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Review Article

Does the Couse of Astragalus-Containing Chinese Herbal Prescriptions and Radiotherapy Benefit to Non-Small-Cell Lung Cancer Treatment: A Meta-Analysis of Randomized Trials

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Background. Radiotherapy has been widely used for non-small-cell lung cancer (NSCLC), while its low efficacy and high toxicity raise big concerns. Astragalus (as a monarch drug)-containing Chinese herbal prescriptions and radiotherapy were frequently coused for NSCLC in China; however, the effects were not systematically analyzed. *Objective.* To evaluate the benefits of Astragalus-containing Chinese herbal prescriptions combined with radiotherapy for NSCLC. *Methods.* The randomized controlled trials involving NSCLC treatment with Astragalus-containing Chinese herbal prescriptions combined with radiotherapy were searched. The Review Manager 5.1 software was employed for data analysis. Funnel plot and Egger's test were applied to evaluate publication bias. *Results.* 29 eligible studies met our criteria. Of the studies, 8, 6, and 4 reported reduced risk of death at one year, two years, and three years, respectively. 26 studies revealed amended tumor response. Six studies showed improved Karnofsky performance status. Among the studies, 14 and 18 displayed a lowered white blood cells (WBC) toxicity and an ameliorated radiation pneumonia, respectively. *Conclusion.* Couse of Astragalus-containing Chinese herbal prescriptions and radiotherapy may benefit the patients with NSCLC via increasing the therapeutic effectiveness and reducing the toxicity of radiotherapy. To confirm the exact merits, further rigorously designed trials are warranted.

1. Introduction

It is estimated that 228,190 new cases of lung cancer are expected in 2013 and account for about 14% of cancer diagnoses [1]. As the leading cause of cancer death worldwide, lung cancer is guesstimated to occupy 26% of all female cancer deaths and 28% of all male cancer deaths in 2013 [2]. In China, the registered lung cancer mortality increased by 464.84% during the past 3 decades, and the crude mortality rates in 2008 were 47.51 per 100,000 men and 22.69 per 100,000 women [3]. Approximately eighty-five percent of all lung cancer occurrences are non-small-cell lung cancer (NSCLC) [4].

Radiotherapy, as a main therapeutic tool, has been widely used for NSCLC. It can be offered as adjunct for operable patients with resectable diseases, the primary local treatment for patients with medically or unresectable diseases, and an important palliative modality for patients with incurable diseases. Conventional radiotherapy has been used for the inoperable patients, but its outcomes were poor, with 5-year overall survival rates of only 15%–24% [5]. With the aid of advances in physics and computer technology, radiation delivery systems have been greatly improved, such as intensity-modulated radiation therapy, stereotactic radiation therapy, and particle therapy have been successfully used. Compared with previous methods, these new technologies can deliver even higher doses precisely to the tumor while minimizing doses to normal tissues, which leads to better tumor control with less toxicity [6]. Despite technological advances, radiotherapy for NSCLC still faces shortages of low efficacy and high toxicity; some patients even can not continue treatment due to serious adverse reactions.

In complementary and alternative medicines, Chinese herbal medicine has become increasingly popular for cancers patients undergoing radiotherapy or chemotherapy. A systematic review has showed that Chinese herbal medicine as an adjuvant therapy can reduce chemotherapy toxicity, prolong survival rate, enhance immediate tumor response, and improve Karnofsky performance score in advanced NSCLC patients [7]. Studies have indicated that traditional Chinese medicines have the potential to be effective systemic radiosensitizers that may be used to amplify radiation-induced toxicity on tumor tissues [8]. Furthermore, certain traditional Chinese medicine herbs may be used as radioprotectors that are able to ameliorate radiation-induced toxicity in normal tissues in cancer patients undergoing radiotherapy [9].

Particularly, the Astragalus-containing Chinese herbal prescriptions are frequently combined with radiotherapy for lung cancer in clinic. Astragali Radix (Astragalus, Chinese name, Huangqi) sourced from medicinal plants *Astragalus membranaceus* and *Astragalus membranaceus* var. *mongholicus* (Leguminosae) has been listed in Chinese pharmacopoeia [10]. As an important herbal drug, Astragalus has been commonly used in Chinese traditional medicine for a long time, and also a variety of biological activities have been reported. Tin et al. have discovered that the total saponins obtained from Astragalus possessed significant antitumorigenic activity in HT-29 human colon cancer cells and tumor xenograft [11]. Study has shown that Astragalus exerted anticarcinogenic activity in colon cancer cells through the modulation of mTOR signaling and downregulation of COX-2, which together reduced VEGF level in tumor cells that could potentially suppress angiogenesis [12]. Cho and coworker have found that Astragalus root extracts could markedly enhance the tumoricidal activity of the peritoneal macrophages, act as a priming agent for the TNF production in tumor-bearing mice partially, restore the depressed immune functions in tumor-bearing mice in vivo, and induce the generation of cytotoxic cells against tumors in vitro [13]. What is more, it has been discovered that Astragalus root extracts also they could increase the IFN-β inducing activity of lactobacillus acidophilus in dendritic cells, which may exert immune-enhancing activity [14]. In clinical practice and most published trials, however, Astragalus usually combined with other herbal medicines as prescriptions, rarely as single-agent. Jinfukang, an oral liquid formulation, is one of the Astragalus-containing herbal preparations and has been approved by China Food and Drug Administration for the treatment of NSCLC. Meta-analysis has shown that Astragalus-based herbal formulas may increase effectiveness and reduce side effects of platinum-based chemotherapy when combined with chemotherapy [15].

There are a large number of published trials of Astragalus-containing Chinese herbal prescriptions, which are constituted in different forms, such as oral administration and intravenous injection, combined with radiotherapy for the treatment of NSCLC. However, the evidence for the effects of Astragalus-containing Chinese herbal prescriptions has not been systematically assessed. In the present study, a comprehensive systematic review is conducted on the efficacy of Astragalus-containing Chinese herbal prescriptions combined with radiotherapy for NSCLC.

2. Methods

2.1. Data Sources and Search Strategies. The literature searches were conducted in PubMed, EMbase, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database (Wanfang), and Chinese Biomedical Literature Database (CBM). All of those searches ended on May 20, 2013.

