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ORIGINAL REPORT

Astragalus-Based Chinese Herbs and Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer: Meta-Analysis of Randomized Trials

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ABSTRACT

Purpose

Systemic treatments for advanced non–small-cell lung cancer have low efficacy and high toxicity. Some Chinese herbal medicines have been reported to increase chemotherapy efficacy and reduce toxicity. In particular, *Astragalus* has been shown to have immunologic benefits by stimulating macrophage and natural killer cell activity and inhibiting T-helper cell type 2 cytokines. Many published studies have assessed the use of *Astragalus* and other Chinese herbal medicines in combination with chemotherapy. We sought to evaluate evidence from randomized trials that *Astragalus*-based Chinese herbal medicine combined with platinum-based chemotherapy (versus platinum-based chemotherapy alone) improves survival, increases tumor response, improves performance status, or reduces chemotherapy toxicity.

Methods

We searched CBM, MEDLINE, TCMLARS, EMBASE, Cochrane Library, and CCRCT databases for studies in any language. We grouped studies using the same herbal combinations for random-effects meta-analysis.

Results

Of 1,305 potentially relevant publications, 34 randomized studies representing 2,815 patients met inclusion criteria. Twelve studies (n = 940 patients) reported reduced risk of death at 12 months (risk ratio [RR] = 0.67; 95% CI, 0.52 to 0.87). Thirty studies (n = 2,472) reported improved tumor response data (RR = 1.34; 95% CI, 1.24 to 1.46). In subgroup analyses, Jin Fu Kang in two studies (n = 221 patients) reduced risk of death at 24 months (RR = 0.58; 95% CI, 0.49 to 0.68) and in three studies (n = 411) increased tumor response (RR = 1.76; 95% CI, 1.23 to 2.53). Ai Di injection (four studies; n = 257) stabilized or improved Karnofsky performance status (RR = 1.28; 95% CI, 1.12 to 1.46).

Conclusion

Astragalus-based Chinese herbal medicine may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy. These results require confirmation with rigorously controlled trials.

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INTRODUCTION

Lung cancer is the leading cause of cancer death in the United States, accounting for 27% and 31% of all cancer deaths in women and men, respectively.[1] Although lung cancer deaths in men have declined substantially (from 92 in 100,000 in 1995, to 84 in 100,000 in 2001), death rates in women only recently began to stabilize in 1995 (at approximately 42 in 100,000 between 1995 and 2001) after increasing for two decades between 4% and 6% per year.[2] Lung cancer is now the leading cause of cancer death in women.[1] Seventy-five percent of all lung cancer occurrences are non–small-cell lung cancer.

Despite treatment advances, new systemic therapies for advanced non–small-cell lung cancer developed in the last few decades continue to have both low efficacy and high toxicity. Meta-analyses have shown that, compared with treatment with surgery alone, adjuvant treatment with chemotherapy reduces the risk of death at 2 years by only 13%[3]; adjuvant chemoradiotherapy reduces that risk by 14%[4]; adjuvant radiotherapy alone conversely increases that risk by 21%.[5,6] The addition of platinum-based drugs to standard chemotherapy protocols increased 12-month survival by 5% and tumor response by 62%, but with significantly increased hematologic toxicity, nephrotoxicity, and

nausea and vomiting.[7] The 12-month survival for platinum-based regimens has been found in meta-analysis to be 34% (95% CI, 33% to 36%).[7] More recently, the addition of the epidermal growth factor receptor tyrosine kinase–inhibitor drug, gefitinib, to carboplatin/paclitaxel chemotherapy in a phase III randomized, controlled trial demonstrated no additional benefit in survival or time to progression.[8] These poor outcomes in survival, tumor response, quality of life, and toxicity for patients with advanced non–small-cell lung cancer emphasize the need for additional improvements in approaches to treatment.

In China, herbal medicine frequently is combined with chemotherapy in the treatment of lung cancer. Of particular interest is the herb *Astragalus membranaceus* (Fisch.), which may potentiate host immune function by stimulating macrophage and natural killer cell activity,[9] and enhance immune recognition of lung cancer cells by inhibiting production of T-helper cell type 2 cytokines[10] (T-helper cell subsets implicated in the development of immunological tolerance to tumor progression).[11] In a recent clinical trial, single-agent *Astragalus* herbal treatment in combination with platinum-based chemotherapy, compared with platinum-based chemotherapy alone, has been shown to significantly reduce risk of death at 12 months (risk ratio [RR] = 0.62; 95% CI, 0.43 to 0.89) and 24 months (RR = 0.75; 95% CI, 0.58 to 0.97).[12] In clinical practice and in most published trials, however, *Astragalus* rarely is used as single-agent therapy; it usually is combined with other herbal medicines.

This meta-analysis was motivated by the large number of published trials of *Astragalus*-based Chinese herbal medicines combined with platinum-based chemotherapy, and the continuing problems with low efficacy and high toxicity in standard chemotherapy treatment of advanced non–small-cell lung cancer. Our a priori hypotheses were that adding *Astragalus*-based Chinese herbal medicine to platinum-based chemotherapy, compared with treatment with platinum-based chemotherapy alone, could prolong survival, increase tumor response, stabilize or improve performance status, and reduce chemotherapy toxicity.

METHODS

Study Identification

We conducted a systematic search of the following databases: CBM China BioMedical Bibliographic Database (1978 to August 2004; www.imicams.ac.cn/cbm), TCMLARS (1984 to August 2004; www.cintcm.com), PubMed (1966 to August 2004; www.pubmed.gov), EMBASE (1974 to August 2004; http://embase.com/), Cochrane Library (1988 to August 2004; http://cochrane.org), and Cochrane Central Register of Controlled Trials (1966 to August 2004; http://cochrane.org). We used an extensive list of search terms (the full search strategy is available on request from the authors). The search was designed to find initially all trials involving non–small-cell lung cancer, chemotherapy, Chinese herbal medicine, and randomized controlled trials (and multiple synonyms for each term). We also searched for references from within the bibliographies of all eligible studies. No restrictions were placed on the publication language. Two reviewers (M.M. and C.S.) independently identified studies and translated abstracts and relevant data portions of eligible studies.

