, and NK cells were assayed to reflect the cellular immunity. Survival rate was also used to assess the efficacy of AGI. A meta-analysis was performed for the primary and secondary outcomes where sufficient and suitable data were presented.

2.5. Data extraction

The full-text articles were reviewed independently by 2 investigators (Ailing Cao and Hailang He) who assessed the eligibility of the studies and extracted the data about the studies, including: basic information such as year of publication and name of the first author; the sample size of each group, age and physical status; and details of interventions and outcomes from each studies. This course had to be cross-checked in order to ensure accuracy and reliability. Differences between the 2 investigators were resolved by the adjudicating senior author (Xianmei Zhou). The authors of articles were approached about

the existence of additional data if insufficient data were presented in the articles.

2.6. Quality assessment

The methodological quality of each RCT was assessed in terms of allocation concealment, random sequence generation, blinding of participants and study personnel, incomplete outcome data, selective reporting, and other sources of bias based on the criteria in the Cochrane evaluation handbook of RCTs. The judgment was categorized as having low, unclear, or high risk of bias according to information provided by the protocol. Any study that does not satisfy the inclusion criteria will be excluded. The final decisions will be made by the third author (Xianmei Zhou).

We rated the confidence in the estimates of effect for each outcome according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach, taking into account study limitations (risk of bias), inconsistency, imprecision, indirectness, and publication bias. For each comparison, 2 team members independently rated the certainty of the effect estimates (i.e., quality of evidence) for each outcome as high, moderate, low, or very low. We resolved discrepancies by consensus and, if needed, by arbitration by a third team member (Xianmei Zhou). The GRADE summary of findings table was generated using the RevMan 5.3 software.

2.7. Statistical analysis

The RevMan 5.3 software (Cochrane Collaboration) was used to perform the meta-analysis. The weighted mean differences (WMD) and relative risk (RR) with 95% confidence intervals (CIs) were calculated to compare continuous and dichotomous variables, respectively. Heterogeneity was mainly wielded to judge whether study components came from the same entity. The sources of heterogeneity were methodological, statistical, and clinical heterogeneity. For the pooling analysis, the judgment of statistical heterogeneity mainly relied on a chi-squared test and I^2 index. The random model was applied in the presence of heterogeneity ($I^2 \geq 50\%$). Otherwise, the fixed model was conducted ($I^2 < 50\%$). The significance level was considered at $P < .05$.

2.8. Publication bias

Funnel plots were generated to detect the potential publication bias for primary outcomes if more than 10 studies were included for a meta-analysis. Stata 12.0 software was further applied to test publication bias by Egger test.

2.9. Sensitivity analysis

In this study, sensitivity analysis was employed to verify the robust and reliable results from our study. We conducted the analysis by deleting the studies of low quality.

3. Results

3.1. Retrieval result

In the aggregate, 273 potentially relevant possible studies were identified by using our search strategies from electronic database searching without restriction to regions, publication, or languages. After removing 143 duplicates, 130 articles were identified for further analysis. Seventy-six irrelevant topic studies were excluded after screening the titles and abstracts. Next, 54 articles were considered for the evaluation of full texts. Nineteen clinical trials were finally involved in this meta-analysis. The flow chart of the detailed searching steps for this meta-analysis is shown in Fig. 1.

3.2. Characteristics of included trials

There were 19 RCTs with 1635 advanced NSCLC patients being included in this meta-analysis (Table 1). The cases of AGI plus chemotherapy and chemotherapy alone were 831 and 804, respectively. As shown, all of the studies were carried out in China and published in Chinese journals. The dosage of AGI was 20 to 60 mL/d. The duration of therapy was 1 to 3 weeks and 2 to 5 cycles by intravenous injection.

3.3. Methodological bias of the included studies

According to the criteria in the Cochrane evaluation handbook of RCTs, the methodological quality evaluation forms were formulated. All the methodological portions of the literature were evaluated by 2 independent reviewers. If a difference in evaluation arose, it was solved through discussion. Figure 2 evaluates the risk of bias based on the quality of the included RCTs. Two trials[15,26] grouped the patients on the basis of the hospital admission sequence which involved an inappropriate method, and 3 studies[11,14,20] were randomized by using a random number table. The remaining trials[8–10,12,13,16–19,21–25] only mentioned randomization but failed to describe the method of randomization. In the articles, controlled blinding was not mentioned at all, that meant the item of blinding in these studies was all judged with unclear risk. All the included trials had an unclear risk of bias of incomplete outcome data for each main outcome. Other bias was evaluated as an unclear risk. Because of the insufficient evidence provided by all of the identified trials, we were unable to judge if selective outcome reporting was examined by the review authors. The detailed information of methodological quality of the included studies is listed in Fig. 2.

3.4. Objective tumor response

Seventeen studies[8–22,25,26] including 1395 cases reported results regarding the ORR. The heterogeneity result showed low heterogeneity ($I^2 = 0\%$). The fixed-effects model was applied for the analysis. The meta-analysis result showed a statistically significant difference (RR = 1.19, 95% CI [1.06, 1.33], $P = .002$), which revealed that the combination treatment of AGI and platinum-based chemotherapy could remarkably improve the ORR of NSCLC patients when compared with chemotherapy alone (Fig. 3).

3.5. Karnofsky performance score

The improvement rates of KPS were definitively extracted from 7 trials,[8,9,11,12,14,16,25] representing a total of 431 patients of NSCLC. Patients who were treated with combination of AGI and chemotherapy (RR = 2.28, 95% CI [1.63, 3.18], $P < .00001$) reported more significant improvement in physical fitness than those patients who were treated with chemotherapy alone, with no significant heterogeneity ($I^2 = 0\%$) (Fig. 4).

3.6. Chemotherapy toxicity

3.6.1. White blood cell. The incidence of white blood cell toxicity was reported in 11 trials,[9–12,14,17–21,26] which included

