Review

Shenqi Fuzheng injection combined with GP chemotherapy in the treatment of advanced non-small cell lung cancer: a meta-analysis

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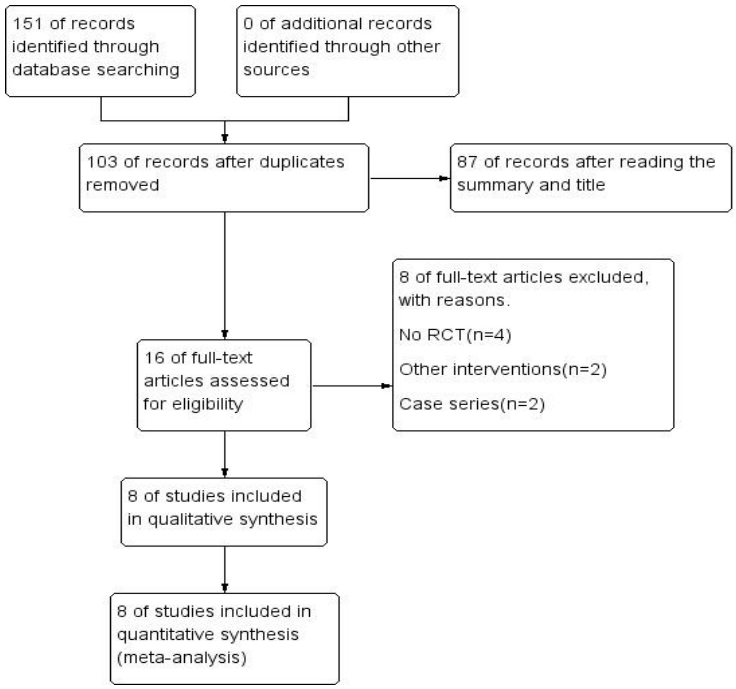
Highlights:

The clinical efficacy of Shenqi Fuzheng injection combined with gemcitabine plus cisplatin in the treatment of advanced non-small cell lung cancer was evaluated. Eight trials were included including a total of 701 patients. The combination treatment could significantly improve the functional status of patients with NSCLC and clinical treatment efficacy, decrease thrombocytopenia, hemoglobin decline and incidence of gastrointestinal reactions.



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Abstract

Objective: To evaluate the clinical efficacy of Shenqi Fuzheng injection combined with gemcitabine plus cisplatin (GP) in the treatment of advanced non-small cell lung cancer (NSCLC). **Methods:** we performed a systematic search in the electronic databases such as Cochrane Library, Pubmed, Embase, Chinese Journal Full-text Database, Chinese Biomedical Literature Database, Chinese Science and Technology Periodical Full-text Database and Wanfang Database up to 30 January 2017. Randomized controlled trials (RCT) of Shenqi Fuzheng Injection combined with GP chemotherapy in the treatment of advanced NSCLC were searched, and all the RCTs were conducted on methodological quality assessment. Data extraction and data analysis were according to standards of Cochrane systematic review. **Results:** Eight trials were included including a total of 701 patients. Meta-analysis results: Shenqi Fuzheng injection combined with GP chemotherapy could significantly improve the functional status of patients with NSCLC (OR = 3.44, 95% CI [2.26, 5.25], $P < 0.0001$) and clinical treatment efficacy (OR = (OR = 0.31, 95%CI [0.20, 0.47], $P < 0.0001$. The rate of leukopenia (OR = .31, 95%CI [0.20,0.47], $P < 0.0001$), thrombocytopenia (OR = 0.58, 95%CI [0.37, 0.91], $P = 0.020$), hemoglobin decline ((OR = 0.31, 95%CI [0.16, 0.59], $P = 0.0004$) and incidence of gastrointestinal reactions (OR = 0.58,P < 0.05) could be reduced. **Conclusion:** Shenqi Fuzheng injection combined with GP chemotherapy in the treatment of advanced NSCLC obtained significantly clinical efficacy. The quality of the literature incorporated is low, the conclusion requires high-quality research to further prove.

Keywords: Shenqi Fuzheng, GP chemotherapy, Advanced non - small cell lung cancer, Meta – analysis

摘要

目的：系统评价参芪扶正注射液联合吉西他滨加顺铂（GP）化疗方案治疗晚期非小细胞肺癌（Non-small cell lung cancer , NSCLC）的临床疗效。

方法：计算机检索 Cochrane Library，Pubmed，Embase，中国期刊全文数据库，中国生物医学文献数据库，中国科技期刊全文数据库和万方数据库等，检索时间限定为建库至 2017 年 1 月 30 日，检索关于参芪扶正注射液联合 GP 化疗方案治疗晚期非小细胞肺癌的随机对照实验（randomized controlled trial，RCT），参照 Cochrane 系统评价的要求，对所有评价参芪扶正注射液联合吉西他滨加顺铂（GP）化疗方案治疗晚期非小细胞肺癌（NSCLC）的随机对照试验进行方法学质量评价、数据提取和数据分析。