The following terms were retrieved in databases as keywords or free-text terms: "non-small-cell lung cancer," "radiotherapy," "Chinese herbal medicine," "*Astragalus membranaceus,*" and "randomized controlled trials" (and multiple synonyms for each term). The bibliographies of the included studies were searched for additional references. No restrictions were placed on the publication language. Two reviewers (Hailang He and Qian Wang) independently identified studies.

2.2. Inclusion Criteria. Studies included in the meta-analysis had to meet all of the following criteria. (1) Participants: NSCLC patients had to be diagnosed by pathological sections and were treated by radiotherapy. (2) Type of studies: only clinical randomized controlled trials (RCTs) were eligible. (3) Type of intervention: studies provided the treatment group with Astragalus-containing Chinese herbal prescriptions in combination with radiotherapy and the control group with radiotherapy alone were included for analysis. (4) Type of outcome measurements: overall survival rate, tumor response, and performance status were the main outcome measurements; other outcome measurements included reduction in the toxicity of radiotherapy, such as the inhibition of white blood cells and radiation pneumonitis, were also considered.

2.3. Data Extraction and Quality Assessment. The detailed method followed the reported one [16]. Two reviewers (Hailang He and Qian Wang) independently extracted data. The extracted data included authors, title of study, year of publication, study size, age and sex of the participants, details of methodological information, name and component of Chinese herbs, treatment process, details of the interventions, outcomes, and adverse effects for each study. Any disagreements were resolved by consensus or by a third reviewer (Xianmei Zhou).

Methodological quality of RCTs was assessed independently by two review authors (Hailang He and Qian Wang) with the criteria in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [17]. Sequence generation, allocation concealment, blinding (or masking), incomplete data assessment, selective outcome reporting, and other sources of bias were assessed with three potential responses: yes, no, and unclear. Disagreements between review authors were resolved by discussion or with the third author (Xianmei Zhou).

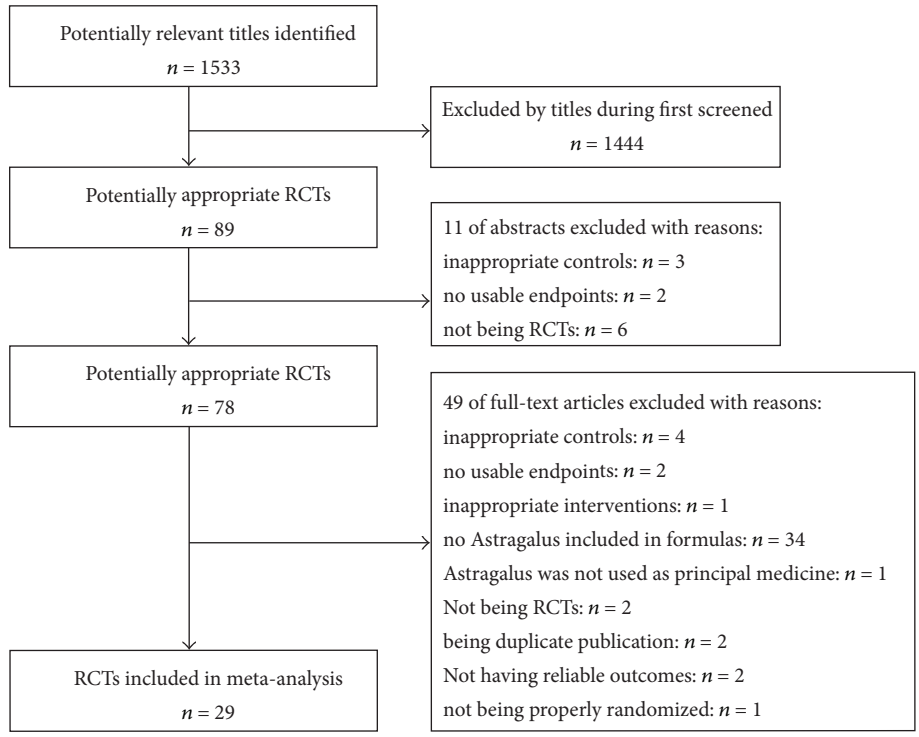


Figure 1: Flow diagram showing the trial selection process for the systematic review .

2.4. Outcome Measures. The risk ratios of death at one, two, and three years were calculated as the proportion that died in the Astragalus-containing Chinese herbal prescriptions plus radiotherapy group divided by this proportion in the radiotherapy alone group. Tumor response was calculated as the number of patients with complete response (CR) plus partial response (PR) based on the WHO scale [18] divided by the total number of patients in each treatment group. The performance status of patients was investigated based on the Karnofsky performance score (KPS) [19], and the improved performance status was calculated as the number of patients with improved performance status (>10-point increase) divided by the total. Radiotherapy toxicity was investigated based on the WHO scale [18]; the reduction of radiotherapy toxicity was calculated as the number of patients with any toxicity (WHO grades 1 2 3 4) divided by the total number of patients in each treatment group (WHO grades 0 1 2 3 4).

2.5. Data Analysis. The Review Manager 5.1 software (http://www.cochrane.org/) was employed for data analysis. The effect data is expressed as relative risk (RR) with 95% confidence interval (CI). If the heterogeneity exists in pooled studies ($I^2 > 50\%$), a random model was applied; otherwise, the fix model was applied. Statistical significant difference was considered as $P < 0.05$. Funnel plot was applied to evaluate the potential publication bias if at least ten trials were available for a meta-analysis [17]. Egger's test was further conducted to evaluate funnel plot asymmetry with STATA 12.1 software.

3. Results

3.1. Description of Studies. After primary search of titles and abstracts from the 6 databases, 1533 trials were screened out from electronic and manual searches as shown in Figure 1, of which 89 were identified as requiring relevant abstracts retrieval. Close reviewing of the 89 abstracts excluded 11 because of inappropriate controls ($n = 3$), no usable endpoints ($n = 2$), and not being RCTs ($n = 6$). 78 Full-text articles were further reviewed for eligibility. 49 Articles were excluded due to inappropriate controls ($n = 4$), having no usable endpoints ($n = 2$), inappropriate interventions ($n = 1$), having no Astragalus included in formulas ($n = 34$), having no Astragalus used as principal medicine ($n = 1$), not being RCTs ($n = 2$), being duplicate publication ($n = 2$), not having reliable outcomes ($n = 2$), and not properly randomized ($n = 1$). Thus, the total of 29 eligible studies were accepted for the current meta-analysis.