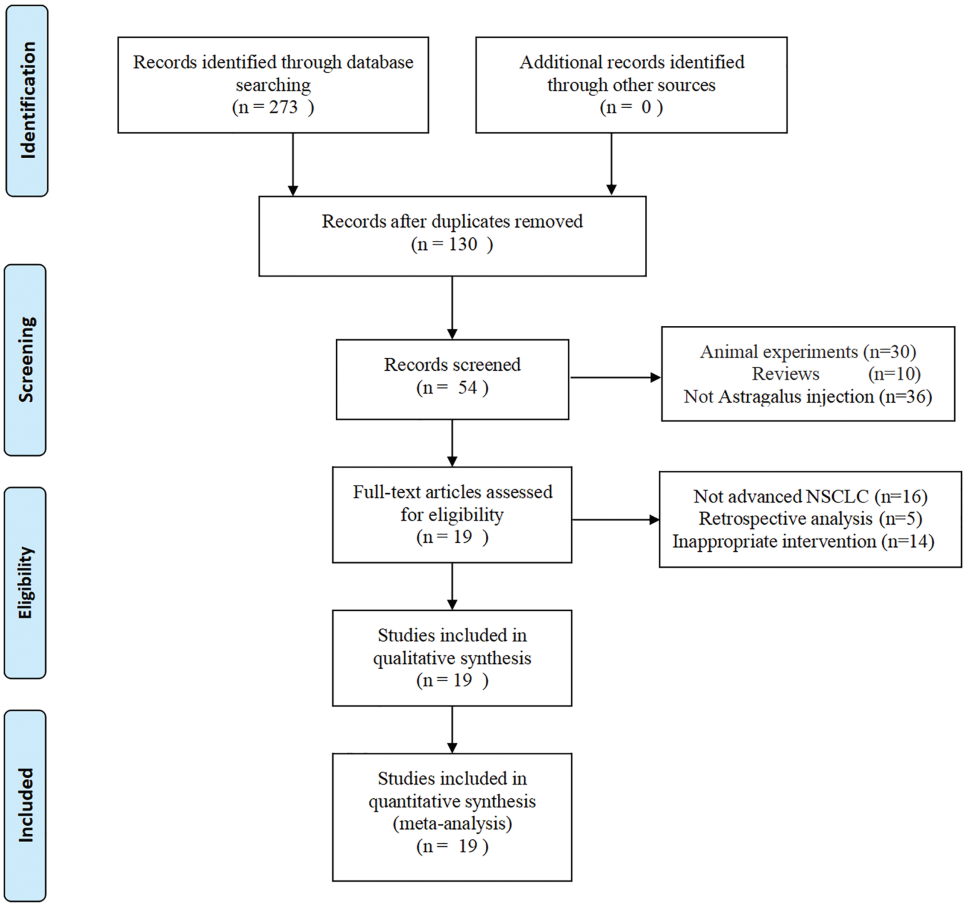

Figure 1. Flow diagram of the literature search process.

Table 1

Baseline characteristics of included studies.

Study	N (T/C)	Mean age (T/C)	Physical condition	Interventions		Outcomes
				T	C	
Cao and Tong[8]	32/27	63/64.3	KPS > 50	AGI 60 mL/d, d1–d20, 2 cycles + control	MVP, CAP	①⑤⑥
Zhang and Li[9]	65/70	58/55	KPS > 50	AGI 60 mL/d, d1–d21, 2 cycles + control	MVP	①②④⑥⑦
Lu and Liu[10]	67/56	57.7/58.3	KPS > 50	AGI 20 mL/d, d1–d3, 2 cycles + control	CTD, IP	①②④⑤
Liu and Zou[11]	30/30	31–72/33–71	KPS > 50	AGI 10 mL/d, d1–d3, 2–3 cycles + control	MVP	①②⑥⑦⑧
Zou and Liu[12]	30/30	31–72/33–71	KPS > 50	AGI 60 mL/d, d1–d8, 2–3 cycles + control	MVP	①②⑥⑦⑧
Wang et al[13]	30/30	31–68/34–69	KPS > 60	AGI 20 mL/d, d1–d21, 3 cycles + control	VP	①
Shi et al[14]	30/30	56.4/56.1	KPS > 50	AGI 20 mL/d, d1–d3, 2 cycles + control	EP	①②⑤⑥
Gan and Chen[15]	69/54	68/67	KPS > 50	AGI 20 mL/d, d1–d20, 2 cycles + control	EP	①⑦⑧
Li and Cao[16]	28/24	58.8/57.6	KPS > 50	AGI 60 mL/d, d1–d20, 2 cycles + control	NP	①⑤⑥
Wan[17]	21/20	57/56	KPS > 60	AGI 60 mL/d, d1–d14, 2 cycles + control	NP	①②
Zhang[18]	35/34	56.1/55.8	KPS > 50	AGI 40 mL/d, 25d, 4–5 cycles + control	NP, GP	①②③④
Liu et al[19]	30/30	45.6/45.1	KPS > 60	AGI 60 mL/d, d1–d8, 2 cycles + control	NP	①②⑤⑦
Zhou and Bao[20]	60/40	60/60.7	KPS > 50	AGI 30 mL/d, d1–d14, 2 cycles + control	MVP	①②③④
Zhong[21]	40/40	51.6/53.2	PS ≤ 3	AGI 60 mL/d, d1–d5, 2 cycles + control	NP	①②
Li et al[22]	83/83	68/68.2	KPS > 50	AGI 20 mL/d, d1–d5, 2 cycles + control	EP	①
Xu[23]	88/92	Unknown	PS ≤ 2	AGI 60 mL/d, d1–d30, 2 cycles + control	TP	⑦
Sun[24]	30/30	55.0 ± 5.7/55.0 ± 5.9	KPS > 50	AGI 10 mL/d, d1–d8, 2–3 cycles + control	MVP	⑦
Dang[25]	30/30	30–71/23–70	KPS > 50	AGI 30 mL/d, d1–d3, 2 cycles + control	TP	①⑥⑧
Liu and Lan[26]	44/43	67.2 ± 5.6/66.9 ± 6.1	KPS > 50	AGI 20 mL/d, d1–d21, 2 cycles + control	EP	①②⑦⑧

AGI = Astragalus injection, C = control, CAP = cyclophosphamide + adriamycin + cisplatin, CTD = cyclophosphamide + taxol + dexamethasone, EP = etoposide + cisplatin, GP = gemcitabine + cisplatin, IP = irinotecan + cisplatin, KPS = Karnofsky performance score, MVP = mitomycin + vinpocetine + cisplatin, N = number of participants, NP = navelbine + cisplatin, PS = performance status, T = treatment, TP = taxol + cisplatin, outcomes, VP = vinpodidine + cisplatin: ① objective tumor response; ② white blood cell toxicity; ③ hemoglobin toxicity; ④ platelet toxicity; ⑤ vomiting toxicity; ⑥ KPS; ⑦ immune function; and ⑧ survival rate.

877 patients (Fig. 5). As the heterogeneity test showed $I^2 = 0\%$, the fixed-effects model was applied to calculate the combined RR and 95% CI. The results indicated that patients who received the combined treatment regimen (AGI along with chemotherapy) had a lower incidence of bone marrow suppression than that of patients treated with chemotherapy alone (RR = 0.52, 95% CI [0.44, 0.61], $P < .00001$).

3.6.2. Platelet. Four[9,10,18,20] trials involving 429 patients were pooled together using the fixed-effects model ($I^2 = 0\%$). The meta-analysis showed that AGI group exhibited significant reduction in platelet toxicity compared with chemotherapy group (RR = 0.62, 95% CI [0.50, 0.76], $P < .00001$) (Fig. 5).

3.6.3. Vomiting. Trials[8,10,14,16,19] containing 356 patients mentioned the occurrence of vomiting reaction. It proved to be homogeneous according to the heterogeneity test ($I^2 = 0\%$), so the fixed-effects model was used in this meta-analysis. As shown in Fig. 5, combination treatment with chemotherapy plus AGI had an advantage in mitigating the toxicity of platelet compared with chemotherapy alone (RR = 0.72, 95% CI [0.60, 0.87], $P = .0006$) (Fig. 5).