结果：最终纳入 8 个研究，共 701 例患者。参芪扶正注射液联合 GP 化疗方案能显著提高晚期非小细胞肺癌患者的功能状态（OR =3.44, 95% CI [2.26, 5.25], $P<0.0001$）和临床疗效（OR=1.54, 95%CI [1.11, 2.13], $Z=2.60$ $P=0.009$），能预防 GP 化疗方案引起的白细胞下降（OR =0.31, 95% CI [0.20, 0.47], $P<0.0001$）、血小板下降（OR=0.58, 95%CI [0.37, 0.91], $P=0.02$）、血红蛋白的下降（OR=0.31，95%CI [0.16, 0.59], $P=0.0004$）及胃肠道反应的发（OR=0.38，95%CI [0.24, 0.60], $P=0.0001$）。

结论：参芪扶正注射液联合 GP 化疗方案治疗晚期非小细胞肺癌临床疗效显著，但纳入文献质量低，结论有待高质量的研究加以证明。

关键词：参芪扶正；GP 化疗方案；晚期非小细胞肺癌；Meta 分析

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

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Introduction

According to data published in 2003 by the World Health Organization, the incidence of lung cancer and mortality ranks first in global cancer; there are more than 1.3 million new cases of global lung cancer each year, and the number of deaths is as high as 1 million [1]. According to pathology and biological behavior of lung cancer, it is mainly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer, and NSCLC accounts for about 80% of the incidence of lung cancer [2-3]. Early symptoms of NSCLC are not obvious, so most NSCLC are in local advanced phase when first diagnosed and missed the chance of surgery. There are many methods to treat advanced NSCLC, such as immunotherapy, targeted therapy, chemotherapy, radiotherapy, radiotherapy and chemotherapy, the majority of patients received chemotherapy as an effective treatment [4]. For advanced NSCLC, cisplatin-based combination therapy is still the primary first-line treatment recommended by the National Comprehensive Cancer Network (NCCN). Gemcitabine combined with cisplatin (GP) regimen is one of the standard first-line chemotherapy regimens for advanced NSCLC treatment with an objectively effective rate of about 30%, but the regimen-related toxicities are serious and can cause severe granulocyte decline and gastrointestinal reactions. These severe side effects affect patient's functional status, and even many patients have to give up treatment because of these adverse effects [5-6]. Advanced NSCLC patients are a special group of people, such as poor constitution, poor chemotherapy tolerance, the tendency to reject treatment is obvious and only few of them could complete the standardized chemotherapy cycle. Therefore, to develop a safe and effective, highly viable treatment program is imminent [7].

The main components of Shenqi Fuzheng injection are Astragalus and Codonopsis, which have the function of supporting the healthy energy and invigorating spleen for benefiting lung. Astragalus has the effect of invigorating yang and qi; Codonopsis has the function of supplementing qi and promoting the production of body fluid. The function of Fuzheng Guben is strengthened when combined with Astragalus. Astragalus and Codonopsis are complementary to each other, with function of anti-fatigue, improve the body immunity, promote tumor cell apoptosis and affect the role of tumor tissue metabolism [8]. In recent years, clinical trials have shown survival benefit when combined Shenqi Fuzheng injection with GP chemotherapy regimen in the treatment of advanced NSCLC. However, these researches were not very persuasive, as with small samples and low test efficiency. The aim of this study was to evaluate the efficacy of Shenqi Fuzheng injection combined with GP regimen in the treatment of advanced NSCLC through a meta-analysis of randomised controlled clinical trials.

Methods

Types of research

Randomized controlled trials (RCT) with or without blindness and allocation hiding were searched in the electronic databases. Language limited to Chinese and English.

Research objects

All patients were diagnosed as advanced (stage Ⅲ ~ Ⅳ) NSCLC (TNM staging according to WTO) by pathology / cytology / cytology examination; survival expectancy was expected to be greater than 3 months; KPS score ≥ 50; patients without chemotherapy or traditional Chinese medicine injection contraindications, no serious liver and kidney dysfunction.

Interventions

The experimental group was treated with Shenqi Fuzheng injection (Lizhu Group Limin Pharmaceutical Factory, Zhunzi Z19990065) combined with GP chemotherapy regimen. The control group was treated with GP chemotherapy alone.

Exclusion criteria

① non-randomized controlled trials; ② case reports or case series; ③ intervention does not meet the requirements of the study; ④ outcome indicators do not meet the requirements of the study; ⑤ repeated published literature; ⑥ data cannot be extracted or there are other chaotic signs of the literature.