A total of 2547 participants were involved in the 29 studies, at which 1,298 patients participated in radiotherapy combined with Astragalus-containing Chinese herbal prescriptions (1 patients dropped out) and 1,241 in radiotherapy alone (7 patients dropped out). All of these studies were conducted in China. The baseline including age, gender, histopathology, and TNM stage of all studies was comparable.

3.2. Characteristics of the Eligible Studies. Table 1 shows characteristics of the eligible studies. As shown, all of the studies were conducted in China and published between 2002 and 2013 in Chinese journals. The stages of NSCLC

Table 1: Characteristics of the eligible studies.

Study	No.	Stage	Protocol*	Herbal ingredients	Dose of RT	Duration (week)
Cai et al., 2002 [30]	92	III	CRT + AP	Astragalus, Codonopsis Radix, Poria, Alismatis Rhizoma, Ophiopogonis Radix, Schisandra Chinensis Fructus, Eriobotryae Folium, Rehmanniae Radix Praeparata, Corni Fructus, Cyperi Rhizoma, and Glycyrrhizae Radix et Rhizome.	60–70 Gy	6-7
Nin et al., 2002 [47]	72	NR	CRT + AP	Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Astragalus, Poria, Lycii Fructus, Lilii Bulbus, Coicis Semen, Armeniacae Semen Amarum, and Chuanxiong Rhizoma.	55–65 Gy (2 Gy/f)	5–7
Lan and Jiang, 2002 [35]	47	III-IV	CRT + AP	Manis Squama, Glehniae Radix, Corni Fructus, Astragalus, Fritillariae Cirrhosae Bulbus, Ophiopogonis Radix, Polygoni Multiflori Radix, Rehmanniae Radix Preparata, Dioscoreae Rhizoma, Alismatis Rhizoma, and Glycyrrhizae Radix et Rhizome.	60 Gy	6
Wu, 2003 [25]	50	IIb-III	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis senticosi Radix et Rhizoma Seu Caulis.	60–70 Gy (2 Gy/f)	6-7
Wen, 2005 [26]	64	II-III	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis senticosi Radix et Rhizoma Seu Caulis.	60–70 Gy (1.8–2.0 Gy/f)	6-7
Huang et al., 2005 [29]	62	II–IV	CRT + AP	Astragalus, Atractylodis Macrocephalae Rhizoma, Pseudostellariae Radix, Lycii Fructus, Spatholobi Caulis, Carthami Flos, Sappan Lignum, Lonicerae Japonicae Flos, Galli Gigerii Endothelium Corneum, Dendrobii Caulis, Glehniae Radix, and Poria.	61–66 Gy	NR
Wang et al., 2006 [31]	85	III	CRT + AP	Astragalus, Pseudostellariae Radix, Angelicae Sinensis Radix, Scutellariae Barbatae Herba, Coicis Semen, Glycyrrhizae Radix et Rhizoma, Paeoniae Radix Alba, Rehmanniae Radix Preparata, Lilii Bulbus, Ophiopogonis Radix, Scrophulariae Radix, Fritillariae Cirrhosae Bulbus, and Platycodonis Radix.	70 Gy (2 Gy/f)	7
Chen and Wang, 2006 [36]	100	III-IV	CRT + KAI	Ginseng Radix et Rhizoma, Astragalus, and Sophorae Flavescentis Radix.	65–70 Gy (2 Gy/f)	6.5–7
Ma, 2006 [37]	69	III-IV	CRT + KAI	Ginseng Radix et Rhizoma, Astragalus, and Sophorae Flavescentis Radix.	65~70 Gy (2 Gy/f)	6.5–7
Zhang et al., 2006 [32]	69	III	3D-CRT + AP	Pseudostellariae Radix, Glehniae Radix, Coicis Semen, Ophiopogonis Radix, Asparagi Radix, Astragalus, Lycii Fructus, Angelicae Sinensis Radix, Schisandra Chinensis Fructus, Schisandra Chinensis Fructus, Hedyotis Herba, Glycyrrhizae Radix et Rhizoma, Lonicerae Japonicae Flos, Atractylodis Macrocephalae Rhizoma, Moutan Cortex, Rehmanniae Radix Praeparata, Codonopsis Radix, and Poria.	56–62 Gy (4-5 Gy/f)	3–5
Tian and Wang, 2007 [38]	75	III-IV	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis Senticosi Radix et Rhizoma Seu Caulis.	60 Gy (1.8–2.0 Gy/f)	6
Wang et al., 2007 [39]	100	III-IV	CRT & 3D-CRT + SQFZI	Codonopsis Radix and Astragalus.	60–70 Gy (2 Gy/f)	6-7

Table 1: Continued.