3.7. Immune function

3.7.1. $CD3^+$. Eight trials[9,11,12,15,19,23,24,26] reported the results of $CD3^+$, which indicated heterogeneity with $P < .00001$ and $I^2 = 92\%$. The results showed that there was statistical difference between 2 groups for $CD3^+$ (WMD = 11.98, 95% CI [8.0, 15.96], $P < .00001$). Subgroups were divided by different therapeutic dose: 2 studies[11,24] followed the dosage of AGI for 10 mL/d, 2 studies[15,26] followed the dosage of AGI for 20 mL/d, and 4 studies[9,12,19,23] followed the dosage of AGI for 60 mL/d. There was significant difference between 3 subgroups ($P = .008$), and evaluations of the 3 showed the same result (Fig. 6).

3.7.2. $CD4^+$. Eight trials[9,11,12,15,19,23,24,26] evaluated the results of $CD4^+$. There was statistical heterogeneity between the 2 groups ($I^2 = 83\%$). The pooled analysis suggested that the difference between the 2 groups was statistically significant (WMD = 2.98, 95% CI [0.45, 5.52], $P = .02$) (Fig. 7). Subgroups were divided as mentioned above: 2 studies[11,24] followed the dosage of AGI for 10 mL/d, 2 studies[15,26] followed the dosage of AGI for 20 mL/d, and 4 studies[9,12,19,23] followed the dosage of AGI for 60 mL/d. There was significant difference between 3 subgroups ($P < .00001$), and evaluations of the 3 showed the different result (Fig. 7).

3.7.3. $CD4^+/CD8^+$. Eight trials[9,11,12,15,19,23,24,26] reported the results of $CD4^+/CD8^+$. The heterogeneity result showed heterogeneity with $P < .00001$ and $I^2 = 85.0\%$. The meta-analysis result revealed that the percentage of $CD4^+/CD8^+$ T cells was statistically different between chemotherapy plus AGI and chemotherapy alone (WMD = 0.33, 95% CI [0.20, 0.46], $P < .00001$). Subgroups were divided by different dosage of AGI: 2 studies[11,24] followed the dosage of AGI for 10 mL/d, 2 studies[15,26] followed the dosage of AGI for 20 mL/d, and 4 studies[9,12,19,23] followed the dosage of AGI for 60 mL/d. There was significant difference between 3 subgroups ($P < .001$), and evaluations of the 3 showed the same result (Fig. 8).

3.7.4. NK cells. The results of NK cells activity in 7 pooled trials[11,12,15,23,24,26] using the random-effects model were with substantial heterogeneity ($I^2 = 68\%$), which indicated that there was a statistically significant difference between the 2 groups (WMD = 9.5, 95% CI [7.25, 11.76], $P < .00001$) (Fig. 9). Subgroups were divided by different dosage of AGI: 2 studies[11,24] followed the dosage of AGI for 10 mL/d, 2 studies[15,26] followed the dosage of AGI for 20 mL/d, and 4 studies[12,23] followed the dosage of AGI for 60 mL/d. There was significant difference between 3 subgroups ($P = .0004$), and evaluations of the 3 showed the same result (Fig. 9).

3.8. One-year survival rate

Five studies[11,12,15,25,26] reported the results of 1-year survival rate. These studies involved 373 cases in total (203 cases in the experimental group and 170 cases in the control group). There was no significant heterogeneity among the trials ($I^2 = 28\%$), so the fixed-effects model was used. The meta-analysis results showed that for the treatment of NSCLC, the 1-year survival rate of the AGI + chemotherapy group was higher than that of the control group, and there was a statistically significant difference between the 2 groups (RR = 1.40, 95% CI [1.16, 1.70], $P = .0005$) (Fig. 10).

3.9. Publication bias

The funnel plot was applied for assessing publication bias of studies included the results of ORR in this meta-analysis. The

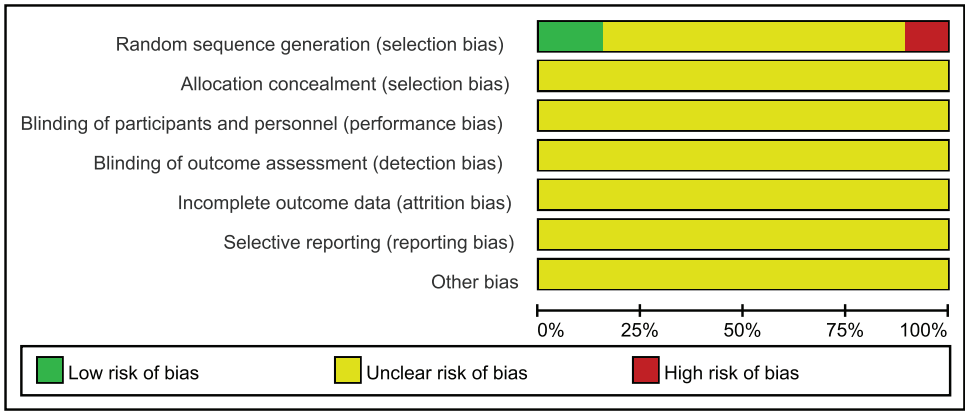

Figure 2. Risk of methodological bias of the included studies. (A) Risk of bias graph. (B) Risk of bias summary.