Study Eligibility

We screened titles and abstracts and retained those that were described as randomized, recruited patients with advanced non–small-cell lung cancer, provided the treatment group with Chinese herbal medicines containing the herb *Astragalus* in combination with standard platinum-based chemotherapy, provided the control group with platinum-based chemotherapy alone, and reported data on at least one of our outcomes of interest (survival, tumor response, performance status, or toxicity) with sufficient detail to permit calculation of the risk ratios of each outcome and 95% CIs. We obtained full-text copies of all abstracts or titles that potentially met our inclusion criteria and conducted a thorough screening of those articles obtained to confirm they met our inclusion criteria.

All inclusion and exclusion criteria and the categorization of outcomes were made before any meta-analysis of the data. Our decision to group together for this meta-analysis those studies using platinum-based chemotherapy was based on the fact that this therapy is currently a standard treatment for advanced non–small-cell lung cancer. Following the example set by D'Addario et al[7] and the Cochrane Collaboration's Non–Small-Cell Lung Cancer Collaborative Group,[3] platinum-based chemotherapy was grouped together as a therapeutic class when assessing efficacy of treatment for non–small-cell lung cancer. Each stage of the planning, design, analysis, and reporting of this meta-analysis was conducted in accordance with the QUOROM Statement guidelines (Fig 1).[13]

Data Extraction

Two reviewers (M.M. and C.S.) independently extracted data on patient characteristics, treatment details, clinical outcomes, and study quality.[14,15] We searched for data on survival outcomes of any type (total survival, cause-specific survival, and disease-free survival, with either crude data or adjusted measures), objective tumor response, reduction in chemotherapy toxicity, and improved or stabilized performance status. To evaluate Chinese herbal medicine in total as a therapeutic system, we first grouped together for meta-analysis the data from all studies meeting our inclusion criteria. Then, to evaluate the efficacy of specific herbal formulas, when we found more than one study using the exact same herbal formula, we grouped together for meta-analysis the data from those specific studies.

Study Quality

We used the Jadad scale, a validated 5-point scale developed to evaluate the quality of the reporting of randomized trials in meta-analysis.[16,17] The scale

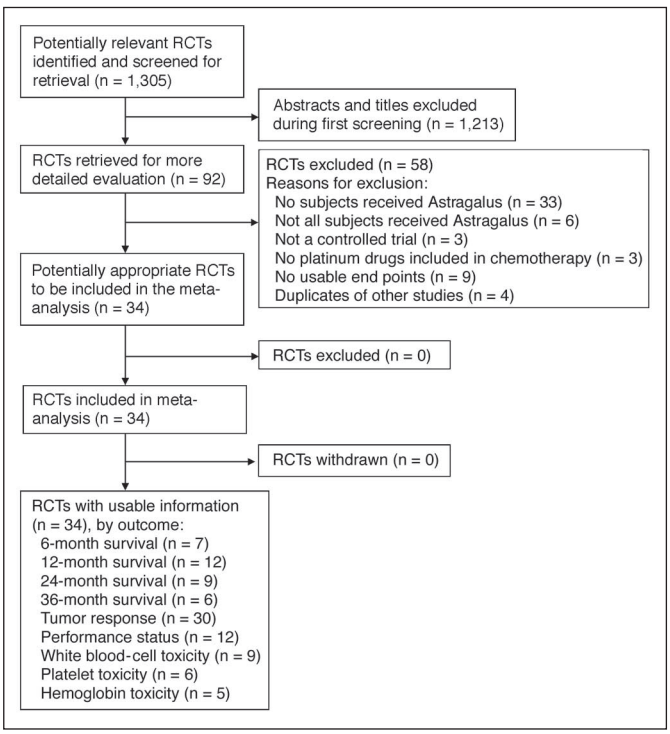

Fig 1. Quorom Statement flow diagram. Because most studies reported more than one outcome, the total of the individual outcomes listed in the lowermost box will be greater than 34. RCTs, randomized controlled trials.

assigns a score of 0 or 1 for each of the following study quality criteria: whether the study was described as randomized, whether the authors reported the method of randomization, whether the use of blinding was reported, whether the method for concealment of allocation was reported, and whether the authors accounted for patient withdrawals and drop-outs. Thus, a perfect study would receive a score of 5, and the lowest quality study according to this scale would receive a score of 0.

Analysis of Outcomes

Survival. Given that all of the studies identified in our systematic search reported crude survival data as the number of patients in each treatment group who died by 6, 12, 24, or 36 months, we calculated the probability of failure (death) as the number of patients who had died by each time point divided by the total number of patients enrolled at the start of the trial for each treatment group. This approach is intentionally conservative: if some patients dropped out of the study, retaining them in the denominator as we have done would lower the estimate of effectiveness. This is analogous to an intention-to-treat analysis.[18] The risk ratios of treatment failure (death) at each time point was calculated as the proportion who died in the *Astragalus*-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors

Table 1. Results

Endpoint	No. of Studies	No. of Patients	RR	95% CI	*P*	Publication Bias (*P*)	Heterogeneity (*P*)
6-month survival							
All studies combined	7	529	0.58	0.48 to 0.71	< .000*	.29	.65
Various *Astragalus* combinations	5	308	0.61	0.49 to 0.78	< .000*		.85
Jin Fu Kang	2	221	0.61	0.28 to 1.34	.22		.14
12-month survival							
All studies combined	12	940	0.67	0.52 to 0.87	.002*	.40	< .000
Astragalus single-agent	1	60	0.62	0.43 to 0.88	.009*		
Various *Astragalus* combinations	9	659	0.67	0.49 to 0.90	.008*		< .000
Jin Fu Kang	2	221	0.91	0.20 to 4.01	.90		.005
24-month survival							
All studies combined	9	768	0.73	0.62 to 0.86	< .000*	.056	< .000
Astragalus single-agent	1	60	0.75	0.58 to 0.97	.026*		
Various *Astragalus* combinations	6	487	0.80	0.66 to 0.96	.016*		.009
Jin Fu Kang	2	221	0.58	0.49 to 0.68	< .000*		.39
36-month survival							
All studies combined	6	556	0.85	0.77 to 0.94	.002*	.38	.091
Astragalus single-agent	1	60	0.89	0.74 to 1.08	.23		
Various *Astragalus* combinations	4	352	0.86	0.73 to 0.998	.047*		.048
Jin Fu Kang	1	144	0.79	0.67 to 0.92	.003*		
Tumor response							
All studies combined	30	2472	1.34	1.24 to 1.46	< .000*	.27	.84
Ai Di injection	7	478	1.19	0.99 to 1.44	.068		1.00
Astragalus single-agent	2	156	1.57	0.85 to 2.93	.15		.11
Various *Astragalus* combinations	18	1427	1.34	1.21 to 1.47	< .000*		.74
Jin Fu Kang	3	411	1.76	1.23 to 2.53	.002*		.84
Improved or stable performance status							
All studies combined	12	1095	1.36	1.21 to 1.54	< .000*	.23	.001
Ai Di injection	4	257	1.28	1.12 to 1.46	< .000*		.58
Astragalus single-agent	1	60	1.22	0.98 to 1.52	.08		
Various *Astragalus* combinations	5	445	1.32	1.16 to 1.49	< .000*		.30
Jin Fu Kang	2	333	1.68	0.82 to 3.44	.15		< .000
Reduction in grade III or IV WBC toxicity							
All studies combined	9	808	0.39	0.24 to 0.63	< .000*	.35	.82
Ai Di injection	2	158	0.37	0.12 to 1.10	.072		.87
Various *Astragalus* combinations	6	460	0.39	0.22 to 0.69	.001*		.50
Jin Fu Kang	1	190	0.45	0.084 to 2.40	.35		
Reduction in grade III or IV platelet toxicity							
All studies combined	6	777	0.36	0.11 to 1.21	.10	.25	0.78
Ai Di injection	1	60	0.33	0.01 to 7.87	.50		
Various *Astragalus* combinations	3	392	0.50	0.09 to 2.82	.43		0.89
Astragalus single-agent	1	135	0.063	0.004 to 1.08	.056		
Jin Fu Kang	1	190	0.90	0.06 to 14.18	.94		
Reduction in grade III or IV hemoglobin toxicity							
All studies combined	5	500	0.26	0.13 to 0.49	< .000*	.92	.95
Ai Di injection	1	60	0.33	0.04 to 3.03	.33		
Various *Astragalus* combinations	3	250	0.27	0.13 to 0.54	< .000*		.97
Jin Fu Kang	1	190	0.08	0.005 to 1.46	.089		

Abbreviation: RR, risk ratio.
*Significant finding for efficacy.

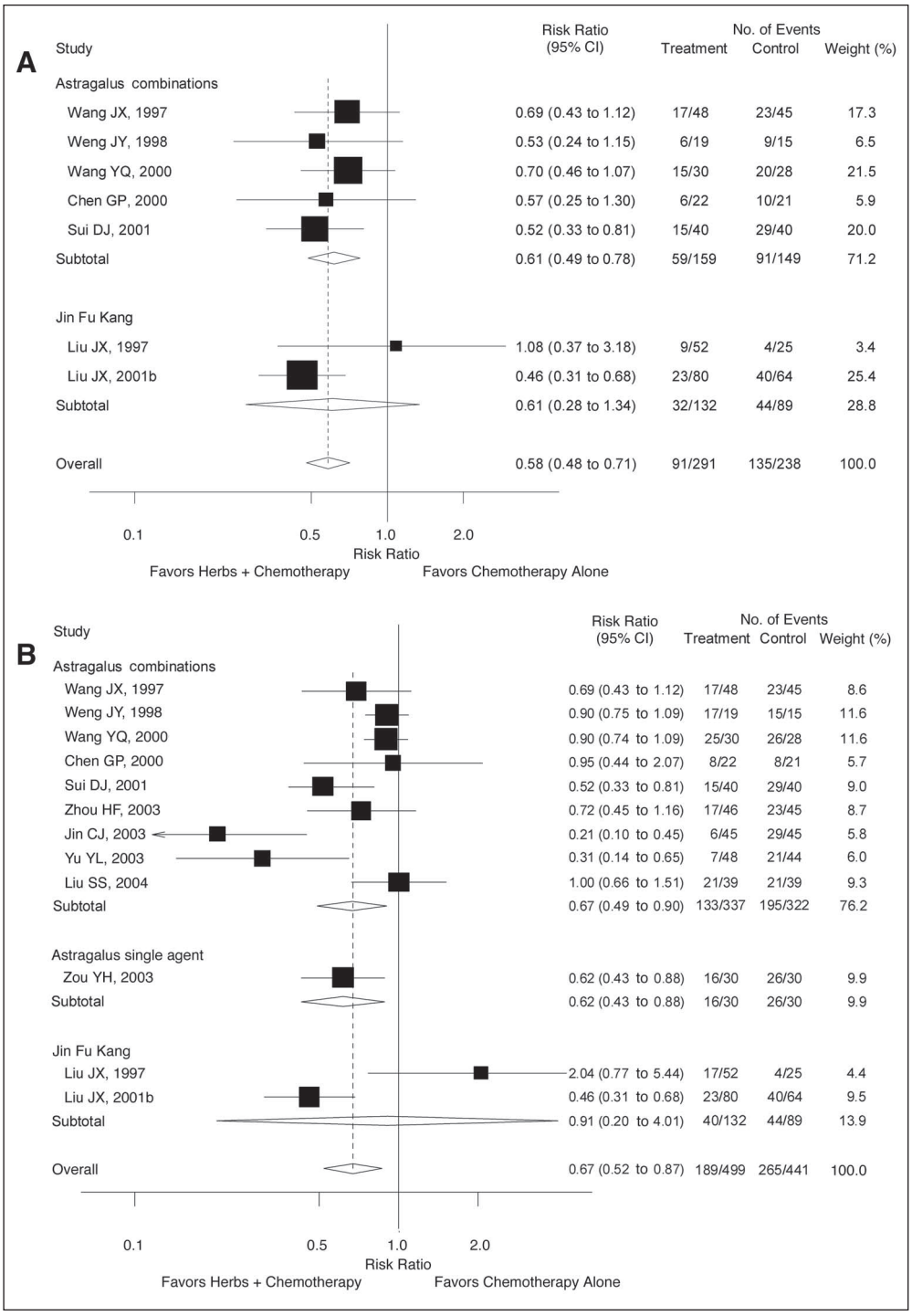

Fig 2. (A) Six-month survival with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone. (B) Twelve-month survival with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

the combination regimen. This is the same approach taken by D'Addario et al[7] in a meta-analysis of 12-month survival rates in the treatment of advanced non–small-cell lung cancer patients with platinum-based versus nonplatinum-based chemotherapy.