Study	No.	Stage	Protocol*	Herbal ingredients	Dose of RT	Duration (week)
Song et al., 2007 [20]	167	I–IV	CRT + AP	Manis Squama, Glehniae Radix, Alismatis Rhizoma, Fritillariae Cirrhosae Bulbus, Astragalus, Corni Fructus, Ophiopogonis Radix, Polygoni Multiflori Radix, Scrophulariae Radix, Rehmanniae Radix Praeparata, Glycyrrhizae Radix et Rhizoma, and Dioscoreae Rhizome.	60–70 Gy (2 Gy/f)	6-7
Jiang and Xu, 2008 [40]	60	III-IV	CRT + DLSI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Bufonis Venenum.	60–70 Gy (1.8–2.0 Gy/f)	6-7
Fu et al., 2008 [48]	148	NR	CRT + ZQFZC	Astragalus and Angelicae sinensis Radix.	60–70 Gy (2 Gy/f)	6-7
Huang and Hou, 2008 [21]	67	I–IV	3D-CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis senticosi Radix et Rhizoma Seu Caulis.	45–55 Gy (5-6 Gy/f)	3-4
Xie et al., 2009 [41]	97	III-IV	3D-CRT + SQFZI	Codonopsis Radix and Astragalus.	60–70 Gy	6-7
Liu et al., 2009 [42]	56	III-IV	CRT + AP	Ganoderma, Hedyotis Herba, Chuanxiong Rhizoma, Stephaniae Tetrandrae Radix, and Astragalus.	64–88 Gy (2 Gy/f)	6–9
Wang et al., 2009 [43]	42	III-IV	3D-CRT + SQFZI	Codonopsis Radix and Astragalus.	70 Gy (2 Gy/f)	7
Qin et al., 2009 [22]	80	I–IV	3D-CRT + APS	Astragalus Polysaccharide.	50–70 Gy (2 Gy/f)	5–7
Jia et al., 2010 [27]	64	IIb-III	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis Senticosi Radix et Rhizoma Seu Caulis.	60–70 Gy (2 Gy/f)	NR
Ji et al., 2011 [44]	162	III-IV	CRT + AP	Codonopsis Radix, Chuanxiong Rhizoma, Atractylodis Macrocephalae Rhizoma, Astragalus, and Rehmanniae Radix Praeparata.	60–70 Gy (2 Gy/f)	6
Zhao et al., 2011 [33]	90	III	SBRT + AP	Astragalus, Atractylodis Macrocephalae Rhizoma, Poria, Rehmanniae Radix, Chuanxiong Rhizoma, Ginseng Radix et Rhizoma, Angelicae Sinensis Radix, Glycyrrhizae Radix et Rhizoma, and Paeoniae Radix Alba.	60–70 Gy (2-3 Gy/f)	5-6
Gao et al., 2012 [23]	158	I–IV	3D-CRT + AP	Ginseng Radix et Rhizoma, Astragalus, Angelicae sinensis Radix, Gastrodiae Rhizoma, Rehmanniae Radix Preparata, Alismatis Rhizoma, Cassiae Semen, Cervi Cornu, Asari Radix et Rhizoma, Lycii Fructus, and Cuscutae Semen.	60–66 Gy (1.8 Gy/f)	6–6.6
Mu et al., 2012 [45]	70	III-IV	CRT & 3D-CRT + SQFZI	Codonopsis Radix and Astragalus.	60–70 Gy	6-7
Wang et al., 2012 [46]	100	III-IV	3D-CRT + KAI	Ginseng Radix et Rhizoma, Astragalus, and Sophorae Flavescentis Radix.	60–70 Gy (2 Gy/fr)	6-7
Cai et al., 2012 [24]	89	I–IV	3D-CRT + AP	Astragalus, Pseudostellariae Radix, Hedyotis Herba, Schisandra Chinensis fructus, Ophiopogonis Radix, Mori Cortex, Armeniacae Semen Amarum, Pinelliae Rhizoma, Trichosanthis Pericarpium, Curcumae Radix, Eriobotryae Folium, and Citri Reticulatae Pericarpium.	60–70 Gy	6-7
Li et al., 2013 [34]	120	III	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis Senticosi Radix et Rhizoma Seu Caulis.	60–70 Gy (2 Gy/f)	6-7

Table 1: Continued.

Study	No.	Stage	Protocol*	Herbal ingredients	Dose of RT	Duration (week)
Yang, 2013 [28]	92	II-III	CRT + ADI	Ginseng Radix et Rhizoma, Astragalus, Mylabris, and Acanthopanacis Senticosi Radix et Rhizoma Seu Caulis.	60–70 Gy (2 Gy/f)	6-7

Abbreviations—No.: number of participants; RT: radiotherapy; AP: Astragalus prescription; CRT: conventional radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; SBRT: stereotactic radiation therapy; ADI: Aidi injection; KAI: Kangai injection; SQFZI: Shenqi fuzheng injection; DLSI: Delisheng injection; ZQFZC: Zhenqifuzheng capsules; APS: Astragalus polysaccharide; f: fraction; NR: not reported.
*Treatment group intervention.

TNM of the patients recruited in the current studies were as follows: 5 studies [20–24] were at I to IV but mentioned ambiguously; 4 [25–28], 1 [29], 5 [30–34], and 12 [35–46] studies were at II to III, II to IV, III, and III to IV, respectively. The other 2 studies [47, 48] did not mention the stage condition. 18 Studies [20, 25–31, 34–38, 42, 44, 47, 48] used the conventional radiotherapy; three-dimensional conformal radiotherapy was applied in 8 studies [21–24, 32, 41, 43, 46]; 2 studies [39, 45] employed conventional radiotherapy combined with three-dimensional conformal radiotherapy; and 1 study [33] adopted stereotactic radiation therapy. The dose of radiation therapy varied from 45 to 70 Gy in the included studies. Of all Astragalus-containing Chinese herbal prescriptions, the oral Astragalus prescriptions were used in 12 studies [20, 23, 24, 29–33, 35, 42, 44, 47] and Aidi injection [21, 25–28, 34, 38], Kangai Injection [36, 37, 46], Shenqifuzheng injection [39, 41, 43, 45] and Delisheng injection [40] were used in 7, 3, 4, and 1 studies, respectively. Astragalus polysaccharide injection was involved in 1 study [22] and 1 study [48] took Zhenqifuzheng capsules. The durations of the treatments varied from 3 to 9 weeks in the included studies.

3.3. Risk of Bias in Included Studies. The risk of bias of each study was assessed by the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. Of all the involved studies that claimed randomization, only 5 provided the specific information on the randomization method. None used a central randomization procedure to ensure concealment of treatment allocation. No trials mentioned the blinding procedures. Of all the trials, only 5 mentioned drop-out data, of which 3 considered the patients who dropped out of the study as the treatment failure (death). This is similar to an intention-to-treat analysis [49]. In general, all of 29 RCTs have an unclear risk of bias.

3.4. Outcome Measures

3.4.1. Survival Status. As shown in Figure 2, 8 studies [20, 23, 25, 31, 32, 34, 35, 37] including 753 patients observed the one-year survival. As the 8 trials did not show homogeneity (chi-square = 34.75, $I^2 = 80\%$, $P < 0.0001$), the random-effects model was used for statistical analysis. The combined effects showed that the patients receiving Astragalus-containing Chinese herbal prescriptions plus radiation therapy had significantly lower risk of death at one year when compared with the radiotherapy alone group (RR 0.53; 95% CI, 0.34 to 0.83).