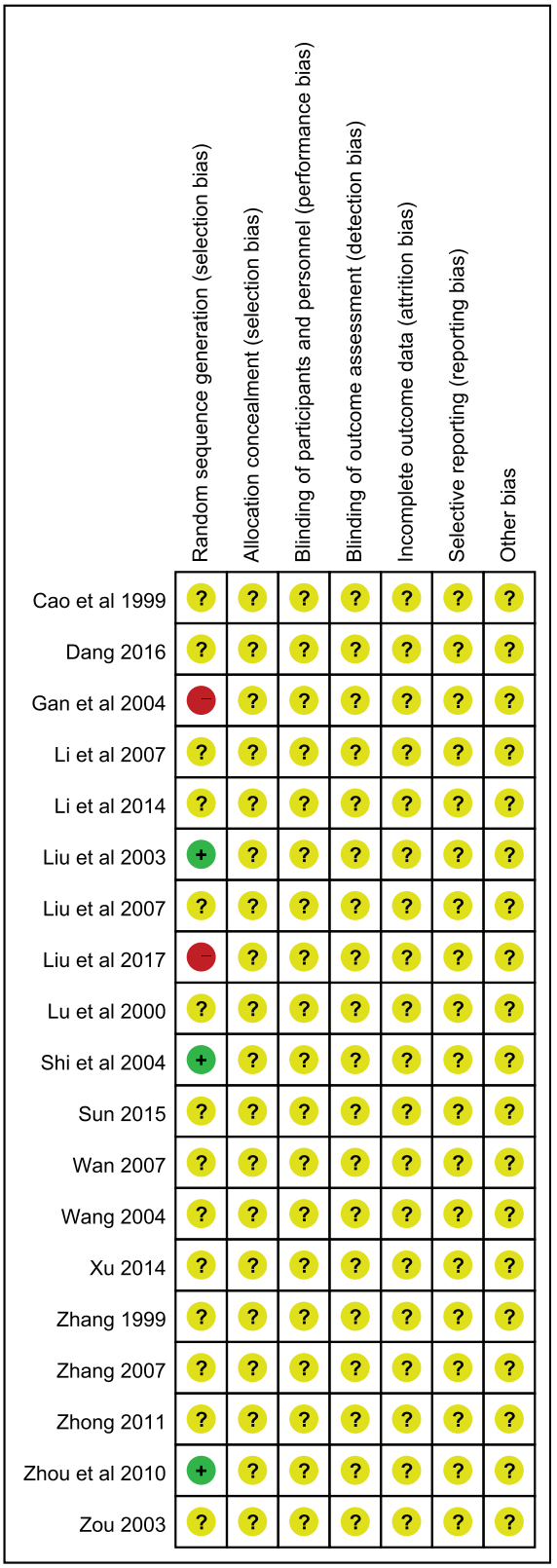

Figure 2. Continued

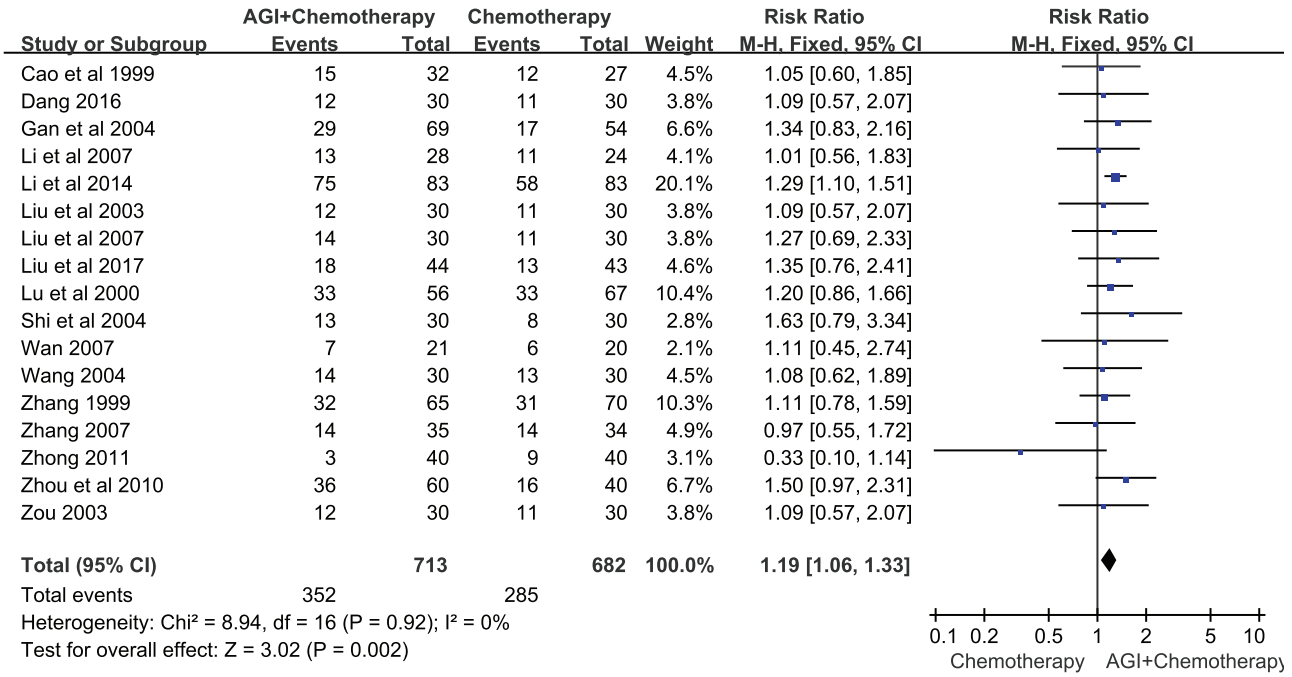

Figure 3. Forest plot of improved objective tumor response. Objective tumor response evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

funnel plots were asymmetric in the studies about ORR, which showed that there was potential risk of publication bias (Fig. 11). Egger test was further performed to assess publication bias. The results for ORR (P=.045) revealed that there might be publication bias in our study that influenced the results of our analysis.

3.10. GRADE evidence quality

GRADE evidence quality was summarized in Table 2. All trials had methodological limitations that lowered the confidence of their effect size estimates. We found evidence of considerable inconsistency for each pooled analysis of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$, prompting us to further downgrade the quality of the evidence. Meanwhile, publication bias also existed in our study. As a result, the recommendation level was weak.

3.11. Sensitivity analysis

The results of the fixed-effects and random-effects models had good consistency. After deleting the low-quality studies with relatively high overall risk of bias, the results were still similar to the results before they were excluded (Table 3), which revealed the results of our meta-analysis were reliable and verifiable.

4. Discussion

In China, it is common to use AGI to treat advanced NSCLC, but no relevant articles or evaluations have been published in the

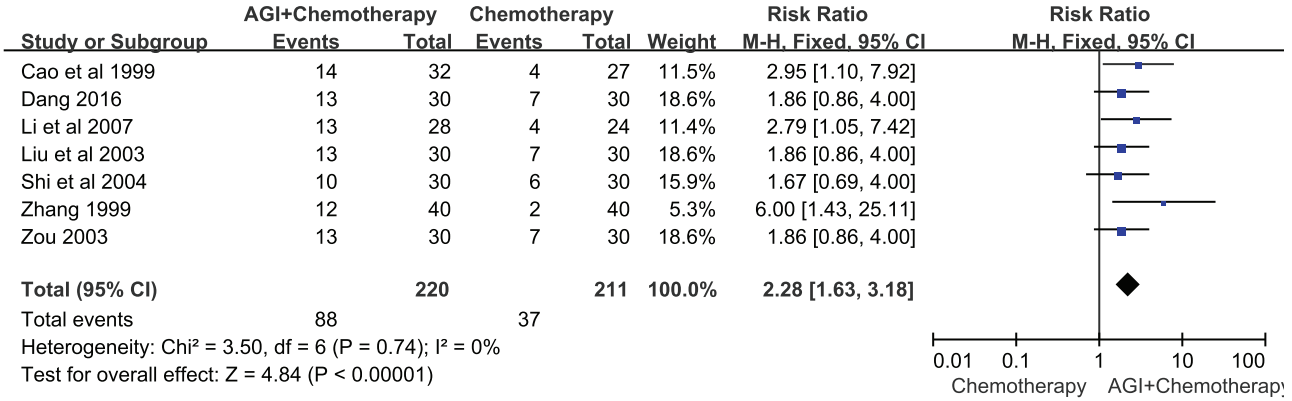

Figure 4. Forest plot of improved KPS. KPS evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone. KPS = Karnofsky performance status.