Objective tumor response. Given that most of the studies identified in our systematic search reported tumor response at conclusion of treatment using the 4-point WHO scale,[19] we calculated the probability of tumor response as the number of patients experiencing any response (complete response plus partial response) divided by the total number of patients in each treatment group (complete response plus partial response plus no change plus progressive disease). The RR of tumor response was calculated as the probability of tumor response in the *Astragalus*-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen. This is the approach for meta-analysis of tumor response recommended by Sutton et al.[14]

Performance status. Many of the studies identified in our systematic search reported performance status using the Karnofsky performance scale,[20] with most using a 10-point change as the cutoff for improved or worse performance status, and a few others using a 20-point change as the cutoff. We

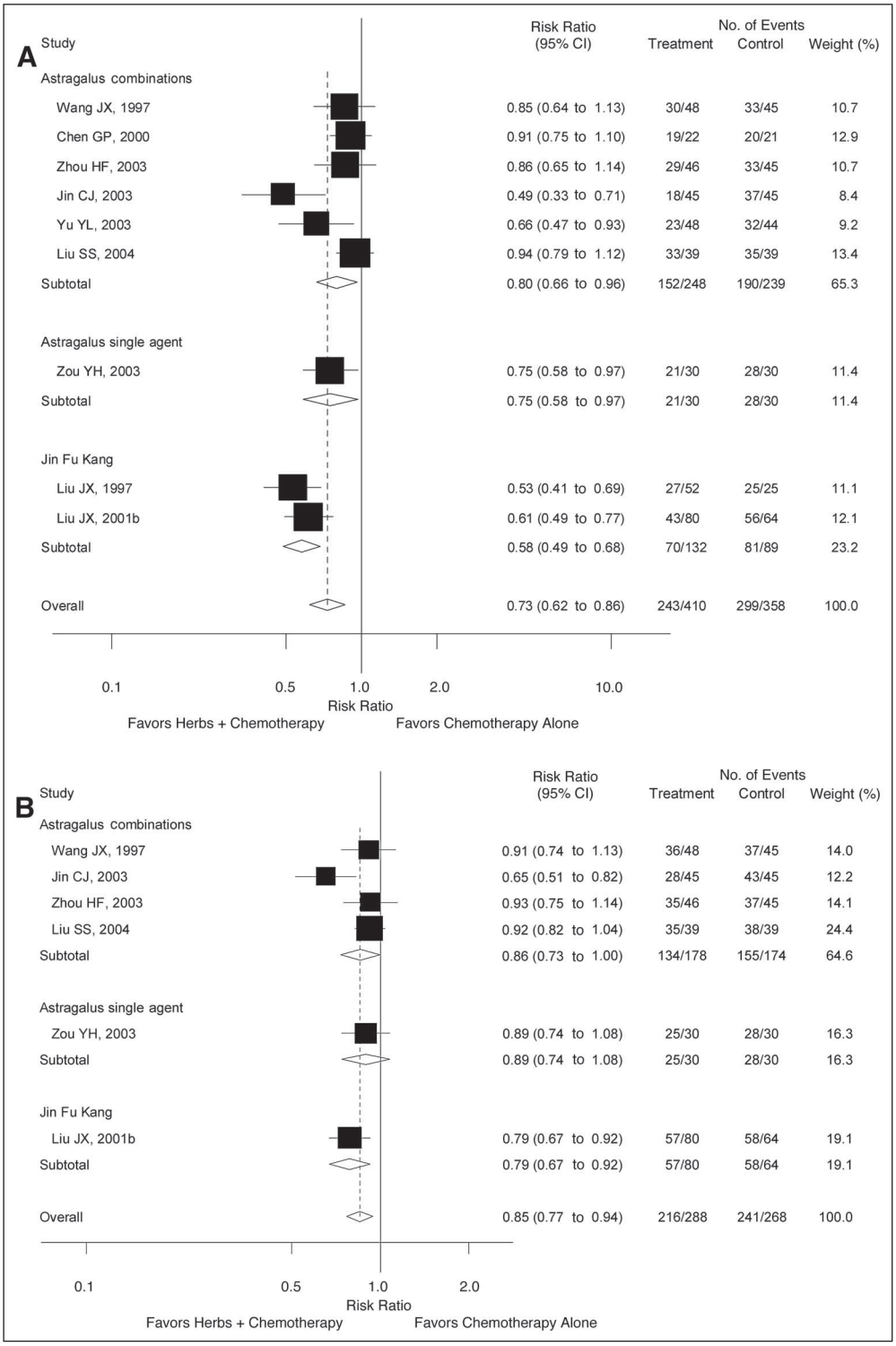

Fig 3. (A) Twenty-four-month survival with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone. (B) Thirty-six-month survival with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

therefore calculated the probability of improved or stable performance status as the proportion of improved or stable performance status: (> 10-point increase plus no change) divided by the total (> 10-point increase, plus no change, plus > 10-point decrease). The RR of improved or stable performance status was calculated as the proportion of improved or stable performance status in the *Astragalus*-based herbal medicine plus platinum-based chemotherapy treatment group, divided by this proportion in the platinum-based chemotherapy group. Thus, RR more than 1 favors the combination regimen.

Reduction in chemotherapy toxicity. Given that most of the studies identified in our systematic search reported occurrence of chemotherapy-related toxicity using the 5-point WHO scale,[19] we calculated the probability of occurrence of toxicity as the number of patients experiencing any severe toxicity (WHO grade 3 or 4) divided by the total number of patients in each treatment group (WHO grades 0 + 1 + 2 + 3 + 4). The RR of reduction in toxicity was calculated as the proportion of severe toxicity in the *Astragalus*-based herbal medicine plus platinum-based chemotherapy treatment group,