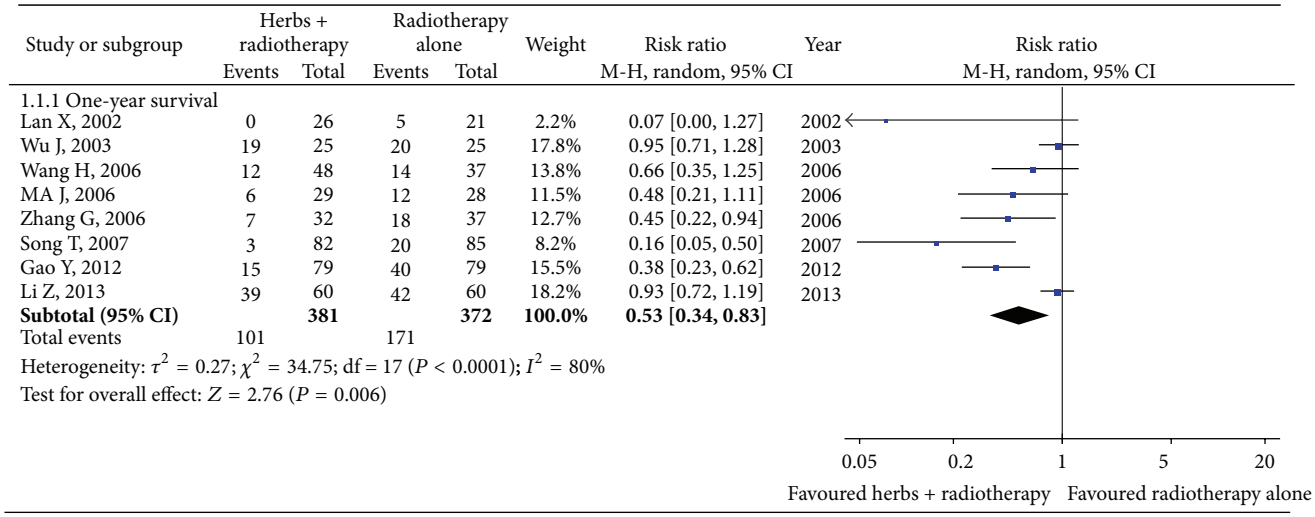
Six trials (Figure 2) including 583 patients exhibited the two-year survival [20, 23, 31, 32, 35, 37]. Due to the homogeneity of the trials (chi-square = 8.97, $I^2 = 44\%$, $P = 0.11$), fixed-effects model was used for the analysis. The results revealed that the patients with the combination treatment of Astragalus-containing Chinese herbal prescriptions and radiation therapy showed significantly lower risk of death at two years compared with the radiotherapy alone group (RR 0.67; 95% CI, 0.58 to 0.77).

The same result was also observed in 4 studies [20, 31, 35, 37] including 356 patients (Figure 2, fixed-effects model was used). The combination treatment displayed significantly lower risk of death at three years (RR 0.76; 95% CI, 0.67 to 0.87).

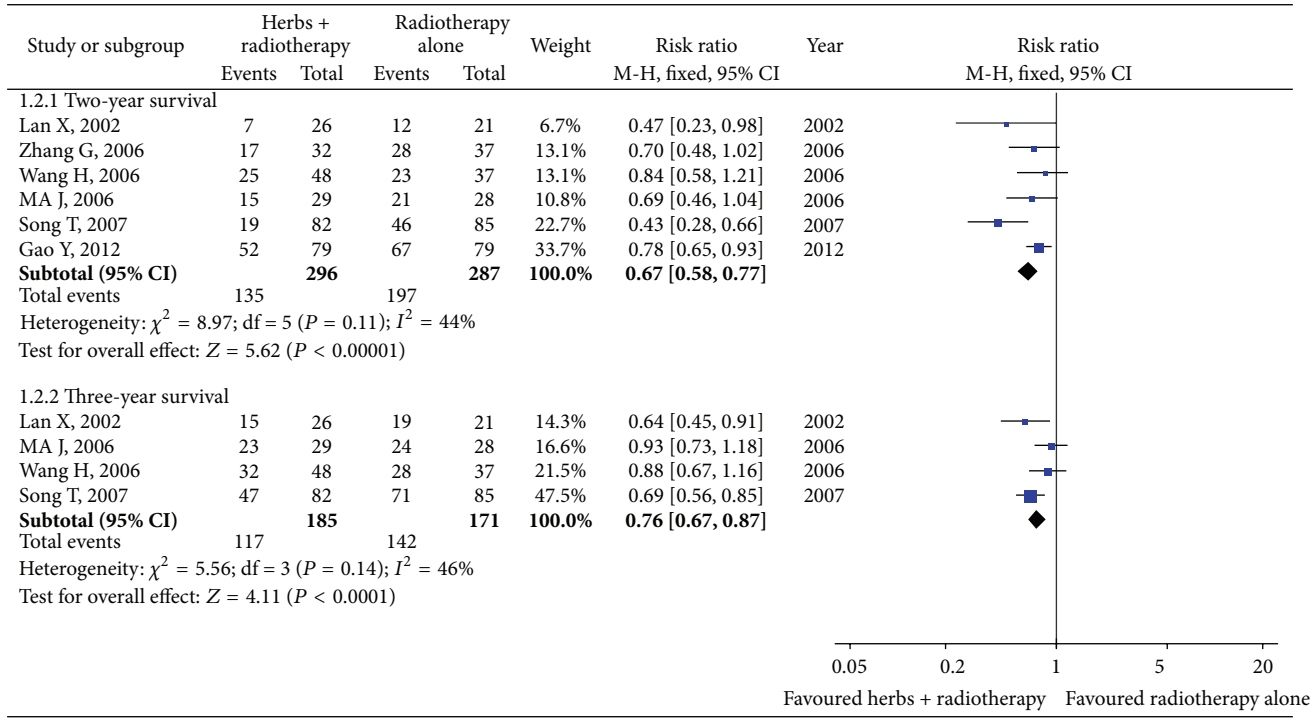
Due to the small number of studies in the survival status analysis, funnel plots were not used to assess the risk of publication bias.

3.4.2. Tumor Response. 26 Studies [20–23, 25–29, 32–48] including 2,273 patients that reported the tumor response were identified (Figure 3). The analytical results with fixed-effects model (homogeneity, chi-square = 30.42, $I^2 = 18\%$, $P = 0.21$) demonstrated that the combination treatment of Astragalus-containing Chinese herbal prescriptions and radiation therapy was associated with a significant increase in the number of patients reported complete and partial response when compared with the radiotherapy alone group (RR 1.34; 95% CI, 1.26 to 1.44). The symmetry of the funnel plot was not clear (Figure 4). Egger's test indicated that the effect of publication bias was significant ($t = 3.35$, 95% CI, 0.74 to 3.11, $P = 0.003$).