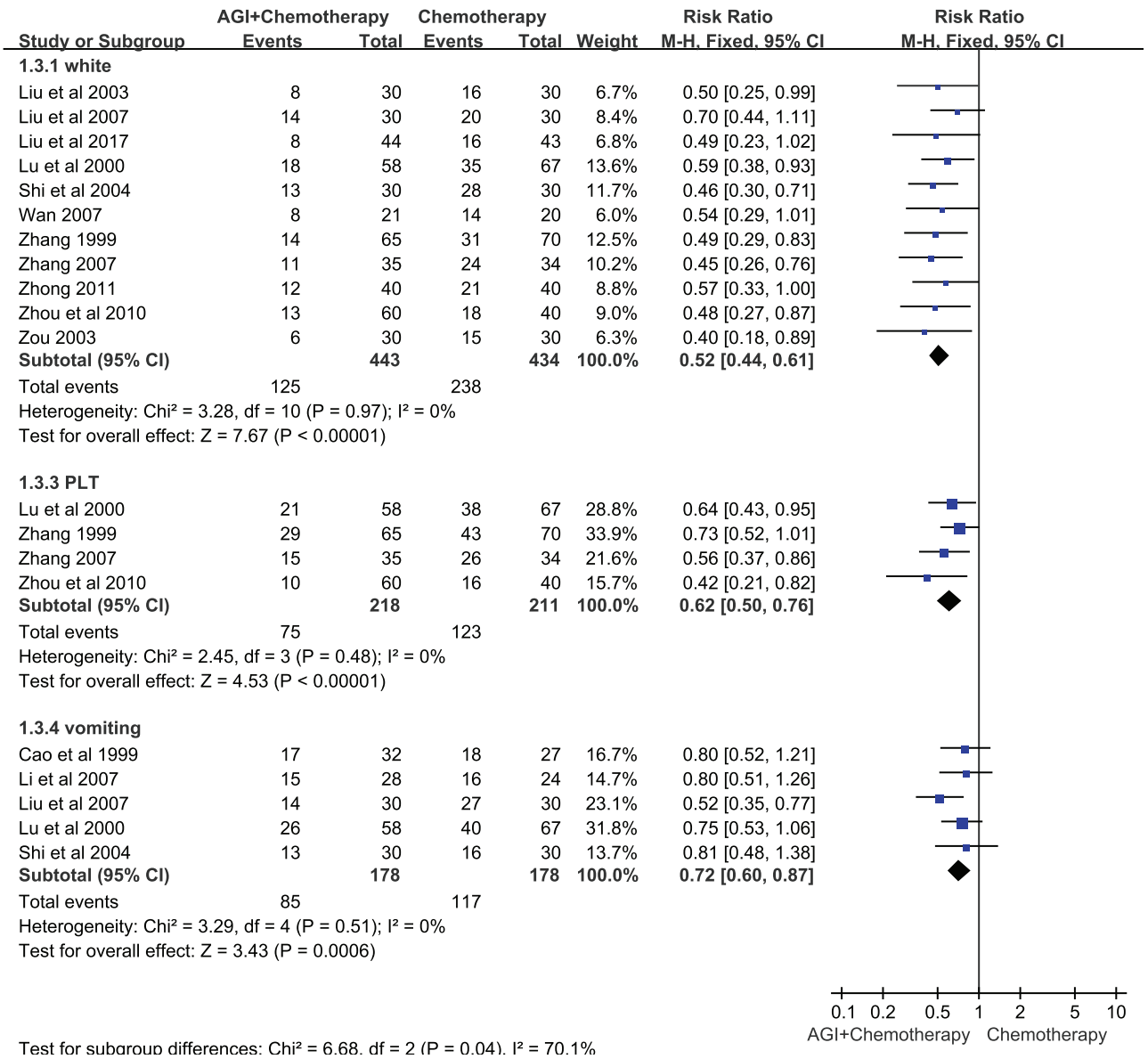

Figure 5. Forest plot of chemotherapy toxicity. White blood cell, platelet, and vomiting toxicity evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

English medical journals, hence reducing its worldwide validity. This study may supply useful information for supplementing the evidence in the treatment of advanced NSCLC.

This meta-analysis provides a quantitative synthesis of the clinical efficacy of AGI combined with chemotherapy for the treatment of advanced NSCLC by integrating outcomes from 19 clinical trials involving 1635 participants. In terms of the clinical effect, ORR is used as an important index to evaluate antitumor response. Notably, the meta-analysis involving 17 studies (1395 cases) demonstrated that the combination of AGI and chemotherapy had a positive effect in tumor shrinkage. Moreover, the in vitro assays have verified that AGI can inhibit the growth of lung cancer A549 cells.[27] In vivo study, AGI have obviously inhibitory effect on lung cancer metastasis through decreasing the tubercle of lung cancer.[28] These results provided evidences for the antitumor mechanisms of AGI in NSCLC.

Chemotherapy often incurs substantial toxicity including nausea, vomiting, fatigue, and myelosuppression. The symptom caused by chemotherapy or lung cancer itself can seriously impact the quality of life for NSCLC patients. Poor quality of life is considered a negative prognostic factor among advanced NSCLC patients. The meta-analysis results showed that AGI could reduce the side effects of chemotherapy and improve the quality of life of patients. It was encouraged to see that chemotherapy-related side effects appeared less frequent and milder in the use of concomitant AGI treatment, which suggested AGI could enhance the compliance to chemotherapy and finally result in improving KPS of patients. Furthermore, the experiment proved that Astragalus could markedly decreased blood urea nitrogen and blood creatinine induced by cisplatin in mice and did not result in any observable loss in antitumor activity of cisplatin.[29] All available evidence lead to the fact that AGI has the attenuation to chemotherapy-related toxic effects in NSCLC.