Outcome indicator

Primary outcome indicators: clinical efficacy according to the current WHO evaluation criteria [9]: complete remission (CR): after treatment, the patient's symptoms disappeared completely, and in the follow-up months without any other complications or new lesions appear; Partial remission (PR): After treatment, lesions were reduced by more than 50%, and stable within one month, no other complications occurred; stable (SD), after treatment, the lesion increased, but only 20% of the treatment before or the lesion decreased, but less than 50% of the lesion before the disease; progress (PD): 25% of the lesion increased after treatment or new negative lesion appeared; the total effective rate was CR + PR ($P < 0.05$). Secondary outcome indicators: functional status score (the Kart score (KPS)) was used for evaluation. The full mark was 100 points, KPS ≥ 10 points was defined as improvement, KPS increased or decreased 10 points

was defined as stability, KPS decreased ≥ 10 points was defined as progress. Side effects included leukopenia, hemoglobin decline, thrombocytopenia, gastrointestinal adverse reactions, phlebitis, liver and kidney function damage, *et al.* (based on WHO toxicity grading standards) [9, 10].

Search strategy

Two researchers carried out the search under the guidance of retrieve teacher, and then summarized the retrieved literatures. Literatures were searched from Cochrane Library, Pubmed, Embase, Chinese national knowledge infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Science and Technology Periodical Full-text Database (VIP) and Wanfang Database, *et al*. The retrieval time was limited to 30 January 2017. For the unpublished literature, their relevant conference papers, academic reports, full-text thesis in WanFang database and references of the literatures were searched simultaneously. Chinese search term included "参芪扶正", "GP 方案", "非小细胞肺癌", "肺癌", "肺肿瘤"; English search terms included "Shenqi Fuzheng Injection","Gemcitabine, Chemotherapy", "Non -small cell lung cancer" "lung cancer","lung neoplasm","NSCLC", according to different databases for keywords and freedom word free collocation search.

Literature screening and data extraction

The Cochrane collaboration system evaluation manual was used as a reference. Firstly, the two researchers read literatures objectively and independently to eliminate the researches which do not meet the inclusion criteria. Then, they selected literatures according to the inclusion criteria and exclusion criteria. The uncertainty literatures were selected through discussion or through a third party. Finally, two researchers applied the pre-designed form to evaluate and extract the original documents independently. Specific projects include: title, first author's name, the term of publication and the source of the literature, baseline comparability of groups of patients, interventions and primary outcome.

Assessment of study quality

Risk biases of included studies were assessed using the criteria of the Cochrane system evaluation manual 5.1.0. (1) Random assignment; (2) allocation concealment; (3) blinding method; (4) data integrity; (5) selective outcome report; (6) other sources of bias. Each item uses the yes, no or no clear answer. Yes (low risk of bias), No (high risk bias), No clear answer (lack of relevant information or bias is uncertain).

Publication bias

Egger linear regression and Begg rank correlation test were used to evaluate the publication bias in Stata 12.0.

Statistical analyses

Meta-analysis was performed by the RevMan 5.3 software provided by the Cochrane Collaboration Network. The enumeration data was measured by relative risk (RR) or odds ratio (OR), the measurement data was measured by weighted mean difference (WMD) or standardized mean difference (SMD) with 95% confidence interval (95% CI). The heterogeneity of the included studies was evaluated using the Chi^2 test. When $P > 0.1$ and $I^2 < 50\%$ (no significant heterogeneity among researches), meta-analysis was performed using the fixed effects model. When $P < 0.1$ and $I^2 > 50\%$, the stochastic effect model was used for meta-analysis. If there is a significant clinical heterogeneity between the studies, descriptive analysis was performed.

Results

Results of document retrieval

151 articles were obtained in the result of initial search, and 48 repetitive literatures were removed by Endnote. 87 literatures were excluded by reading abstracts, which obviously did not meet the requirements. Finally, through the full text of reading, researches which combined with other interventions in experimental group, case reports and non-randomized controlled studies were excluded. Finally, 8 literatures were included for meta-analysis (Figure 1) [11-18].