3.4.3. Performance Status. As can be seen in Figure 5, 6 studies [23, 36, 37, 40, 44, 45] including 615 patients that reported the performance status about the improvement of KPS (ten-point cutoff) were involved. The 6 trials showed homogeneity (chi-square = 5.58, $I^2 = 10\%$, $P = 0.35$), and fixed-effects model was used. The combination treatment with Astragalus-containing Chinese herbal prescriptions plus radiation therapy significantly improved the performance status when compared with the radiotherapy alone group (RR 1.66; 95% CI, 1.36 to 2.01). The number of studies reporting performance status was less than ten, so a funnel plot was not applicable.



(a)



(b)

Figure 2: One-year, two-year, and three-year survivals with Astragalus-containing Chinese herbal prescriptions and radiotherapy versus radiotherapy alone.

3.4.4. Reduction in Radiotherapy Toxicity. The radiation pneumonia is one of the main side effects that radiation therapy resulted in. We identified 18 studies [23, 24, 26, 28–32, 34, 37, 38, 41, 43–46, 48] including 1,675 patients with the radiation pneumonia (Figure 6). The statistical analysis with random-effects model revealed that Astragalus-containing Chinese herbal prescriptions plus radiation therapy had a significant decrement in radiation pneumonia when compared with the radiotherapy alone group (RR 0.47; 95% CI, 0.36 to 0.61). The funnel plot revealed an asymmetrical distribution of studies around the line of identity, indicating the possibility of publication bias (Figure 7). Egger's test showed that the effect of publication bias was significant ($t = -3.74$, 95% CI, −2.83 to −0.78, $P = 0.002$).

As mentioned above, the toxicity is a severe problem that radiotherapy is facing. As can be seen in Figure 6, 14 studies [23, 24, 28–30, 32, 34, 38–41, 44, 46, 48] including 1,427 patients reported the WBC toxicity. The results demonstrated that Astragalus-containing Chinese herbal prescriptions plus radiation therapy possessed a significant reduction in WBC

Study or subgroup	Herbs + radiotherapy Events	Total	Radiotherapy alone Events	Total	Weight	Risk ratio M-H, fixed, 95% CI	Year
1.3.1 Tumor response							
Lan X, 2002	15	26	14	21	2.6%	0.87 [0.55, 1.35]	2002
Nin Y, 2002	15	34	7	38	1.1%	2.39 [1.11, 5.17]	2002
Wu J, 2003	18	25	10	25	1.7%	1.80 [1.05, 3.08]	2003
Wen X, 2005	23	32	13	28	2.4%	1.55 [0.98, 2.44]	2005
Huang J, 2005	28	32	22	30	3.9%	1.19 [0.93, 1.54]	2005
MA J, 2006	23	33	13	32	2.3%	1.72 [1.07, 2.76]	2006
Chen F, 2006	34	50	20	50	3.4%	1.70 [1.15, 2.51]	2006
Zhang G, 2006	29	32	29	37	4.6%	1.16 [0.94, 1.42]	2006
Wang T, 2007	41	50	27	50	4.6%	1.52 [1.14, 2.02]	2007
Tian YP, 2007	29	38	14	37	2.4%	2.02 [1.29, 3.16]	2007
Song T, 2007	51	82	50	85	8.4%	1.06 [0.83, 1.35]	2007
Jiang M, 2008	20	30	12	30	2.0%	1.67 [1.00, 2.76]	2008
Fu T, 2008	29	74	27	74	4.6%	1.07 [0.71, 1.62]	2008
Huang Z, 2008	31	35	21	32	3.7%	1.35 [1.02, 1.78]	2008
Wang Y, 2009	18	21	14	21	2.4%	1.29 [0.91, 1.82]	2009
Xie Y, 2009	30	46	26	51	4.2%	1.28 [0.91, 1.80]	2009
Liu Y, 2009	15	28	7	28	1.2%	2.14 [1.03, 4.44]	2009
Qin H, 2009	35	40	29	40	5.0%	1.21 [0.96, 1.51]	2009
Jia Y, 2010	24	33	15	31	2.6%	1.50 [0.99, 2.29]	2010
Zhao G, 2011	32	60	16	30	3.6%	1.00 [0.66, 1.51]	2011
Ji Y, 2011	58	83	48	79	8.4%	1.15 [0.92, 1.44]	2011
Wang H, 2012	41	50	27	50	4.6%	1.52 [1.14, 2.02]	2012
Gao Y, 2012	57	79	45	79	7.7%	1.27 [1.00, 1.60]	2012
Mu Y, 2012	24	35	17	35	2.9%	1.41 [0.94, 2.12]	2012
Li Z, 2013	42	60	31	60	5.3%	1.35 [1.01, 1.82]	2013
Yang Z, 2013	38	46	25	46	4.3%	1.52 [1.13, 2.04]	2013
Subtotal (95% CI)		**1154**		**1119**	**100.0%**	**1.34 [1.26, 1.44]**	
Total events	800		579				

Heterogeneity: $\chi^2 = 30.42$; df = 25 ($P = 0.21$); $I^2 = 18\%$

Test for overall effect: $Z = 8.68$ ($P < 0.00001$)

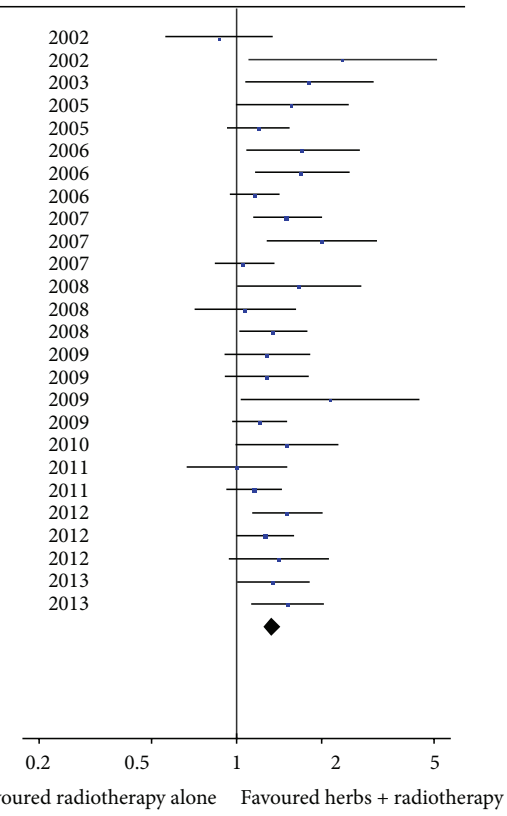


Figure 3: Tumor response with Astragalus-containing Chinese herbal prescriptions and radiotherapy versus radiotherapy alone.

