REVIEW
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The effect of Cordyceps Sinensis in the prognosis on patients receiving chemotherapy with malignant tumors: A systematic review and meta-analysis

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Highlights

The combination therapy of Cordyceps Sinensis (CS) and chemotherapeutic drugs can reduce the inhibitory effect of bone marrow induced by chemotherapeutic drugs. CS can prevent leukocytes and white blood cells from decreasing in cancer patients during chemotherapy and radiotherapy. However, the prognostic role of CS in patients with malignant tumors after chemotherapy is still not clear. The mechanism of Chinese medicine treatment of tumor is a promising direction.

Abstract

Objective: The efficacy of Cordyceps Sinensis (CS) on malignant tumors remains controversial. We undertook a systematic meta-analysis of randomized controlled clinical studies on this issue. **Method:** A comprehensive literature search (by the end of Sep. 31, 2017) was conducted in following electronic databases: China National Knowledge Infrastructure (CNKI), VIP database, Wan fang database (VIP), PubMed, Medline, and EMBASE. Relevant studies were included according to inclusion criteria. Pooled relative risk was estimated by using the fixed effects model or random effects model according to heterogeneity. Data were extracted independently and the standardized mean deviation (SMD) of the calculated results was obtained. **Result:** After selection, 8 of 729 studies were included. The result showed that CS combined with chemotherapeutic drugs was favorable for the treatment of malignant tumor. The amount of $CD3^+$ T cells in the experimental group was significantly higher than that in the control group (SMD = 0.86; 95% CI = 0.02, 1.70; $P < 0.01$; $I^2 = 91\%$). The amount of $CD4^+$ T cells in the experimental group was significantly higher than that in the control group (SMD = 0.95; 95% CI = 0.22, 1.68; $P < 0.01$; $I^2 = 88\%$). The amount of $CD8^+$ T cells in the experimental group was significantly higher than that in the control group (SMD = -0.07; 95% CI= -0.30, 0.17; $P = 0.32$; $I^2 = 14\%$). The rate of $CD4^+/CD8^+$ T cells in the experimental group was higher than that in the control group (SMD = 27.76; 95% CI = 25.25, 30.28; $P = 0.39$; $I^2 = 0\%$). And CS may retard the declining trend of KPS functional status evaluation (RR = 0.46, 95% CI = 0.2780, 0.7350; $P < 0.01$), thus improving the patients' life quality. **Conclusion:** The current evidence suggested that CS is favorable to improve the efficacy of chemotherapeutic drugs in patients with malignant tumors, probably by improving immune system function.

Keywords: Cordyceps Sinensis, Chemotherapy, Meta-analysis, Prognosis, Malignant tumor, Immune system

***Competing interests*:**

The authors declare that there is no conflict of interest.

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Introduction

On a global level, cancer is now one of the world's most pressing health challenges. Seven out of 10 cancer deaths occur in Africa, Asia, and Central and South Africa [1]. By the year 2030, these cancer deaths will increase globally by as much as 80%, according to WHO estimates [2, 3]. Even during the survival time of palliative care, tumor cachexia such as anorexia, weakness, anemia, loss of appetite, fever, severe pain has severely affected patients' living quality. Many treatment options for cancer exist, with the primary ones, including surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy, and palliative care. Chemotherapy is one of the most commonly used methods to treat diseases [4]. However, chemotherapeutic drugs often suppress the immune function of the patients and produce a variety of adverse drug reactions (ADRs), such as nausea, vomiting, thrombocytopenia, and liver function damage [5, 6]. How to reduce these side-effect reactions and improve the quality of life of patients has become a concern of researchers.