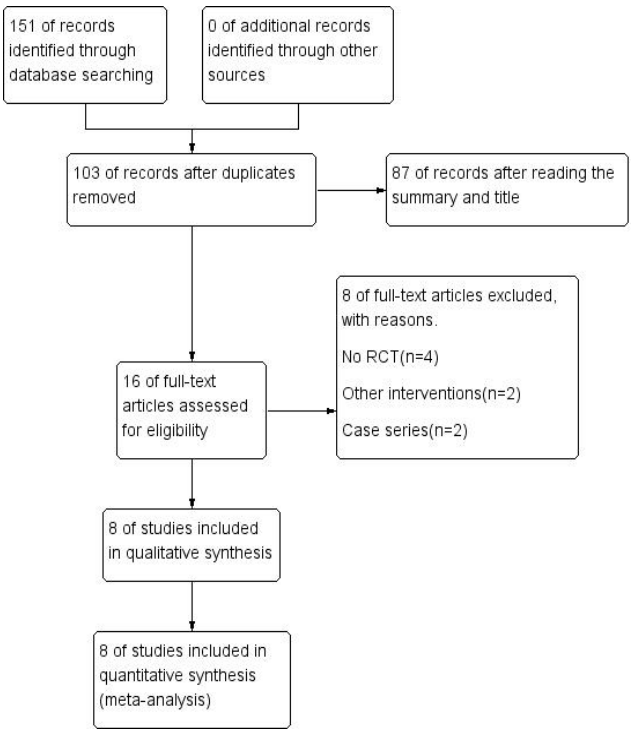

Figure 1 Flow chart of records

Basic characteristics of the literature

In this study, 8 literatures were included in the meta-analysis with a total of 308 patients in the treatment group and 304 cases in the control group [11-18]. Three studies did not mention survival life and KPS score [11, 17, 18]. All studies have described the staging of non-small cell lung cancer. All the patients in the 8 studies received at least one course of GP regimen (21d for one cycle) [11-18]. The dose of Cisplatin was 20mg/m^2 - 100mg/m^2. The doses of Gemcitabine in most of the studies were 1000 mg/m^2 [11-14,16,18], while in other two studies, they were 1500 mg/m^2 [17] and 1250 mg/m^2 [15]. 250 ml of Shenqifuzheng injection were given by intravenous infusion, while, in one study, 260ml Shen qi fu zheng injection were reported [17] (Table 1).

Risk bias assessment results

The study used the Cochrane Systematic Review Manual 5.1.0 to assess the risk bias for the included studies. Two study used random number table method [14, 18], three did not mention randomized methods [12, 13, 18], and the rest was mentioned only random without detailed explanation [11, 15, 16]. All studies did not mention the allocation of hidden programs and blinding. The risk biases were low for for incomplete data outcomes and selective reporting bias (Figure 2, 3).