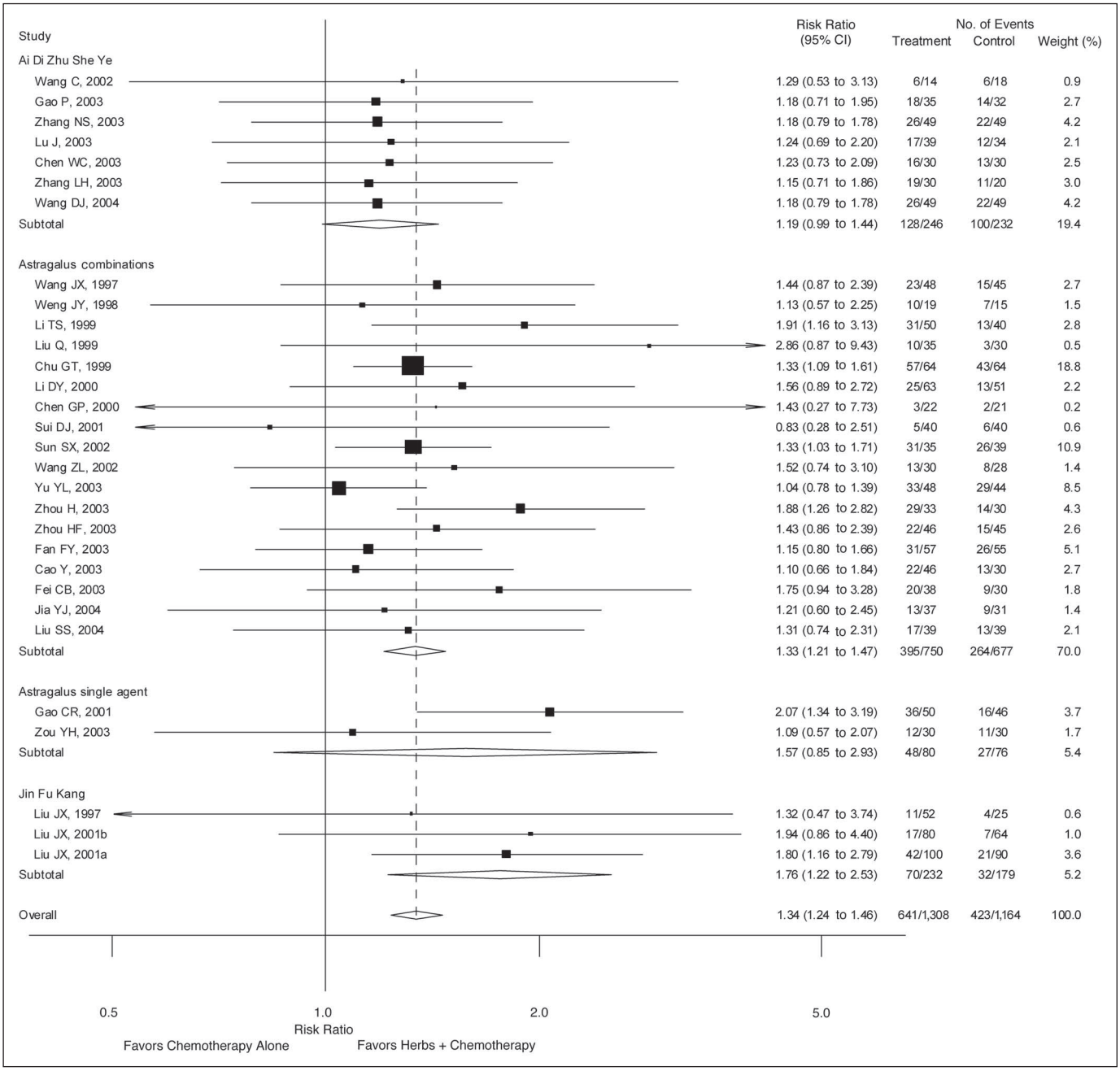

Fig 4. Tumor response with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

divided by this proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors the combination regimen. This is the same approach taken recently by Delbaldo et al,[21] who reported the odds ratio for the occurrence of grade 3 or 4 toxicity in a meta-analysis of single-agent versus two-agent chemotherapy for non–small-cell lung cancer.

Meta-Analysis, Between-Study Heterogeneity, and Publication Bias

We used the random-effects model of DerSimonian and Laird[22] to estimate the summary RR for each of the four outcomes: risk of death (at 6, 12, 24, and 36 months), tumor response, performance status, and severe chemotherapy toxicity. We used the χ^2 statistic to assess between-study heterogeneity.[23,24] To assess publication bias, we used the Begg test, which examines the association between the effect estimates of individual studies and their variances; significant correlation between these two factors identifies publication bias.[25]

RESULTS

Studies Retrieved

Our systematic search identified 1,305 potentially relevant abstracts, of which 92 were identified as requiring full-text article retrieval. Close screening of these 92 studies excluded 58 because no patients received *Astragalus* (n = 33), patients randomly assigned to herbal therapy in some cases received herbal medicine not actually