In recent years, an increasing number of studies have proved that the traditional Chinese medicine (TCM), especially in combination with chemotherapeutic drugs, play an essential role in the treatment of diverse cancers by improving the effectiveness and immunomodulation [7, 8]. Additionally, TCMs can reduce the toxic and side effects caused by chemotherapy medicament [9-11]. As a TCM, Cordyceps Sinensis (CS) is recorded by Herbal Foundation Compendium as "Winter-worm, summer-herb is the fungi, plant, and animal to gather for the whole body like outstanding represent". Furthermore, modern pharmacology has confirmed that CS, a macro fungus of biomedical importance, contains several bioactive components [12]. Previous reports have shown that Exopolysaccharide Fraction (EPSF) [13-15], H1-A [16-18], Cordycepin [19-23] and Acid polysaccharide (APS) [24-27] extracted from the culture supernatant of CS can intensively regulate the function of human immune cells, while Cordyglucan [28] and monosaccharide Saponins et al. [29]. Exhibit anti-tumor effects. Other components such as amino acids, galactose, nucleoside, vitB12 et al. have been proven to have sound pharmacological effects on the circulatory system, immune system, respiratory system, and digestive system. Also, the existing research data shows that the combination therapy of CS and chemotherapeutic drugs can reduce the inhibitory effect of bone marrow induced by chemotherapeutic drugs, and auxiliary increase the number of platelet and white blood cells, especially in patients with advanced lung cancer or elderly patients with malignant tumor who have lost the chance of operation, thus improving the tolerance to chemotherapy by releasing the symptoms of fatigue and respiratory tract infection induced by chemotherapy, enhancing the immune function and inhibiting the growth of tumor [30].

However, for all we know, there was not a meta-analysis to evaluate the efficacy of CS on patients receiving chemotherapy with malignant tumors. The purpose of this study is to investigate the prognostic role of CS in patients with malignant tumors after chemotherapy, to provide references for making relevant clinical treatment protocols and guidelines, and ultimately improving the quality of patients' life.

Materials and Methods

The current meta-analysis was designed according to the latest version of the PRISMA checklist for meta-analysis guidelines.

Information Sources

An electronic search of the following databases was performed: China National Knowledge Infrastructure (CNKI), VIP database, Wan fang database (VIP), PubMed, Medline, and EMBASE. The language was restricted to Chinese and English only, and all were up to September 2017. The search strategy containing the following keywords ("CS" OR "Chinese caterpillar fungus" OR " winter worm summer herb " OR " aweto" OR "Braun CAPSule" OR "Corbrin CAPSule") AND ("tumor" OR "cancer" OR "malignant tumor ") OR "carcinoma" AND "chemotherapy" AND ("randomized" OR "randomize" OR "random"). References lists of retrieved articles and other reviews were screened. When necessary, we attempted to contract researchers to identify missing data that were not included in the original publication.

Eligibility criteria

All articles from potential eligible studies were screened independently by two authors using strict inclusion and exclusion criteria. A comprehensive search was conducted for published randomized cohort studies (RCTs) in full-text or abstract comparing patients who had received CS (or its medicaments) in combination with chemotherapy (treatment group) and chemotherapeutic drugs monotherapy groups (control group). Also, a priori decision was made only to include reports utilizing chemotherapy-CS combination therapy. Discrepancies were resolved by a third investigator through re-reviewing the original publications, figuring out reasons, providing solutions, and finally reaching a consensus.

Inclusion criteria Studies that met our defined inclusion criteria were considered eligible for the meta-analysis. We included articles following PICO. (1) Participants (P): patients with malignant tumors after chemotherapy in hospital, among which render,

age, TNM periodization, duration of the disease were not limited, but there were no significant differences in baseline level. (2) Intervention (I): CS followed by chemotherapy on malignant tumors, was the intervention of interest. (3) Comparison (C): chemotherapeutic drugs monotherapy groups in RCTs were set as control groups, no matter using a single-blind or double-blind method. (4) Outcome (O): the quality of life (KPS functional evaluation), immune reactions ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$) and toxic side effects were pooled.

Exclusion criteria We excluded: (1) zoopery-related articles; (2) research progress, review, mechanism-related study; (3) repeated publications; (4) items not including RCTs our control and items using CS; (5) combined with other drugs that may have effects on the medical evaluation of CS; (6) simple-study description; (7) articles whose information and data cannot be extracted.

Data Collection

Two reviewers extracted relevant data from each eligible study, including the author, year, the number of samples, intervention methods, outcome indexes, and the proportion of both experimental groups and control groups. Pooled odds ratios and pooled standard mean differences (SMD), with their 95% confidence intervals (CIs) were calculated to estimate the strength of the association by using R software.