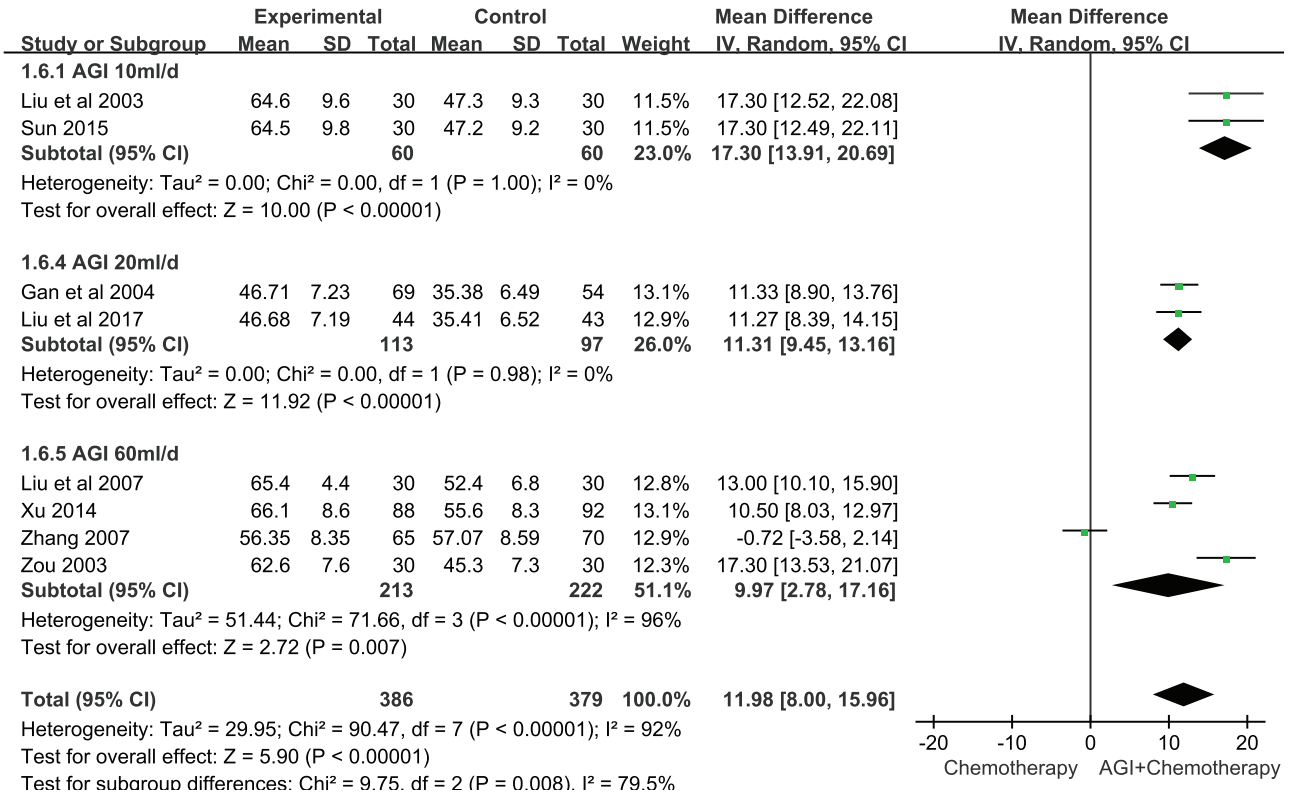

Figure 6. Forest plot of $CD3^+$. $CD3^+$ cells evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

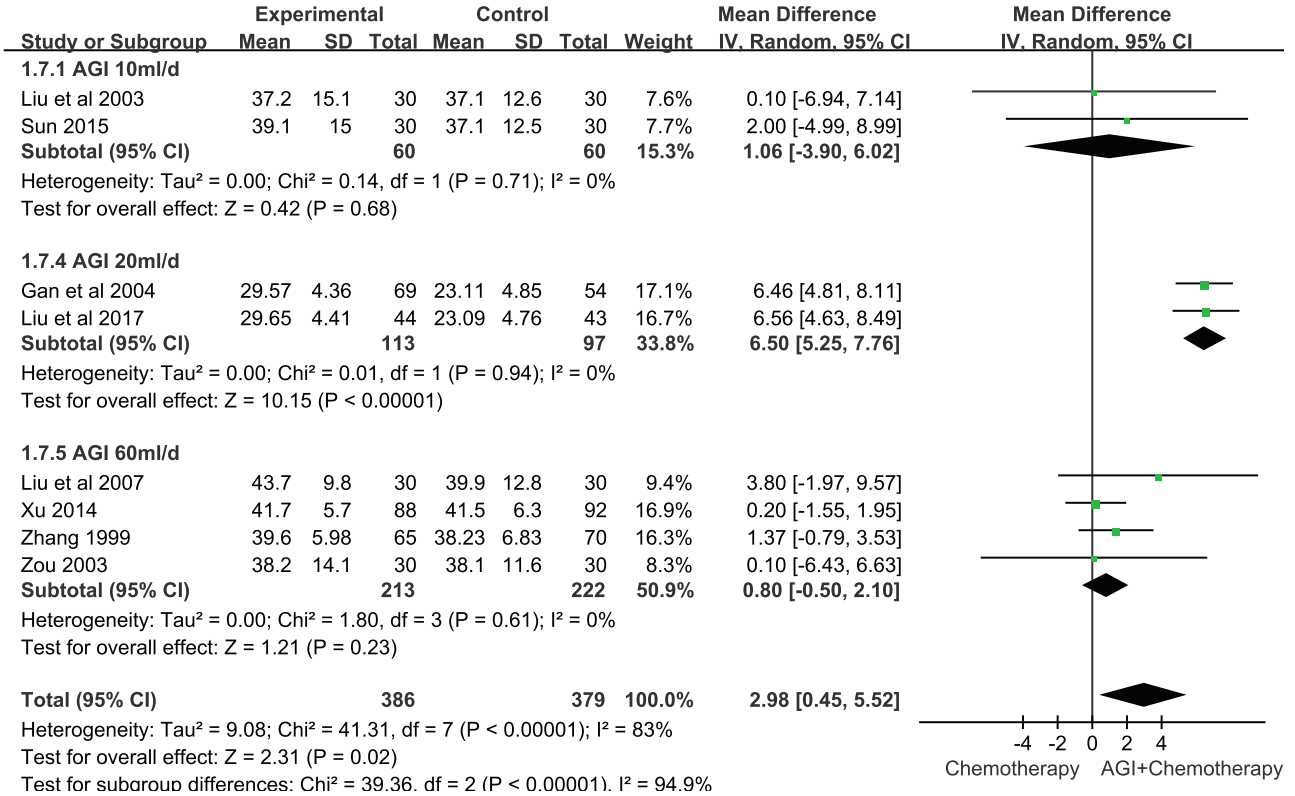

Figure 7. Forest plot of immune $CD4^+$. $CD4^+$ cells evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