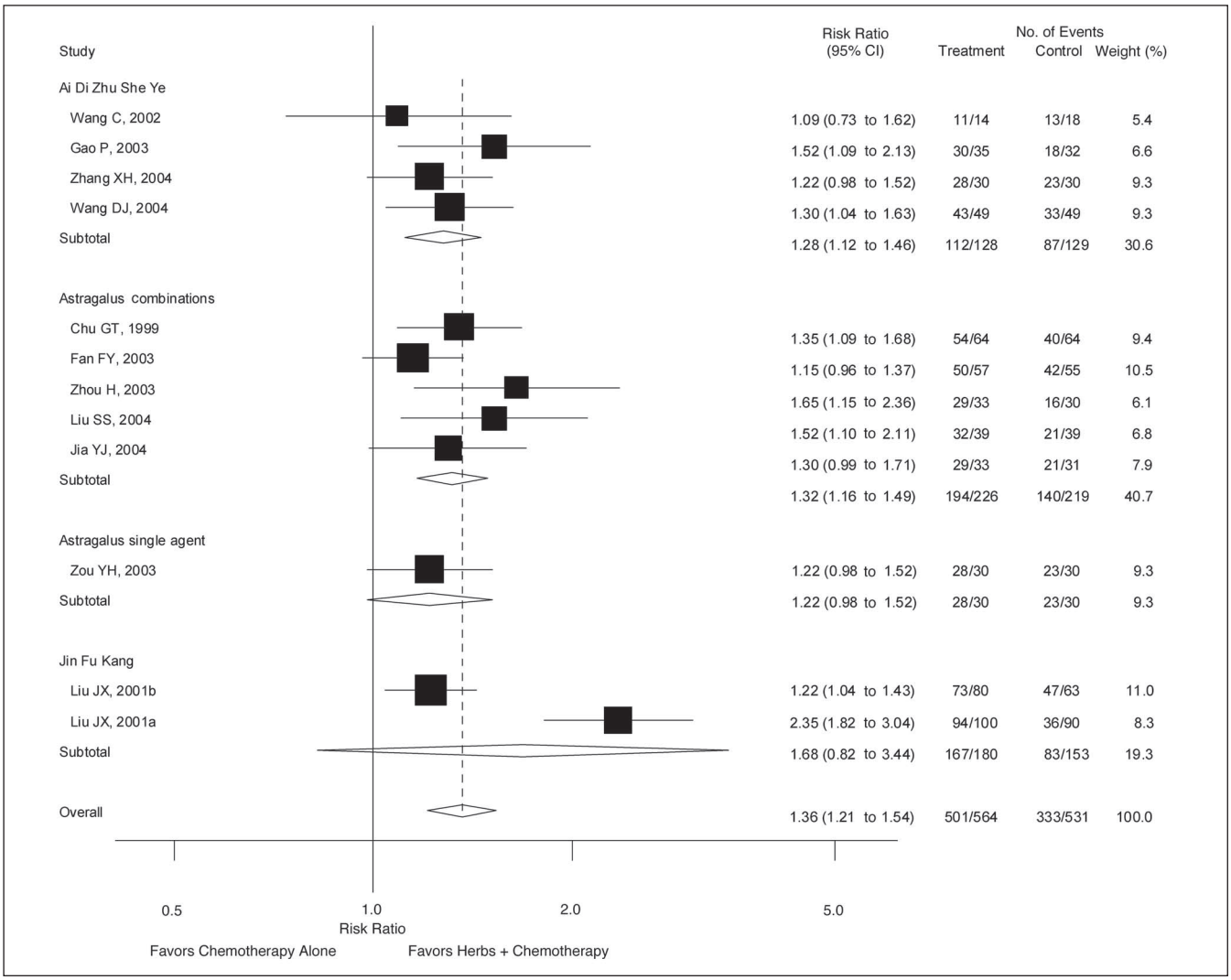

Fig 5. Stable/improved Karnofsky performance status with *Astragalus*-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

containing the specific herb *Astragalus* (n = 6), the article did not describe a controlled trial (n = 3), no platinum drugs were included in chemotherapy (n = 3), there were no usable end points (n = 9), or the article was a duplicate of another study (n = 4). This resulted in 34 studies accepted for meta-analysis (Fig 1).

Survival

We identified seven studies reporting a total of 529 patients that reported reduced risk of death at 6 months for *Astragalus* combinations versus chemotherapy alone (RR = 0.58; 95% CI, 0.48 to 0.71): five using various *Astragalus*-based combinations (RR = 0.61; 95% CI, 0.49 to 0.78)[26-30] and two using a specific herbal formula, Jin Fu Kang (RR = 0.61; 95% CI, 0.28 to 1.34; Table 1 and Fig 2).[31,32] We identified 12 studies with a total of 940 patients that reported reduced risk of death at 12-months (RR = 0.67; 95% CI, 0.52 to 0.87): one using single-agent *Astragalus* (RR = 0.62; 95% CI, 0.43 to 0.88),[12] nine using various *Astragalus*-based combinations (RR = 0.67; 95% CI, 0.49 to 0.90),[26-30,33-36] and two using formula Jin Fu Kang (RR = 0.91; 95% CI, 0.20 to 4.01; Table 1 and Fig 2).[31,32] We identified nine studies with a total of 768 patients that reported reduced risk of death at 24 months (RR = 0.73; 95% CI, 0.62 to 0.86): one using single-agent *Astragalus* (RR = 0.75; 95% CI, 0.58 to 0.97),[12] six using various *Astragalus*-based combinations (RR = 0.80; 95% CI, 0.66 to 0.96),[27,29,33-36] and two using formula Jin Fu Kang (RR = 0.58; 95% CI, 0.49 to 0.68; Table 1 and Fig 3).[31,32] We identified six studies with a total of 556 patients that reported reduced risk of death at 36 months (RR = 0.85; 95% CI, 0.77 to 0.94): one using single-agent *Astragalus* (RR = 0.89; 95% CI, 0.74 to 1.08),[12] four using various *Astragalus*-based combinations (RR = 0.86; 95% CI, 0.73 to 0.998),[27,33,35,36] and one using formula Jin Fu Kang (RR = 0.79; 95% CI, 0.67 to 0.92; Table 1 and Fig 3).[32]

Among studies reporting median survival, none included confidence intervals, *P* values, or variance. We were therefore unable to perform a meta-analysis of median survival.

Tumor Response

We identified 30 studies representing a total of 2,472 patients that reported tumor response data (RR = 1.34; 95% CI, 1.24 to 1.46): seven using specific formula Ai Di injection (RR = 1.19; 95% CI, 0.99 to 1.44),[37-43] two using single-agent *Astragalus* (RR = 1.57; 95% CI,