Methodological Assessment

The methodological quality of each study was assessed according to the modified Jadad scale. Methods are as follows: (1) mentioning random for 1 point, describing random methods for 2 points; (2) the narrative approach for experimental blinding for 0 points, and mentioning double-blinding for 1 point, describing the concrete double-blinding methods for 2 points; (3) describing the loss ratio of follow-up and its reasons for 1 point. Studies scoring from 3 to 5 points in the Jadad scale were considered to be of "excellent" quality, while studies scoring 1 or 2 points were of "fair" condition.

Statistical Analysis

We pooled data across studies using fixed-effect models and random-effect models. Relative ratio (RR) with 95% confidence intervals (CIs) was extrapolated as a statistical indicator of outcomes, and SMD with 95% confidence CIs were calculated for continuous data. Chi-square test (P-value < 0.1 or I^2 measure > 50%) was used to assess the heterogeneity of the data. Additionally, the D-L method was applied for correction tests.

Results

Literature research and study characteristics

The results of the article selection were described in Figure 1. The initial search from the electronic database yielded a total of 729 articles. According to the inclusion and exclusion criteria, 137 studies remained. Then 127 materials were included after screening the title and abstract. Finally, 7 publications of RCTs eligible for analysis were included. All trials covered a totally 251 patients with malignant tumors receiving CS-chemotherapy combination therapy and 208 patients receiving chemotherapeutic drugs monotherapy as controls. Table 1 provides the details of the included study characteristics.

Quality assessment

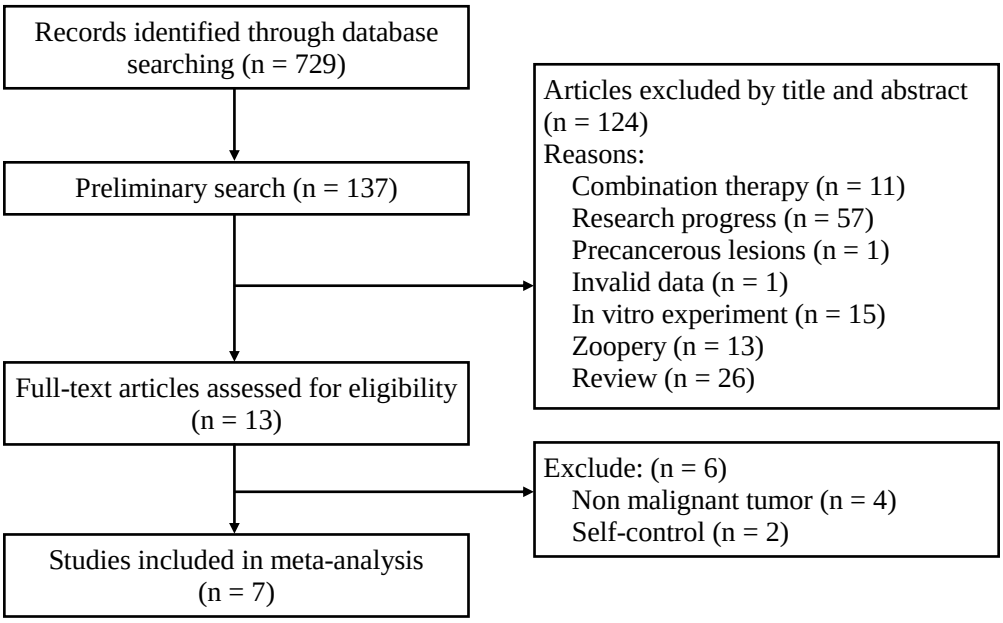

Figure 1 Flow diagram of study selection for the current meta-analysis

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Table 1 Characteristics of eligible studies and quality assessment

Author (year)	Number (T/C)	Treatment	Control	Course	*P*-value	Indicator	Jadad score
Hao L (2007) [34]	17/16	Chemotherapy + oral Cordyceps granules	only chemotherapy	9-12 w	$P > 0.05$	(2) (3)	2
Sun Y (2006) [31]	40/28	Chemotherapy + oral Cordyceps preparation	only chemotherapy	4-8 w	$P > 0.05$	(3)	3
Zou YQ (2009) [36]	30/30	Chemotherapy + oral Cordyceps preparation	only chemotherapy	4 w	$P > 0.05$	(1) (3)	2
Sun Y (2002) [32]	30/30	Chemotherapy + oral Compound CS Liquid	only chemotherapy	4 w	$P > 0.05$	(2)	3
Chen CJ (2012) [35]	50/50	Chemotherapy + oral Cordyceps preparation	only chemotherapy	NG	$P > 0.05$	(1)	3
Zhou RY (2002) [33]	50/25	Chemotherapy + oral Cordyceps granules	only chemotherapy	30 d	$P > 0.05$	(1) (2) (3)	2
Xu JZ (2002) [30]	34/29	Chemotherapy + oral Artificial cultivation of CS	only chemotherapy	6 w	$P > 0.05$	(2)	2