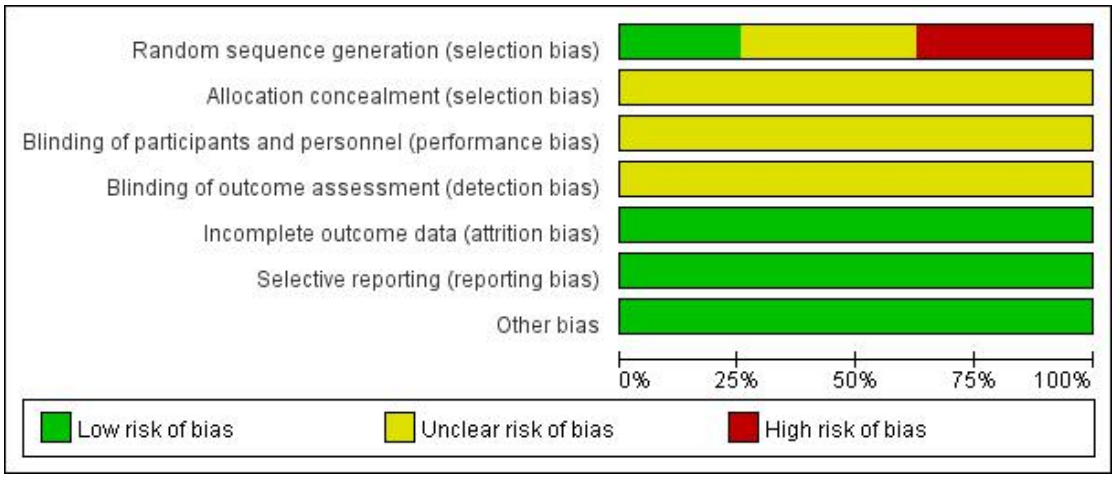

Figure 2 Risk assessment

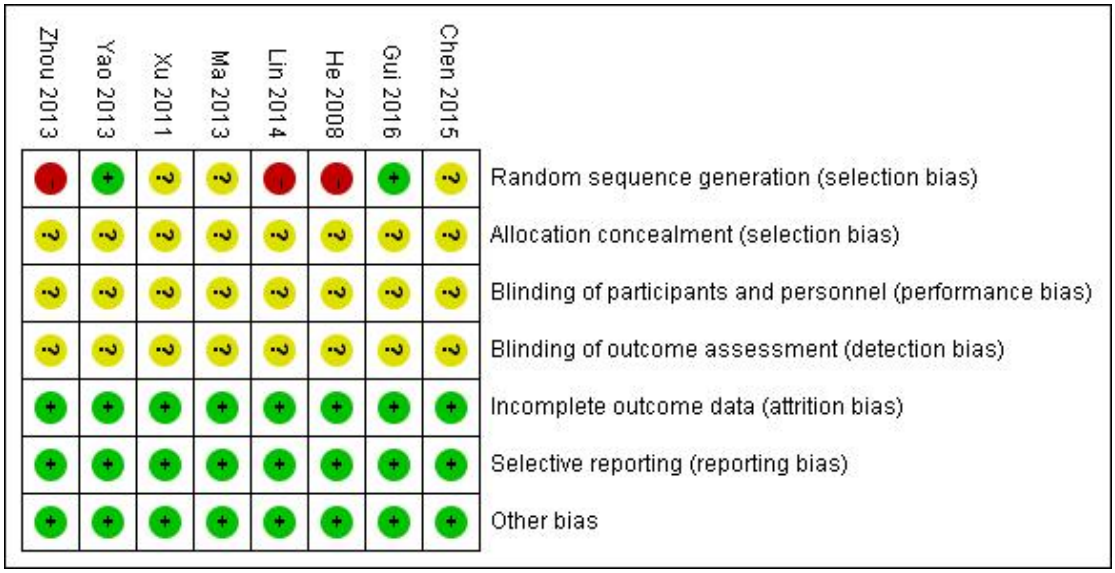

Figure 3 Summary of risk assessment

Table 1 Table of literature characteristics

Study ID	T/C	Survival Period(month)	Tumor staging	KPS	Trials	Controls	Duration	Outcomes
Chen 2015	34/33	none	IIIa/IIIb/IV period	70-90	Cisplatin 75mg/㎡ d2-d4; Gemcitabine 1000mg/㎡ d1, d8; Shenqifuzheng 250ml, 1 times / d, once every 15d	Cisplatin 100mg/㎡ d2-d4; Gemcitabine 1000mg/㎡ d1, d8	42d	Clinical efficacy, functional status, adverse reactions
Lin 2014	32/30	3	III/IV period	>60	Cisplatin 75mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1,d8; Shenqifuzheng 250ml, 1 times / d, once every 14d	Cisplatin 75mg/㎡ d1-d3;Gemcitabine1000mg/㎡ d1,d8	42d	Clinical efficacy, functional status, symptom change, weight
He 2008	35/35	3	IIIb/IV period	50-80	Cisplatin 25mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1, d8; Shenqifuzheng250ml, 1 times / d, once every 10d	Cisplatin 25mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1, d8	42d-63d	Clinical efficacy, functional status, adverse reactions, blood routine
Yao 2013	50/50	3	III/IV period	≥70	Cisplatin 50mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1,d8; Shenqifuzheng250ml, 1 times / d, once every 14d	Cisplatin 50mg/㎡ d1-d3;Gemcitabine 1000mg/㎡ d1,d8	42d	Clinical efficacy, functional status, adverse reactions, blood routine
Xu 2011	40/40	3	III/IV period	>60	Cisplatin 20mg/㎡ d1-d5; Gemcitabine 1250mg/㎡ d1,d8; Shenqifuzheng250ml, 1 times / d, once every 42d	Cisplatin 20mg/㎡ d1-d5; Gemcitabine 1250mg/㎡ d1,d8	42d	Clinical efficacy, functional status, adverse reactions, blood routine
Ma 2013	28/28	3	IIIa/IIIb/IV period	>50	Cisplatin 60mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1,d8; Shenqifuzheng250ml, 1 times / d, once every 7d	Cisplatin 60mg/㎡ d1-d3; Gemcitabine 1000mg/㎡ d1,d8	63d	Clinical efficacy, functional status, adverse reactions, blood routine
Gui 2016	45/48	none	IIIb/IV period	none	Cisplatin 70mg/㎡ d1,d8; Gemcitabine 1500mg/㎡ d1,d8; Shenqifuzheng260ml, 1 times / d, once	Cisplatin 70mg/㎡ d1,d8; Gemcitabine 1500mg/㎡ d1,d8	84d	Clinical efficacy, functional status, adverse reactions, blood routine

					every 10d			
Zhou 2013	44/40	none	Ⅲ/Ⅳ period	none	Cisplatin 75mg/㎡ d1,d8; Gemcitabine 1000mg/㎡ d1,d8; Shenqifuzheng250ml, 1 times / d, once every 10d	Cisplatin 75mg/㎡ d1,d8; Gemcitabine1000 mg/㎡ d1,d8	21d	Clinical efficacy, adverse reactions, blood routine

Meta-analysis results

The total clinical efficiency

A total of 8 subjects were included in the study with 308 in the treatment group and 304 in the control group [11-18]. There was no statistical heterogeneity (P = 0.81, I^2 = 0%), so the fixed effect model was adopted. Meta-analysis results showed that Shenqifuzheng injection combined with GP regimen chemotherapy group can improve the clinical efficacy of patients with advanced non-small cell lung cancer (OR = 1.54, 95% CI, Z=2.60 (P = 0.009) [1.11, 2.13]. The difference was statistically significant (Figure 4).

Functional status score

7 studies reported card scores with 214 patients in the treatment group and 214 patients in the control group [11-17]. Heterogeneity test showed that there was no statistical heterogeneity in the seven studies (P = 0.51, I^2 = 0%), so the fixed effect model was used for the analysis. Meta-analysis showed that there was significant difference between Shenqifuzheng injection combined with GP regimen chemotherapy group and simple GP regimen chemotherapy group (P < 0.01). Compared with the GP alone chemotherapy group, Shenqi Fuzheng injection combined with GP regimen chemotherapy group can effectively improve the functional status of patients with advanced non-small cell lung cancer (OR = 3.44, 95% CI [2.26, 5.25]) (Figure 5) .