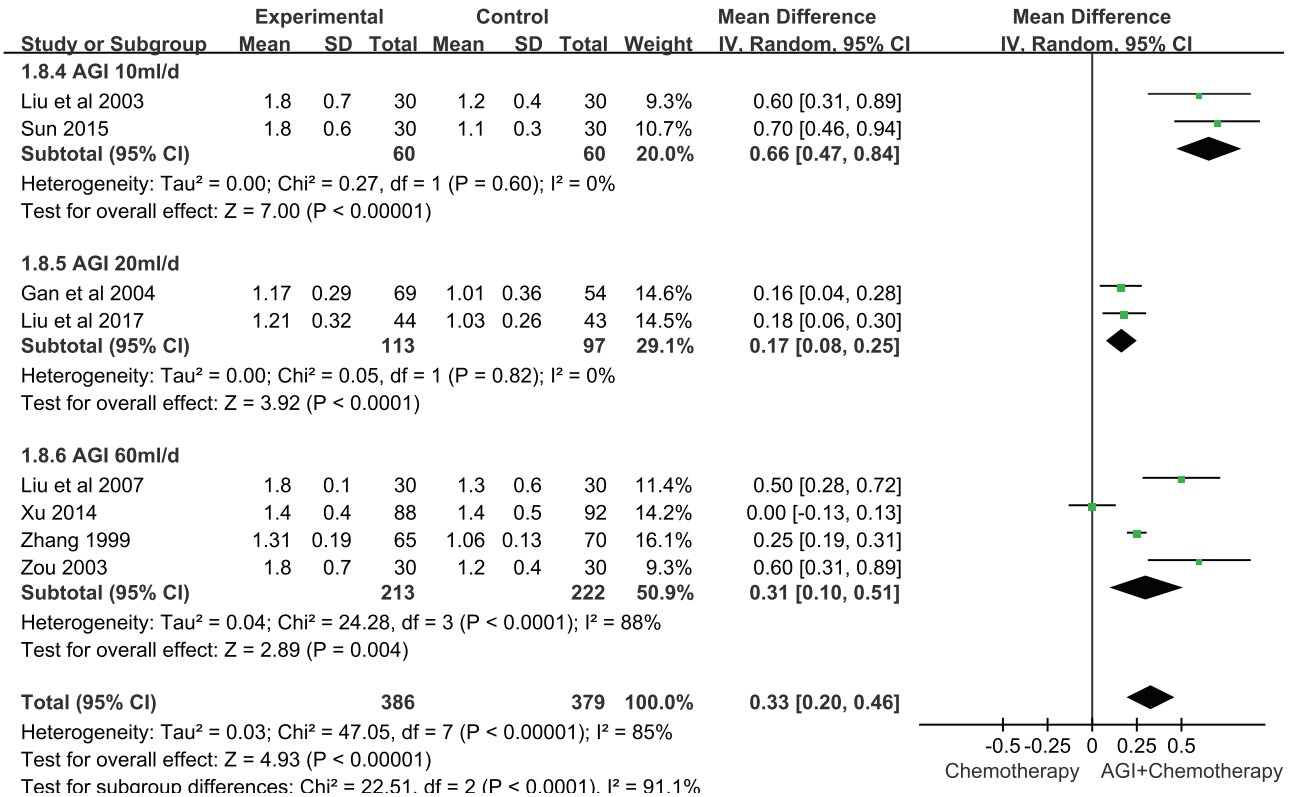

Figure 8. Forest plot of $CD4^+/CD8^+$. $CD4^+/CD8^+$ evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

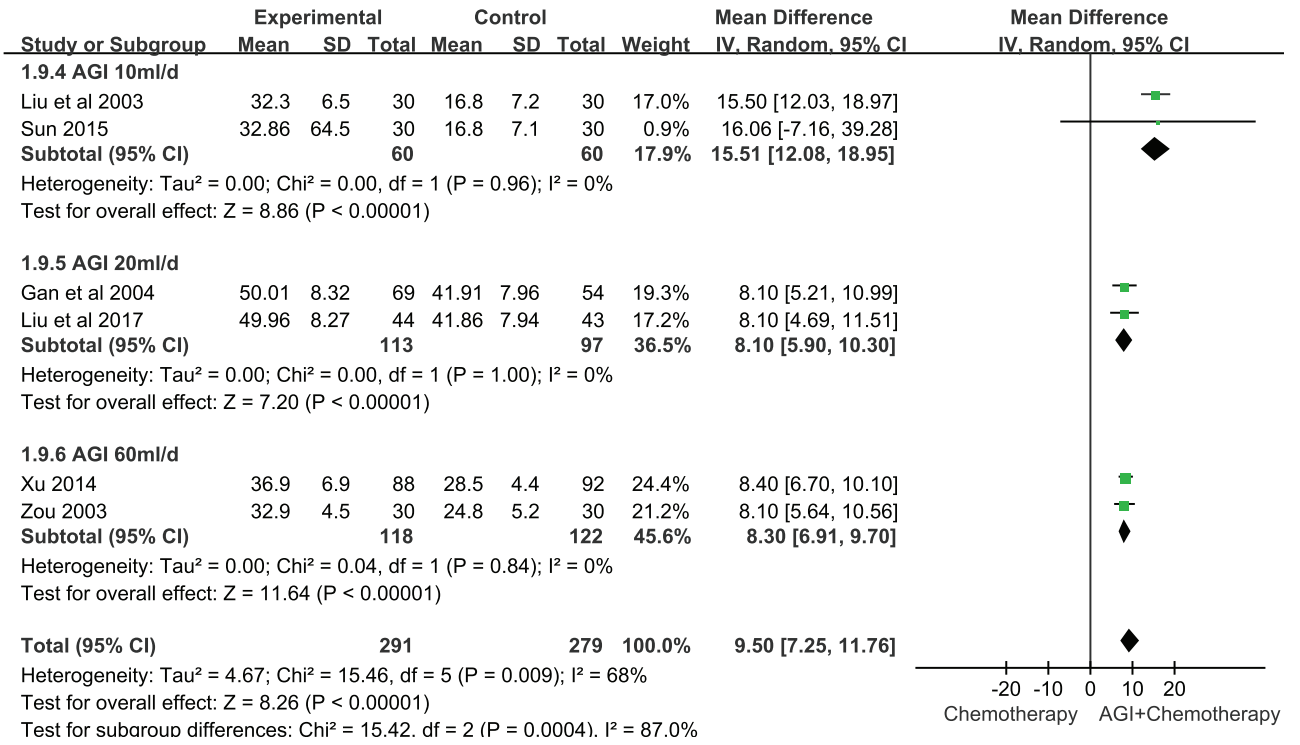

Figure 9. Forest plot of NK cells. NK cells evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

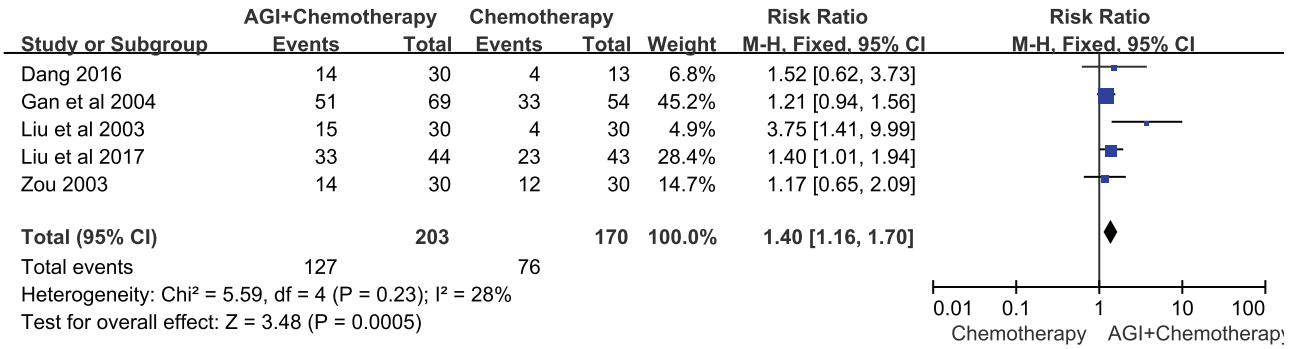

Figure 10. Forest plot of 1-year survival rate. One-year survival rate evaluated from meta-analysis of pair-wise comparisons in patients with chemotherapy combined Astragalus injection versus chemotherapy alone.