Note: Exegesis (1) Clinical symptoms (2) Toxic side effects (3) T-cell subset.

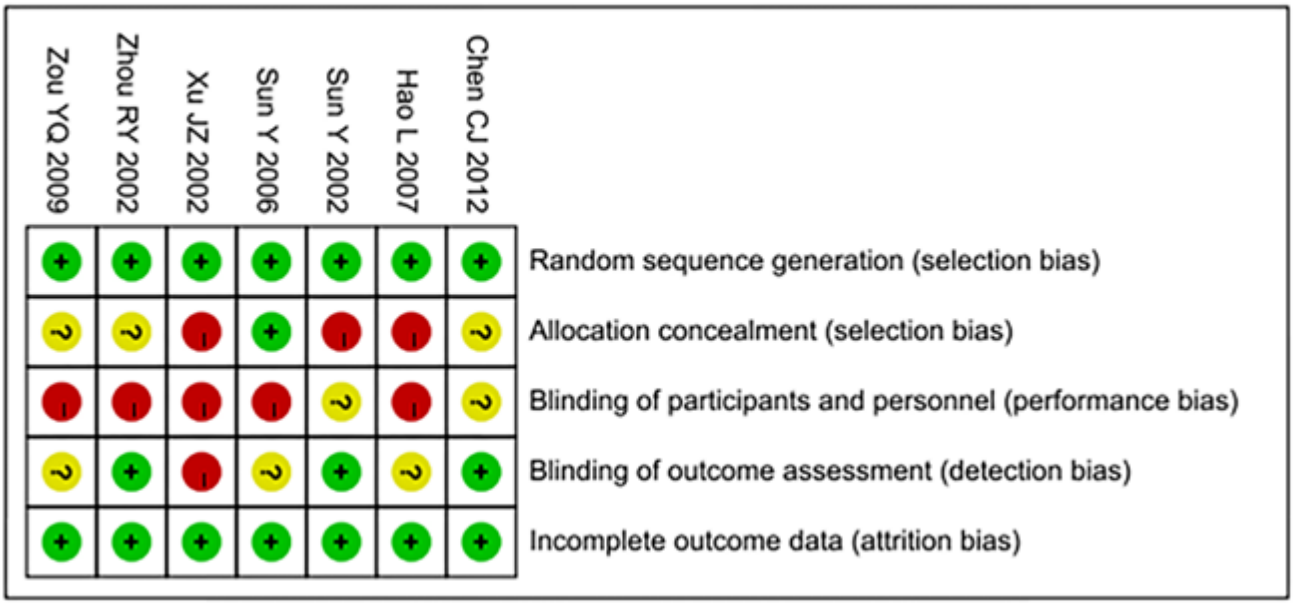

Figure 2 The assessment of the risk of bias for the included studies. Each item was described as low risk (+), high risk (-) or unclear risk (?)

We identify the risk of bias included in the study by generating the risk of bias mAPS. The charts show that the studies included in our meta-analysis generally have good methodological quality. Random sequence generation and incomplete outcome data in all reviews experienced low risk. However, blinding of participants and personnel of six studies experienced high risk and may have an impact on our research results. In
summary, the quality of the research included is right on the whole. The results of deviation risk assessment are shown in Figure 2.

Meta-analysis results

Meta-analysis of the effects of CS-chemotherapy combination therapy in the prognosis of malignant tumors compared with chemotherapeutic drugs monotherapy, including 271 treatment groups and 228 control groups, indicating a statistically significant difference. Due to $P < 0.01$, the random-effects model was utilized, while $P > 0.01$, we shifted to use the fixed-effects model.