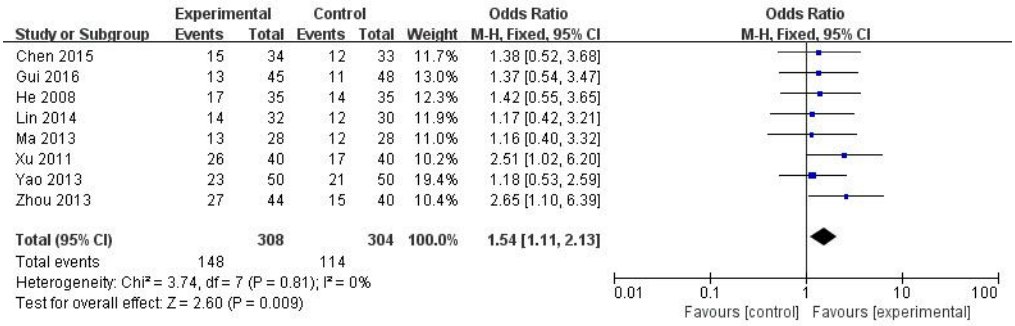

Figure 4 Recent effects of forest map

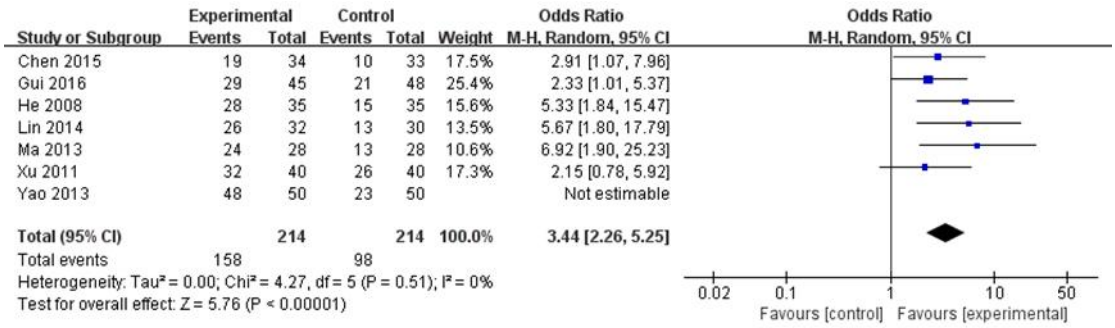

Figure 5 Quality of life forest map

White blood cell

6 studies [11, 13-17] reported the decline of white blood cells before and after treatment, with 232 cases in the treatment group and 234 cases in the control

group. The heterogeneity test showed that there was no statistical heterogeneity (P = 0.93, I^2 = 0%), and the fixed effect model was used. Meta-analysis showed that the difference was statistically significant (P < 0.01). Compared with GP alone chemotherapy group, Shenqi Fuzheng injection combined with GP regimen chemotherapy group can reduce the decline of white blood cells (OR = 0.31, 95% CI = (0.20, 0.47)) (Figure 6).

5 studies [13-17] used blood platelet decline as a therapeutic index with 198 cases in the treatment group and 201 cases in the control group. The heterogeneity test: P = 0.60, I^2 = 0%, the fixed effect model was used. Meta-analysis showed that Shenqi Fuzheng injection combined with GP regimen can reduce the decrease of blood platelet, the difference was statistically significant [OR = 0.58, 95% CI = (0.37, 0.91), Z = 2.36 (P = 0.02)] (Figure 7).