Table 2. Study Characteristics

Study	No. of Patients	Protocol*	Ingredients	Stage†	Jadad Quality Scale
Cao[54]	76	CAP/NP + *Astragalus* combination	*Adenophora verticillata, Ophiopogonis japonicis, Schisandra chinensis, Astragalus membranaceus, Oldenlandia diffusa, Eriobotrya japonica, Fritillaria cirrhosa, Arisaema amurense*	III/IV	1
Cheng[29]	43	CAP + *Astragalus* combination	*Codonopsis pilosula, Astragalus membranaceus, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Dioscoreae opposita, Oldenlandia diffusa, Houttuynia cordata, Patrina villosa, Scutellaria barbata, Agrimonia pilosa, Ziziphus jujube*	III/IV	1
Chen[41]	60	FDH + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoii*	III/IV	1
Chu[48]†	128	EAP + Radiation + *Astragalus* combination	*Astragalus, Panax ginseng, Atractylodis macrocephala, Psoralea corylifolia, Asparagus cochinchinensis, Ophiopogonis japonicis, Scrophularia ningpoensis, Rehmannia glutinosa, Sparganium stoloniferum, Curcuma zeodoraria, Manis pentadactyla, Ostrea gigis shell, Trichosanthes kirilowii, Arisaema amurense, Scutellaria barbata, Oldenlandia diffusa*	III/IV	1
Fan[50]	112	CAP + *Astragalus* combination	*Codonopsis pilosulae, Atractylodis macrocephala, Glycyrrhiza uralensis, Astragalus, Ligustricum lucidum, Poria cocos, Salvia miltiorrhiza, Prunus persica*	III/IV	1
Fei CB, 2003[52]	68	MVP + *Astragalus* combination	*Astragalus, Codonopsis pilosulae, Rehmannia glutinosae, Asparagus cochinchinensis, Ophiopogonis japonicis, Scrophulariae ningpoensis, Cimicifuga foetida, Houttuynia cordata, Smilax glabra, Aloe vera*	III/IV	1
Gao[44]	96	MVP/CAP + Astragal.	*Astragalus*	III/IV	1
Gao[38]	67	GCN + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	1
Jia YJ, 2004[53]	68	MVP/NP + *Astragalus* combination	*Curcuma longa, Curcuma aromatica, Snake, Prunellae vulgaris, Concha ostrea, Oldenlandia diffusa, Astragalus, Panax qinquefolium*	III/IV	1
Jin[33]	90	MVP + *Astragalus* combination	*Astragalus, Polygonatum chinense, Ligustricum lucidum, Ganoderma lucidum, Salvia chinensis, Paris polyphylla, Drynaria fortunei, Citrus reticulate*	III/IV	0
Li[47]	114	CE/CAP + *Astragalus* combination	*Astragalus, Polygonatum chinense, Panax ginseng, Agrimonia pilosa, Houttuynia cordata, Rheum palmatum, Polyporus umbellatus, Lobelia chinensis, Oldenlandia diffusa, Arisaema amurense, Coix lachryma, Prunus persica, Trichosanthes kirilowii, Prunella vulgaris*	III/IV	1
Li[55]	90	CE/CAP + *Astragalus* combination	*Astragalus, Adenophora verticillata, Lilium brownii, Ophiopogonis japonicis, Coix lachryma, Scutellaria barbata, Akebia trifoliata, Selaginella doederleinii, Agrimoniae pilosa, Polistes japonicus, Fritillaria thunbergii, Houttuynia cordata, Pinellia ternate, Glycyrrhizae*	III/IV	1
Liu[31]	77	MAP + Jin Fu Kang	*Astragalus, Adenophora verticillata, Ophiopogonis japonicis, Ligustricum lucidum, Selaginella doederleinii, Paris polyphylla*		2
Liu[56*]	190	CAP/MVP + Jin Fu Kang	*Astragalus, Adenophora verticillata, Ophiopogonis japonicis, Ligustricum lucidum, Selaginella doederleinii, Paris polyphylla*	II, III or IV	4
Liu[32]	144	MAP + Jin Fu Kang	*Astragalus, Adenophora verticillata, Ophiopogonis japonicis, Ligustricum lucidum, Selaginella doederleinii, Paris polyphylla*		2
Liu[49]	65	EAP/CAP + *Astragalus* combination	*Astragalus, Pseudostellaria heterophylla, Adenophora verticillata, Atractylodis macrocephala, Rehmannia glutinosae, Coix lachryma, Poria cocos, Curcuma zeodoaria, Saliva miltiorrhiza, Panax notoginseng, Citrus aurantium, Cremastra variabilis, Prunus armeniaca*	III/IV	1

(continued on following page)

Table 2. Study Characteristics (continued)

Study	No. of Patients	Protocol*	Ingredients	Stage†	Jadad Quality Scale
Liu SS, 2004[36]	78	CAP/MVP/CE + *Astragalus* combination	*Pseudostellaria heterophylla, Astragalus, Atractylodis macrocephala, Poria cocos, Ophiopogonis japonicis, Oldenlandia diffusa, Scutellaria barbata, Taraxicum mongolicum, Paris polyphylla, Fritillaria thunbergii, Ligustricum lucidum, Buthus martensi, Scolopendra subspinipes, Hirudo nipponica, Coix lachryma, Glycyrrhizae uralensis*		1
Lu[39]	73	NP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	1
Sui[30*]	80	MVP + *Astragalus* combination	*Lilium brownii, Rehmannia glutinosa, Scrophularia ningpoensis, Angelicae sinensis, Ophiopogonis japonicis, Paeonia lactiflora, Adenophora verticillata, Astragalus, Ligustricum lucidum, Paris polyphylla, Oldenlandia diffusa, Houttuynia cordata, Fritillaria cirrhosa, Cremastra variabilis* (*with individualized additions*)	II, III or IV	0
Sun[45]	74	CE-CAP/MVP/TC + *Astragalus* combination	*Ganoderma lucidum, Pseudostellaria heterophylla, Coix lachryma, Atractylodis macrocephala, Astragalus, Lycium chinense, Curcuma zeodoaria, Scolopendra subspinipes, Smilax glabra,*	III/IV	1
Wang[37]	32	NP/MVP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	1
Wang[43]	98	NP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	1
Wang[27]	93	MOP + *Astragalus* combination	*Adenophora verticillata, Asparagus cochinchinensis, Ophiopogonis japonicis, Pseudostellaria heterophylla, Astragalus, Curcuma zeodoaria, Atractylodis macrocephala, C. aromatica, Paeonia rubra, Paeonia lactiflora, Oldenlandia diffusa, Scutellaria barbata*		1
Wang[26]	58	Cisplatin + *Astragalus* combination	*Astragalus, Panax ginseng, Lilium brownii, Adenophora verticillata, Ophiopogonis japonici, Fritillaria cirrhosa, Morus alba, Trichosanthes kirilowii, Scutellariae baicalensis, Paris polyphylla, Scutellaria barbata, Solanum nigrum, Lepidium apetalum, Atractylodis macrocephalae, Poria cocos, Phaseolus carcaratus, Ziziphus jujube*	III/IV	1
Wang[46]	58	CAP/MVP + *Astragalus* combination	*Panax ginseng, Astragalus, Asparagus cochinchinensis, Ophiopogonis japonicis, Adenophora verticillata, Angelicae sinensis, Dioscoreae opposita, Dendrobium nobile, Polygonatum chinense, Schisandra chinensis, Ziziphus spinosa, Glycyrrhizae uralensis, Citrus reticulate*	III/IV	1
Weng[28]	34	CAP + *Astragalus* combination	*Codonopsis pilosulae, Astragalus, Atractylodis macrocephala, Poria cocos, Pinellia ternata, Citrus reticulata, Dioscorea opposita, Oldenlandia diffusa, Houttuynia cordata, Patrina villosa, Scutellaria barbata, Agrimonia pilosa, Ziziphus jujube*		1
Yu[34†]	92	MAP + radiation + *Astragalus* combination	*Astragalus, Pseudostellaria heterophylla, Poria cocos, Amomum xanthioides, Salvia miltiorrhiza, Paeonia rubra, Spathalobus suberectus, Schisandra chinensis, Glycyrrhizae uralensis* (*with individualized additions*)	III/IV	0
Zhang[40]	50	NP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	0
Zhang[42]	98	NP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	0
Zhang[57]	60	EP + Ai Di injection	*Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylabirs cichoi*	III/IV	0
Zhou[51]	63	CAP + *Astragalus* combination	*Panax ginseng, Atractylodis macrocephala, Poria cocos, Astragalus, Polygonatum chinense, Ophiopogonis japonicis, Cordyceps chinensis, Lycium chinense, Ephedra sinica, Prunus armeniaca, Trionyx sinensis, Prunellae vulgaris, Oldenlandia diffusa, Scutellaria barbata, P. notoginseng*	III/IV	1