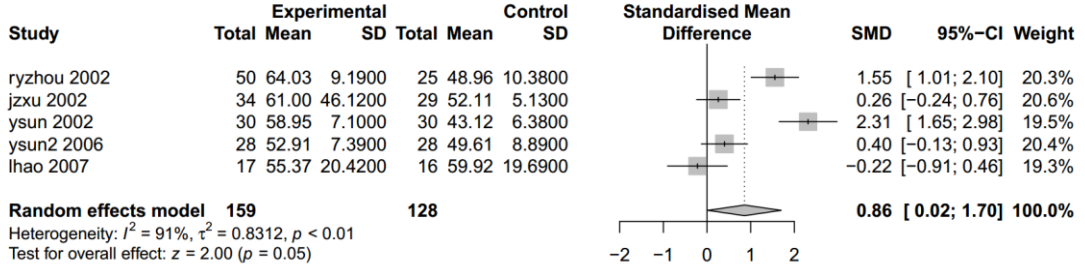

Figure 3 Forest plot of CS' effects on the amount of $CD3^+$ T cells

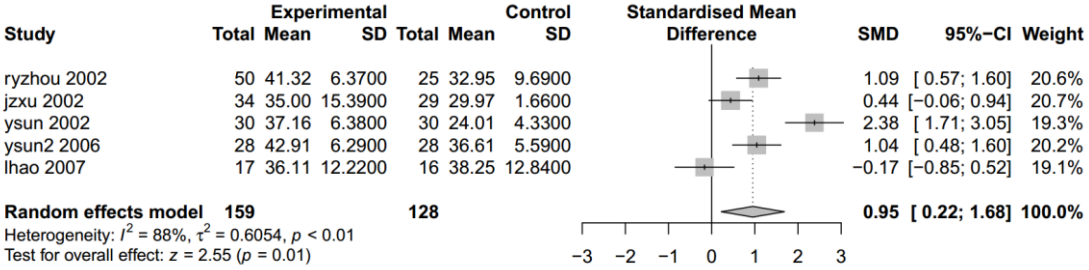

Figure 4 Forest plot of studies of CS' effects on the amount of $CD4^+$ T cells

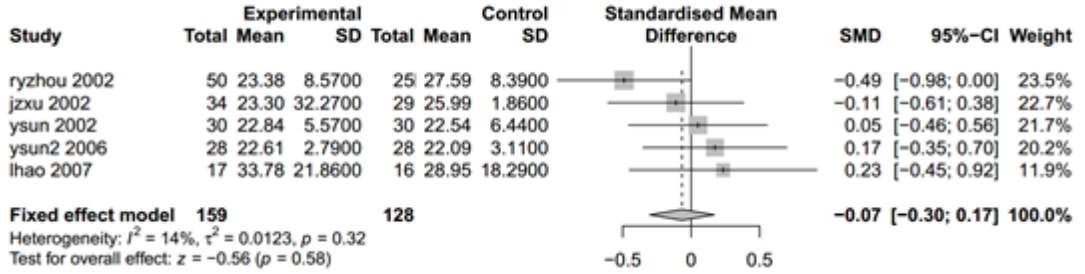

Figure 5 Forest plot of studies of CS' effects on the amount of $CD8^+$ T cells

The effects of CS on the amount of $CD3^+$ T cells Five studies containing $CD3^+$ T cells [30-34] were included totally accounted for 159 experimental groups and 128 control groups, and then the random-effects model was applied to make meta-analysis. There was heterogeneity in results (SMD = 0.86; 95% CI = 0.02, 1.70; P < 0.01, I^2 = 91%), indicating that there was an increase in the amount of $CD3^+$ T cells (Figure 3).

The effects of CS on the amount of $CD4^+$ T cells Meta-analysis of five studies containing $CD4^+$ T cells [30-34], which cover 159 experimental groups and 128 control groups showed heterogeneity in results (SMD = 0.95; 95% CI = 0.22, 1.68; P < 0.01, I^2 = 88%). Results of the random-effects model indicated that there was an obvious increase in the amount of $CD4^+$ T cells in patients receiving CS-chemotherapy (Figure 4).