Blood platelets

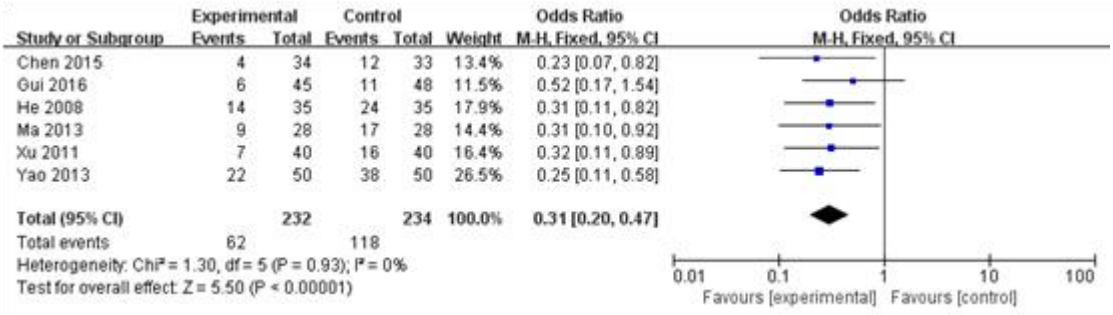

Figure 6 Leukocyte descent forest map

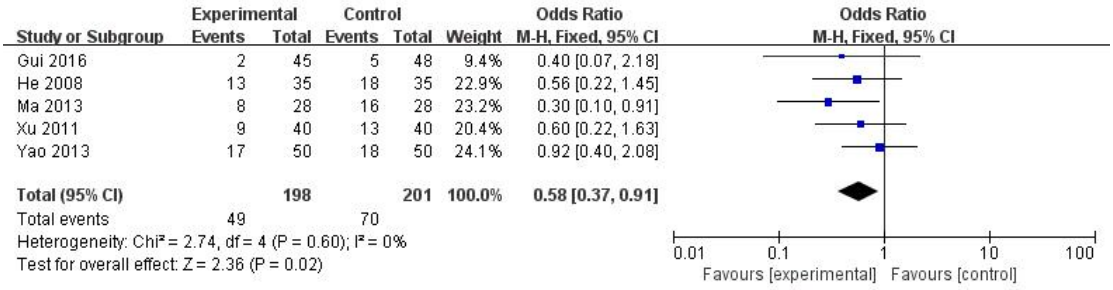

Figure 7 Platelet descent forest map

Hemoglobin

A total of 3 studies [13, 14, 17] used Hemoglobin decline as a therapeutic index with 130 cases in the treatment group and 133 cases in the control group. The heterogeneity test: P = 0.70, I^2 = 0% and the fixed effect model was used. Meta-analysis showed that Shenqi Fuzheng injection combined with GP regimen can increase the level of hemoglobin, the difference was statistically significant [OR=0.31, 95%CI = (0.16, 0.59), Z = 3.54(P=0.0004)] (Figure 8).

Gastrointestinal reaction

A total of 5 studies [13, 16-18] used gastrointestinal reaction as a therapeutic index with 192 cases in the treatment group and 191 cases in the control group. The heterogeneity test: P = 0.19, I^2 = 35%, and the fixed effect model was used. Meta-analysis showed that Shenqi Fuzheng injection combined with GP regimen chemotherapy group can reduce the gastrointestinal reaction, the difference was statistically significant [OR = 0.38, 95% CI = (0.24, 0.60), Z = 4.19 (P = 0.0001)] (Figure 9).

Funnel plots for Meta analysis

Publication bias was assessed for overall clinical effectiveness. Results obtained by Egger linear regression (P = 0.216) and Begg rank correlation test (P = 0.764) indicated no publication bias (Figure 10).