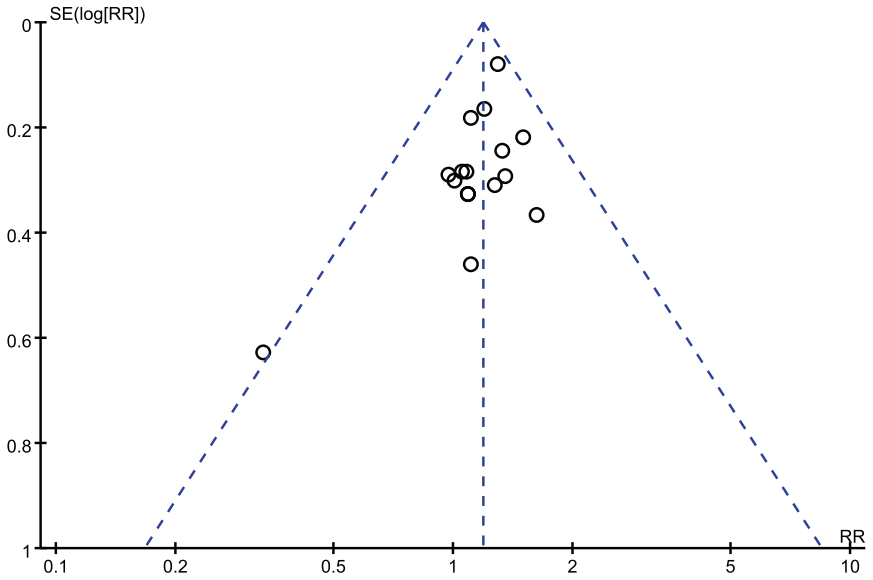

Figure 11. The funnel plots for assessing publication bias.

Table 2

GRADE summary of findings table.

Outcomes	No. of participants (studies)	Absolute effect estimates (per 1000)		Relative effect (95% CI)	Quality of the evidence
		Control	Experiment		
ORR	1395 (17 studies)	418	497 (443–556)	1.19 (1.06–1.33)	Low
KPS	431 (7 studies)	175	400 (286–558)	2.28 (1.63–3.18)	Low
Vomiting	356 (5 studies)	657	473 (394–572)	0.72 (0.6–0.87)	Low
White blood cell	877 (11 studies)	548	285 (241–335)	0.52 (0.44–0.61)	Low
PLT	429 (4 studies)	583	361 (291–443)	0.62 (0.5–0.76)	Low
Survival rate	373 (5 studies)	447	626 (519–760)	1.4 (1.16–1.7)	Low
$CD3^+$	765 (8 studies)	—	11.98 Higher (8–15.96 higher)	—	Very low
$CD4^+$	765 (8 studies)	—	2.98 Higher (0.45–5.52 higher)	—	Very low
$CD4^+/CD8^+$	765 (8 studies)	—	0.33 Higher (0.2–0.46 higher)	—	Very low
NK cell	570 (6 studies)	—	8.52 Higher (4.35–12.7 higher)	—	Very low

CI = confidence interval, KPS = Karnofsky performance status, ORR = objective response rate, PLT = platelet.

Table 3

Sensitivity analysis of this study.

Outcomes	N	RR or WMD (95% CI)	I^2, %	Excluded the studies	N	RR or WMD (95% CI)	I^2, %
ORR	17	1.19 (1.06, 1.33)	0	[15, 26]	15	1.17 (1.04, 1.31)	0
WBC	11	0.52 (0.44, 0.61)	0	[26]	10	0.52 (0.44, 0.62)	0
Survival rate	5	1.40 (1.16, 1.70)	28	[15, 26]	3	1.40 (1.11, 1.77)	46
$CD3^+$	8	11.98 (8.0, 15.96)	92	[15, 26]	6	12.30 (6.48, 18.13)	91
$CD4^+$	8	2.98 (0.45, 5.52)	83	[15, 26]	6	2.82 (0.44, 5.07)	78
$CD4^+/CD8^+$	8	0.33 (0.20, 0.46)	85	[15, 26]	6	0.42 (0.22, 0.61)	86
NK cell	6	9.5 (7.25,11.76)	68	[15, 26]	6	10.52 (6.87, 14.17)	79

CI = confidence interval, N = the number of trials, ORR = objective response rate, RR = relative risk, WBC = white blood cell, WMD = weighted mean differences.

Immune function damage is a serious adverse reaction, including lower antitumor and anti-infective immunity induced by platinum-based chemotherapy. Determining lymphocyte subgroups in the peripheral blood is an effective assessment method about the immune function. The meta-analysis indicated that the percentages of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$, and NK cells were significantly improved, respectively. According to the relevant content of modern pharmacology, AGI was available to effectively promote the immune response of tumor bearing host through increasing proportion of subsets $CD4^+$ T, $CD8^+$ T in mice's splenic cell, and serum IL-2/IL-4 ratio.[28] Meanwhile, Astragalus can convert the imbalanced state of Th1/Th2 cytokines and has a good regulatory effect on Th1/Th2 cytokines of lung cancer host.[30] The astragalus plays a role in immunological improvement and bidirectional regulation. AGI could exhibit both in vitro and in vivo antitumor effects and achieve through activating the antitumor immune mechanism of the host.[31] However, the statistical heterogeneity evidently existed when we pooled studies with continuous data. When subgroups were divided by different dosage of AGI, evaluations of the 3 subgroups about $CD4^+$ showed the different result. This needs to be verified by large-sample RCTs with high quality.

The pooled data had shown that the adjunctive use of AGI with chemotherapy might extend the survival rate in advanced stage. However, the small samples degraded the validity of the evidence of the meta-analysis. So far there has been no reliable evidence to prove the long-term effect. This needs to be verified by new authorized evidence.

Although our meta-analysis demonstrated favorable outcomes in a combination of AGI and chemotherapy, it had certain limitations that must be taken into account. First, all the included trials demonstrated at least some methodological deficiencies which led to potential risks of bias. The randomization, concealment allocation, and the blinding were not described in detail in some of the included studies, resulting in potential risk of selection bias, performance bias, and detection bias. Second, among the included trials, only 5[11,12,15,25,26] mentioned follow-ups and most of the identified trials included small sample sizes. This might lead to an inadequate assessment to the clinical efficacy of AGI for advanced NSCLC patients comprehensively and objectively. Third, the study was limited to East Asian patients, and the results required replication in other patients from varied backgrounds. Fourth, statistically significant results are 3 times more likely to be published than papers with null results.[32] Therefore, a certain degree of potential selection bias might exist and influenced the results of our analysis. Previously published systematic reviews of Chinese herbal medicine also have confronted same problems.[33,34] Altogether, the methodological quality of the included trials is insufficient and additional high-quality, controlled, and reproducible RCTs are warranted to generate a high level of clinical evidence.

5. Conclusion

Astragalus has attenuation and synergistic efficacy to platinum-based chemotherapy patients. The positive results described from the 19 studies of low quality are of questionable significance. No well-designed, randomized placebo-controlled trial with objective outcome measures has been conducted. Most of the trials were of very low methodological quality and the interpretation of any positive findings for the efficacy of the included AGI for treating NSCLC patients should be made with caution. Based on this systematic review, there is no strong evidence to support the objective effectiveness and safety of AGI combined platinum-based chemotherapy for NSCLC. High-quality, multicenter, and large sample size researches, particularly in the descriptions of methodology and study processes, are urgently needed to generate conclusive results.

Author contributions

Xianmei Zhou and Hailang He conceived and designed the project. Ailing Cao performed the review. Qian Wang, Lei Li, and Yajuan An analyzed the data. Ailing Cao wrote the paper. Xianmei Zhou was responsible for quality control of the study. Dr Ailing Cao and Dr Hailang He contributed equally to this work.

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