The effects of CS on the amount of $CD8^+$ T cells Five studies containing $CD8^+$ T cells [30-34] were included, in which a total of 159 treatment groups and 128 control groups were covered. The results of random-effects model showed no significant statistical heterogeneity (SMD = -0.07; 95% CI = -0.30, 0.17; P = 0.32, I^2 = 14%). While fixed-effects model (RR with its 95% CI = -0.3030, 0.1691) showed there was some intersection with baseline, which means that there were no significant heterogeneities in the amount of $CD8^+$ T cells between treatment and control groups (Figure 5).

The effect of CS on the rate of $CD4^+/CD8^+$ T cells Four studies containing $CD4^+/CD8^+$ T cells [30-34] were included, covering 142 treatment groups and 112 control groups. Statistical results (SMD = 27.76; 95% CI = 25.25, 30.28; P = 0.39, I^2 = 0%) showed little heterogeneities between groups. The result of fixed-effects model (RR with its 95% CI = 25.2497, 30.2763; P < 0.01) indicated that treatment group has a higher rate in $CD4^+/CD8^+$ T cells ratio, showing a positive effect on anti-tumor reactions (Figure 6).

The effects of CS on KPS quality of patients with a malignant tumor A total of three studies containing KPS functional status score [34-36], including 96 treatment groups and 96 control groups. The statistical results (P = 0.93, I^2 = 0%) showed no significant heterogeneities between the two groups. Then the fixed-effects model was applied to calculate the (RR

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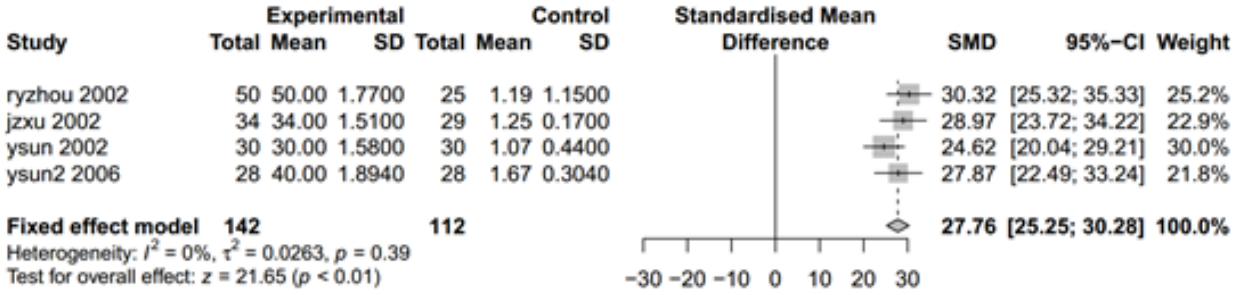

Figure 6 Forest plot of studies of CS' effects on the rate of $CD4^+/CD8^+$ T cells

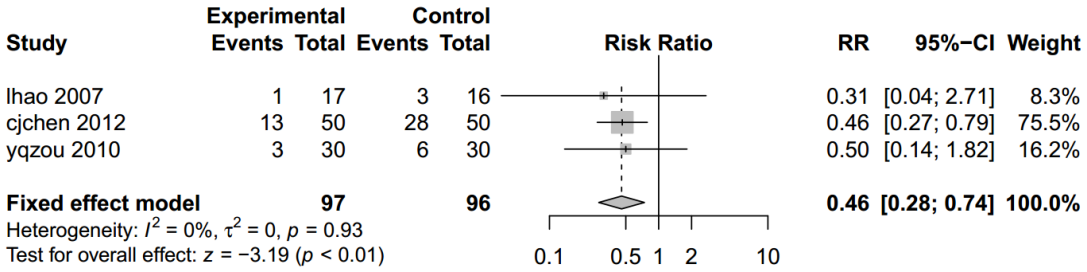

Figure 7 Forest plot of studies on KPS quality of patients with malignant tumor

and its 95% CI = 0.2780, 0.7350; P < 0.01). The result indicated that treatment groups had a less decreasing trend of KPS score than the control group. It means that CS has a positive effect on enhancing the functional recovery of patients with malignant tumors and improving their living standards (Figure 7).