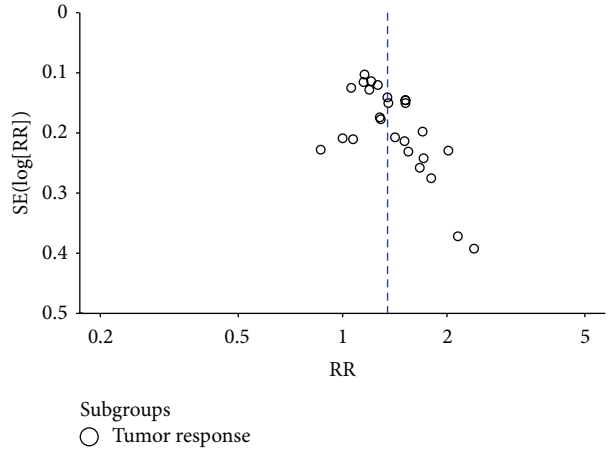


Figure 4: Funnel plot of studies testing for tumor response.

toxicity when compared with the radiotherapy alone group (RR 0.49; 95% CI, 0.38 to 0.63). The funnel plot revealed an asymmetrical distribution of studies around the line of identity, indicating the possibility of publication bias (Figure 8). Egger's test indicated that the effect of publication bias was significant ($t = -4.66$, 95% CI, −2.93 to −1.06, $P = 0.001$).

4. Discussion

In the present meta-analysis, 29 studies with 2,547 individuals suffering from NSCLC were selected out. The main findings revealed that combining radiotherapy with Astragalus-containing Chinese herbal prescriptions in the treatment of NSCLC may increase survival, tumor response, and

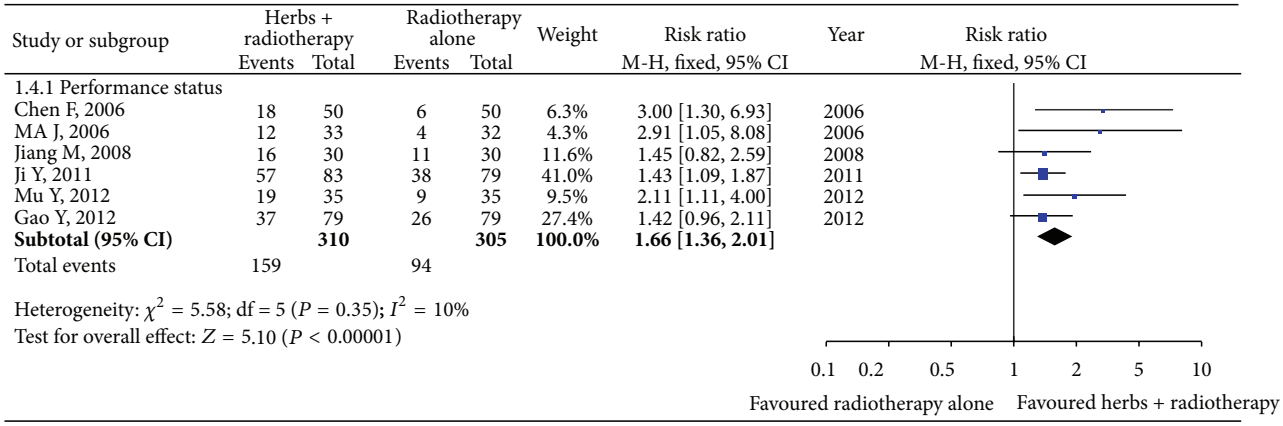


Figure 5: Improved Karnofsky performance status with Astragalus-containing Chinese herbal prescriptions and radiotherapy versus radiotherapy alone.