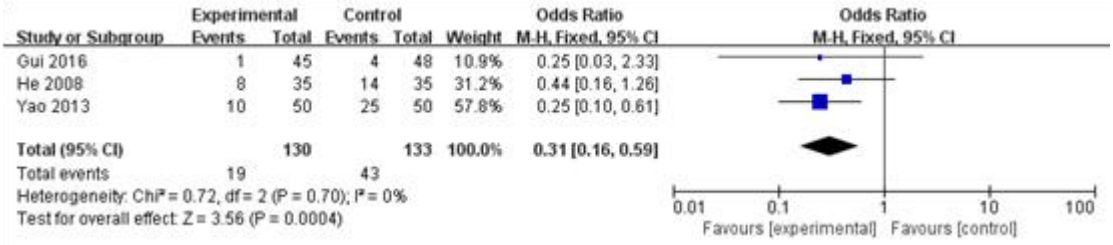

Figure 8 Hemoglobin drop forest map

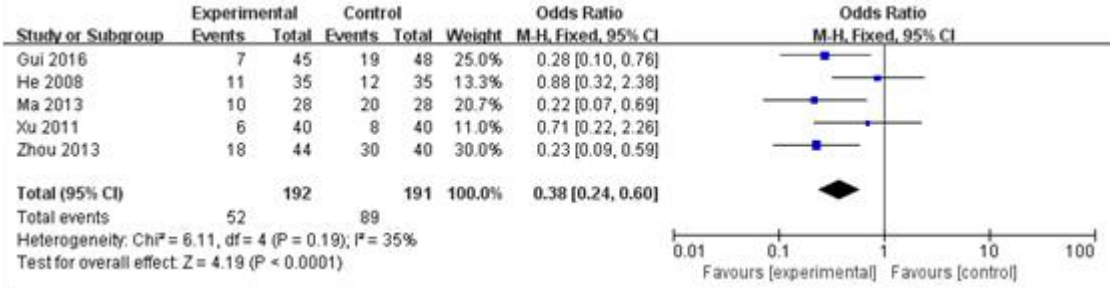

Figure 9 Gastrointestinal response to forest map

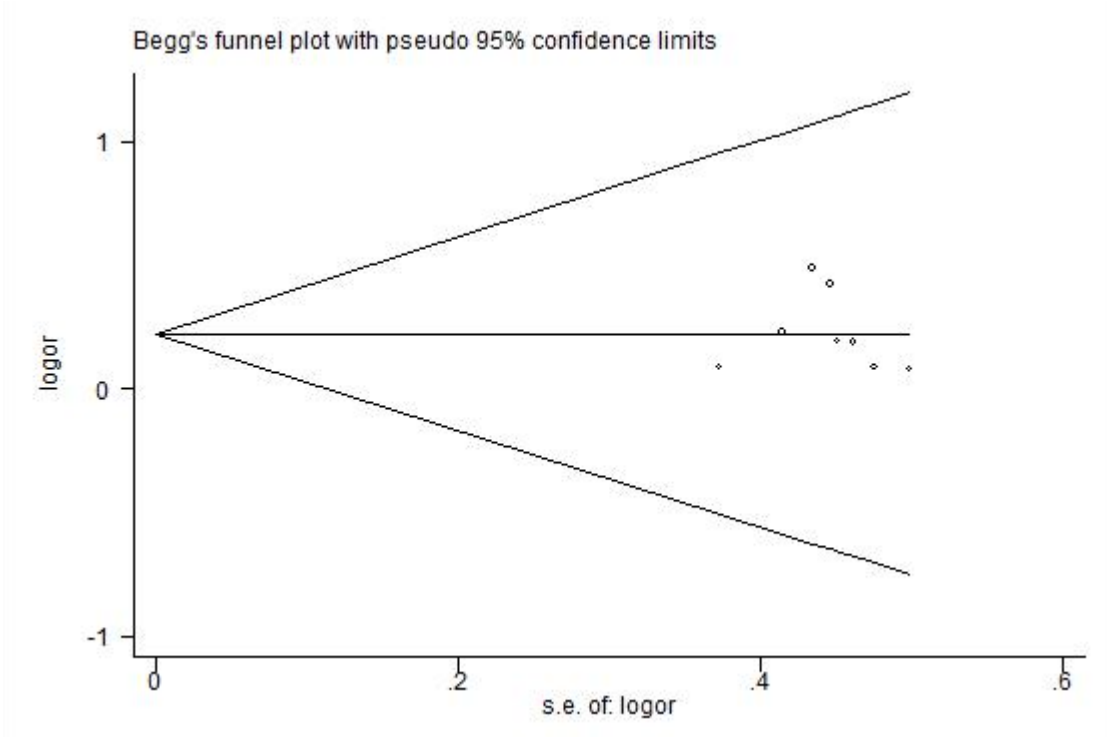

Figure 10 Begg funnel chart

Discussion

The main components of Shenqi Fuzheng injection were *Codonopsis*, *Astragalus*, *sodium chloride*. *Astragalus* was the most effective herb which invigorating Qi. *Codonopsis* can promote qi and promote fluid production, and can help strengthen the function of spleen. *Codonopsis* combined with

Astragalus could improve the functions of anti-fatigue and enhancing immunity [20].

Meta-analysis showed that Shenqi Fuzheng injection combined with GP chemotherapy regimen could significantly improve the survival time of patients with the advanced non-small cell lung cancer [19]. The immune system of the human body itself has the ability to eliminate the tumor. The body anti-tumor immune cells include T cells, K cells, NK cells, macrophages, etc. Together with immune factors, anti-tumor immune cells could destroy tumor cells [21] However, when the human immune function is low, the body defense ability is reduced, the immune system can not kill tumor cells in time, resulting in its unlimited growth.

Shenqifuzheng injection, with the effect of invigorating Qi, can enhance the body internal disease resistance, improve immune function and inhibit tumor cell growth. When combined with the cytotoxic drug, it could eliminate the tumor cells without adverse reaction. Related studies [22] showed that Shenqi Fuzheng injection may reduce the expression of tumor necrosis factor (TNF-α) and transforming growth factor (TGF-β1) to improve the immune function of patients with lung cancer. Modern pharmacological studies [23, 24] show that *Codonopsis* can improve the phagocytosis of the reticuloendothelial system, increase the lymphocyte transformation rate of cancer patients, improve the immune and leukopenia. *Astragalus* can induce the body to produce interferon, promote mononuclear - megakaryocyte function, enhance the vitality of MK cells, regulate the body's cellular immunity and humoral immunity. Therefore, Shenqi Fuzheng injection can not only protect the bone marrow, reduce the inhibition of chemotherapy on bone marrow hematopoietic function, but also can improve the patient's cellular immune function, reduce the incidence of adverse reactions in patients with chemotherapy and improve clinical symptoms.

However, there are some shortcomings in this study: the dose of the selected dose is not uniform and the course of treatment is different, which increased the heterogeneity. The quality of the inclused researches is not high. Most of the random method is not clear; Allocation concealment and blind were difficult to come true.

In summary, compared with the use of GP chemotherapy alone, Shenqi Fuzheng injection combined with GP chemotherapy regimen can significantly improve the functional status of patients with advanced non-small cell lung cancer and the recent clinical efficacy. In side effects, Shenqi Fuzheng injection combined with GP chemotherapy regimen can reduce severe bone marrow suppression (white blood cell decline, blood platelets decline, hemoglobin decline). However, the qulity of current studies on Shenqi Fuzheng injection combined with GP chemotherapy regimen were low, the conclusions of the study is less convincing.

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