Discussion

Result discussion

To the best of our knowledge, this study is the first meta-analysis with a focus on the efficacy of CS plus chemotherapeutic drugs in malignant tumors patients. In strict accordance with study selection criteria and data extraction criteria, we reviewed 7 full-texts of RCTs (including 459 patients) and analyzed the effects of Medicaments of CS on the immunity function during the prognosis process of patients with malignant tumors after chemotherapy. The pooled results exhibited that CS combined with chemotherapeutic drugs, could be a preferable treatment option for malignant tumor patients.

Although surgical treatment has made significant progress, the overall survival of malignant tumors is still not optimistic. In recent years, chemotherapy can prolong the lives of patients and improve the patients' quality of life [37]. Nevertheless, the commonly chemotherapeutic regimens often seriously impair the life quality of the patients and cause severe constraints on the use of chemotherapeutic drugs. It is urgent to seek more optimized combination chemotherapy [38]. T lymphocytes play an essential role in the immune system. Sensitized T lymphocytes have a specific killing effect on tumor cells. When the organism is in the state of tumor, infection, injuries, or affected by some medicines (e.g. chemotherapy drugs), the level of histamine in the body increases, $CD4^+$ T helper cells coordinate B cell differentiation to produce antibody. $CD8^+$ T cells could inhibit the synthesis, secretion of antibodies, and proliferation of T cells. Moreover, $CD3^+$ T cells are the total number of T lymphocytes, including $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and $CD45RO^+$ memory T cells [39]. The level or proportion of T cell subsets will cause some changes in immune function [40]. Our subgroup meta-analysis suggested that CS plus chemotherapeutic drugs could significantly increase the number of $CD3^+$ (SMD = 0.86; 95% CI = 0.02, 1.70; P < 0.01, I^2 = 91%) T cells, $CD4^+$ T cells (SMD = 0.95; 95% CI = 0.22, 1.68; P < 0.01, I^2 = 88%) and ratio of $CD4^+/CD8^+$ T cells (RR with its 95% CI = 25.2497, 30.2763; P < 0.01), which means that the regulating function of CS in immunity system includes increasing peripheral lymphocyte cells and regulating the ratio of them, thus in some way protecting patients' immunity system and accelerating the pace of prognosis.

At present, the immune system has been identified as playing an essential role in the fight against cancer. The immune system plays a vital role in the control of tumor growth as the main component of the anti-tumor immune response. The immune system exerts pressure on tumor cells but also plays an immunogenic role in the development of tumor cells [41]. Improving immune function helps the immune system suppress cancer cells and play an immunogenic role in the development of cancer cells.

To some degree, the appearances of some typical

clinical symptoms and poor immunity state in the process of chemotherapy are probably the main reasons leading to exacerbation or even death. TCM can relief this kind of harm and play an essential role in the recovery process. Owing to the fact that medicaments made of CS, such as Bailing capsule, Jinshuibao capsule et al. can directly stimulate the proliferation of T cells, and they have been confirmed positive on the enhancement of immune function by modern pharmacology. It also can prevent leukocytes and white blood cells from decreasing in cancer patients during chemotherapy and radiotherapy [30]. Polysaccharides and alkaloids from CS increase the nutritional serum volume of the spleen, the activity of immune cells, and the content of antibodies in body fluids [41]. The analysis result showed that the combination of CS and chemotherapeutic drugs slowed down the declining rate of patients' KPS score comparing with control groups, illustrating that the immune function and life quality were significantly improved in patients with malignant tumors by applying CS plus chemotherapeutic drugs treatment [35]. Therefore, we expected this analysis to build a solid basis for guiding clinical drug combinations, further improving the cure rate of malignant tumors, optimizing patients' living standards, and prolonging their life spans.

Limitations

The eligibility citations and RCTs we included is in a small sample size of average quality, though we searched databases comprehensively, all the included articles relating to CS combined with chemotherapeutic drugs versus chemotherapeutic drugs monotherapy for malignant tumors were only found in China, and most of them lacked analysis on adjusting for baseline factors and other differences that exist between studies, indicating that publication bias might exist. Also, it remains a problem on how to perform systematical analysis among different survival scoring charts, which is conducive to evaluate the life quality of patients with malignant tumors comprehensively and objectively, improve the authenticity and dependability of data as well. In conclusion, this conclusion still needs to be verified by further prospective large sample, multicenter, high-quality RCTs.

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