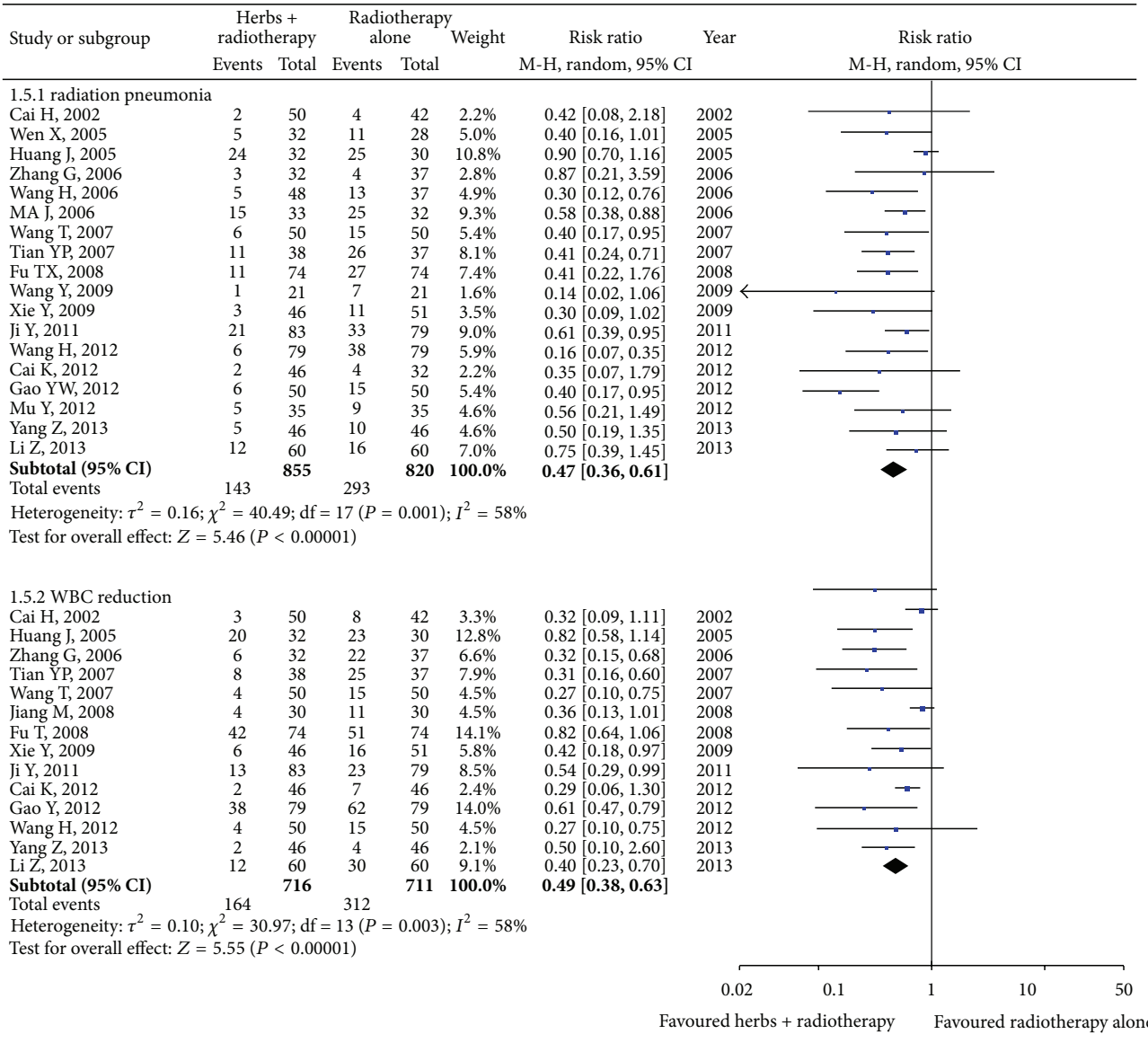


Figure 6: Radiation pneumonia and WBC reduction with Astragalus-containing Chinese herbal prescriptions and radiotherapy versus radiotherapy alone.

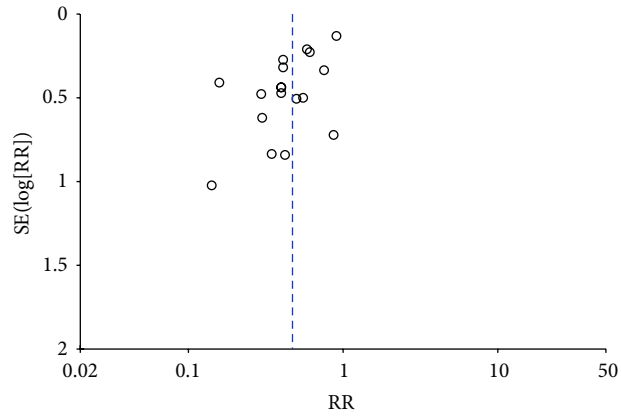


Figure 7: Funnel plot of studies testing for radiation pneumonia.

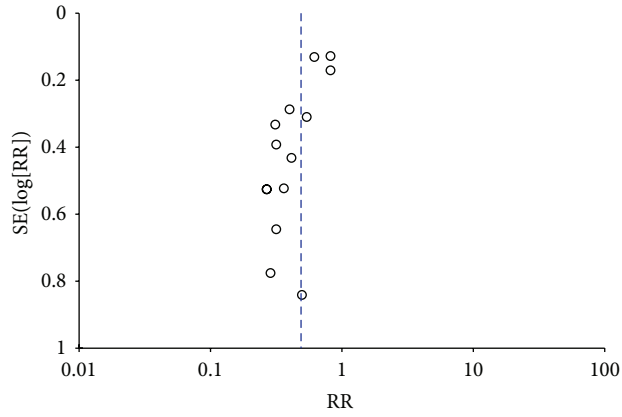


Figure 8: Funnel plot of studies testing for WBC reduction.

performance status and reduce radiotherapy toxicity when compared with the radiotherapy alone. However, due to the generally weak methodological quality of the currently included studies, we are unable to make solid conclusions, and confirmation must await investigation in future trials.

The methodological quality and report of the majority of trials were variable and often inadequate. Of 29 trials, only 5 provided information on the randomization method and none reported a central randomization procedure to ensure concealment of treatment allocation. Blinded assessors were not mentioned in any study. To analyze survival time, it is essential that standards in the quality of the studies require the authors to specify how they handle patients who are lost to followup, the percentage of patients lose to followup, and whether those patients are monitored in the analysis [50]. However, only 3 reported considering the patients who were lose to followup as they had died; none of the other studies provided this information in current meta-analysis. The lack of information in many reports may not necessarily indicate poor implementation within the trial, but without this information, the level of bias within each trial is difficult to assess. In addition, there was between-study heterogeneity in the evidence for improved survival at one year, as well as in the evidence for reduced radiotherapy toxicity. Moreover, all studies included in this systematic review used an "A + B versus B" design where patients were randomized to receive Chinese herbal prescriptions plus radiotherapy versus radiotherapy alone, without a rigorous control for placebo effect. This kind of design is likely to generate false positive results [51]. What is more, although the radiation technology was the same between the groups of Chinese herbal prescriptions plus radiotherapy and the radiotherapy alone in every eligible trail, of all the trails included in this meta-analysis, some used the conventional radiotherapy, some used three-dimensional conformal radiotherapy, and one adopted stereotactic radiation therapy. Hence, performance bias could be caused. Besides, funnel plots and Egger's test showed that there was evidence of publication bias which was another limitation of the present meta-analysis.

Astragalus possesses an important position in traditional Chinese medicine system. It has been used for almost all the disease caused by "qi deficiency" (life energy), which has been associated with cellular immune dysfunction [52]. The main constituents of Astragalus are triterpene saponins, flavonoids, and Astragalus polysaccharides [53]. Among the constituents, especially, the astragalus polysaccharide integrated with vinorelbine and cisplatin (VC) showed a significantly improved quality of life in patients with advanced NSCLC compared with VC alone [54]. Furthermore, as an immunomodulator [55], the astragalus polysaccharides enhances the immune responses [56] and resists the immunosuppression [57]. As a key ingredient of the current herbal prescriptions, those effects might directly associate with the benefits to the patients with NSCLC when coused with radiotherapy. However, to clarify the herbal prescriptions function as an adjunct to radiotherapy, future studies focused on the specific mechanisms and bioactive components of herbal prescriptions themselves are essential. What is more, improvement in the methodological quality of randomized controlled trials is critical for future research and more methodologically rigorous studies are justified to confirm or refute the effects reported here. Besides, future trials need to ensure that the reporting follows the CONSORT guidelines [58].

5. Conclusion

In conclusion, we found evidence that Astragalus-containing Chinese herbal prescriptions may increase effectiveness and reduce the toxicity of radiotherapy when combined with radiotherapy. To confirm the exact merit, further rigorously controlled trials are warranted.

Conflict of Interests

All authors declare that they have no conflict of interests.

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