(continued on following page)

Table 2. Study Characteristics (continued)

Study	No. of Patients	Protocol*	Ingredients	Stage†	Jadad Quality Scale
Zhou[35]	91	Cisplatin + *Astragalus* combination	*Adenophora verticillata, Ophiopogonis japonicis, Pseudostellaria heterophylla, Paris polyphylla, Astragalus, Scutellaria barbata, Curcuma zeodoaria, Atractylodis macrocephala, Paeonia rubra, Paeonia lactiflora, Oryza sativa, Hordeum vulgare, Massa fermenta, Crataegus pinnatifida, Cremastra variabilis, Curcuma aromatica, Citrus reticulata*	III/IV	1
Zou[12]	60	MAP + *Astragalus*	*Astragalus*	III/IV	1
Total	2,815				

Abbreviations: CAP, cyclophosphamide, doxorubicin, cisplatin; NP, vinorelbine, cisplatin; FDH, hydroxy camptothecin, fluorouracil, leucovorin, cisplatin; EAP, etoposide, doxorubicin, cisplatin; MVP, mitomycin-C, vindesine, cisplatin; TC, paclitaxel, carboplatin; GCN, gemcitabine, cisplatin, vinorelbine; CE, cisplatin, etoposide; MAP, mitomycin, doxorubicin, cisplatin; EP, etoposide, cisplatin; MOP, mitomycin, vincristine, cisplatin.

*In studies that included stage II patients, all patients received systemic therapy, and no patients received surgery.

†In studies in which patients received radiation in addition to chemotherapy, all patients in both groups received radiation and chemotherapy. The only difference between the two groups was whether they received *Astragalus*-based herbal medicine.

0.85 to 2.93),[12,44] 18 using various *Astragalus*-based combinations (RR = 1.34; 95% CI, 1.21 to 1.47),[27-30,34-36,45-55] and three using formula Jin Fu Kang (RR = 1.76; 95% CI, 1.23 to 2.53; Table 1 and Fig 4).[31,32,56]

Performance Status

We identified 12 studies representing a total of 1,095 patients that reported performance status data (RR = 1.36; 95% CI, 1.21 to 1.54): four using specific formula Ai Di injection (RR = 1.28; 95% CI, 1.12 to 1.46),[37,38,43,57] one using single-agent *Astragalus* (RR = 1.22; 95% CI, 0.98 to 1.52),[12] five using various *Astragalus*-based combinations (RR = 1.32; 95% CI, 1.16 to 1.49),[36,48,50,51,53] and two using formula Jin Fu Kang (RR = 1.68; 95% CI, 0.82 to 3.44; Table 1 and Fig 5).[32,56]

Reduction in Chemotherapy Toxicity

We found no significant results for specific herbal formulas in reducing severe WBC, platelet, or hemoglobin toxicity.

Publication Bias and Study Quality

We did not find evidence for publication bias according to the Begg test (Table 1). Most studies had a quality score of only 0 or 1 on the Jadad scale. Only three studies had a score of 2 or higher (Table 2).[31,32,56]

DISCUSSION

These findings are subject to several limitations. Our meta-analysis results suggest that combining platinum-based chemotherapy with Chinese herbal medicine in the treatment of non–small-cell lung cancer may increase survival, tumor response, and performance status, as well as reduce chemotherapy toxicity, when compared with treatment with platinum-based chemotherapy alone; however, because the studies we found were of poor quality, we are unable to make firm conclusions and confirmation must await investigation in future trials.

Only one of these studies,[56] using the formula Jin Fu Kang, described the method of randomization used. None of the other studies provided any details of the randomization method used, an unfortunate oversight given the availability of low-cost computers and free random number–generating software. Even more problematic was the lack of discussion in any study about whether the investigators knew which patients were randomly assigned to receive *Astragalus*-based herbal medicine. However, failure to describe randomization procedures fully is not limited to Chinese medical journals. Surprisingly, nearly 10 years since publication of the Consolidated Standards of Reporting Trials statement,[58] which was intended to improve the quality of reporting in randomized trials, more than 40% of trials published in 2004 in Western medical journals either failed to use adequate randomization methods or failed to report the method for concealment of allocation.[59]

Current standards in the quality of reporting in studies that analyze survival time require that the authors specify how they handled patients who were lost to follow-up, the percentage of patients lost to follow-up, and whether those patients were censored in the analysis.[59] No studies reported this information. Although there exists the possibility of censoring, which could bias our survival findings, our analysis would tend toward underestimation of any effects of this potential bias. These findings may be limited by the low quality of published studies identified in our systematic searching. In addition, there was between-study heterogeneity in the evidence for improved survival at 6, 12, and 24 months, as well as in the evidence for improved performance status.

Additional research is needed to further understand the specific immunologic and cytotoxic mechanisms by which *Astragalus* may function as an adjunct to chemotherapy for the treatment of advanced non–small-cell lung cancer. Such work would also assist in the identification of which specific herbal combinations most strongly and reliably enhance the action of *Astragalus*. Although we did not locate any published evidence of interaction between platinum chemotherapy and *Astragalus*, such interactions are possible, and should be investigated further.

The Institute of Medicine, Washington, D.C., recently concluded that complementary and alternative medicines should face rigorous testing.[60] An efficient method for identifying compounds or combinations of compounds with potential antitumor activity and clinical efficacy may be to critically evaluate the evidence from clinical studies published in China. Although such studies have been reported to be of low quality, nevertheless they many contain

credible evidence pointing the direction toward herbal medicines worthy of additional study. Because clinical trials are so expensive and difficult, these findings can help to pick the most promising agents for study.

Other systematic reviews of published studies from Chinese journals have identified specific journals with better study quality, and also found trends in improvement of study quality over time.[61] It is hoped that systematic reviews and meta-analyses such as this one will help specify where further improvements in the design and reporting of research conducted and published in China are needed.

We found evidence that *Astragalus*-based Chinese herbal medicine may increase effectiveness (by improving survival, tumor response, and performance status) and reduce toxicity of standard platinum-based chemotherapy for advanced non–small-cell lung cancer. However, confirmation of these conclusions in rigorously controlled, randomized trials is required before more firm conclusions about this therapy can be drawn.

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