

Astragalus-containing Chinese herbal combinations for advanced non-small-cell lung cancer: a meta-analysis of 65 clinical trials enrolling 4751 patients

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Background: Non-small-cell lung cancer (NSCLC) is a leading cause of death. Interventions to reduce mortality in patients with NSCLC represent a patient-important field of research. Little is known about interventions used outside the Western world for NSCLC. One intervention widely used in Asia is astragalus-based herbal preparations.

Methods: We conducted a comprehensive systematic review of all published randomized clinical trials (RCTs) evaluating astragalus-based herbal preparations in NSCLC patients. We searched independently, in duplicate, 6 English language electronic databases and 2 Chinese-language databases. We abstracted data independently, in duplicate on studies reporting of methods, survival outcomes, tumor responses, and performance score responses. We applied a random-effects meta-analysis and report outcomes as relative risks (RR) with 95% confidence intervals (CIs).

Results: We included 65 RCTs enrolling 4751 patients. All trials included the herbal preparations plus platinum-based chemotherapy versus chemotherapy alone. We pooled 7 studies ($n = 529$) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45 to 0.65, $P \leq 0.0001$). We included 20 trials ($n = 1520$) on survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54 to 0.79, $P \leq 0.0001$). This effect was consistent at 24 and 36 months. When we applied a composite endpoint of any tumor treatment response, we pooled data from 57 trials and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26 to 1.44, $P \leq 0.0001$). Statistical heterogeneity was low across trials.

Limitations: The quality of reporting the RCTs was generally poor. There is also reason to believe that studies reported as randomized may not be.

Conclusions: We found a large treatment effect of adding astragalus-based herbal treatment to standard chemotherapy regimens. There is a pressing need for validation of these findings in well-conducted RCTs in a Western setting.

Keywords: astragalus, non-small-cell lung cancer, herbal preparations

Introduction

Lung cancer is the leading cause of cancer death worldwide.^{1,2} In the United States, lung cancer is the leading cause of death, where it is estimated that 219,440 new cases of lung and bronchus cancer will be diagnosed in 2009; leading to 159,390 lung cancer-related deaths.³ Only 15% of all lung cancer patients are alive 5 years or more after diagnosis.³

The World Health Organization divides lung cancer into 2 major classes: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts

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for over 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types) and (2) squamous cell (epidermoid) carcinoma.⁴

The clinical guidelines for patients with NSCLC include combinations of cytotoxic chemotherapy and targeted biologic therapies, such as bevacizumab and erlotinib.⁴ Unfortunately, these current treatments involve non-specific, non-selective cytotoxic chemotherapy, which results in only a modest increase in survival and causes significant toxicity to the patient.⁵ According to a meta-analysis of 33 Phase III randomized controlled trials (RCTs), platinum-based chemotherapy offers symptomatic relief and modest improvements in survival (rarely >2 months).⁶ Data from 3 RCTs showed that platinum-based chemotherapy provided a median survival time of approximately 7 to 10 months.⁷⁻⁹

In China, traditional Chinese medicines (TCM), which are herbal and/or animal/insect-based combinations, are frequently combined with chemotherapy for the treatment of cancer.¹⁰ One commonly used herbal compound, astragalus, appears to have a number of immunomodulatory properties.¹¹⁻¹³ Astragalus appears to have antitumor activity where it potentiates LAK cell activity *in vitro* when used in combination with IL-2¹⁴. Astragalus appears to restore *in vitro* T-cell function, which is suppressed in cancer patients.¹⁵ A meta-analysis of 34 RCTs found that Chinese medicines containing the herb astragalus (*Astragalus membranaceus*) may increase effectiveness of platinum-based chemotherapy when combined with chemotherapy.¹⁶ When compared to chemotherapy alone, astragalus-based Chinese medicines reduced risk of death at 12 months (risk ratio [RR] = 0.67; 95% confidence interval [CI], 0.52 to 0.87), improved tumor response data (RR = 1.34; 95% CI, 1.24 to 1.46), reduced risk of death at 24 months (RR = 0.58; 95% CI, 0.49 to 0.68), increased tumor response (RR = 1.76; 95% CI, 1.23 to 2.53) and stabilized or improved Karnofsky performance status (RR = 1.28; 95% confidence interval [CI], 1.12 to 1.46).¹⁶

There are a large number of published RCTs on astragalus-based Chinese medicines combined with platinum-based chemotherapy.¹⁶ Although a meta-analysis was conducted on NSCLC treatments using astragalus-based Chinese medicines along with platinum-based chemotherapy,¹⁶ this study did not include Chinese language studies in its search strategy. In a previous meta-analysis on TCM treatments for hepatocellular carcinoma, 44/45 RCTs extracted were in Chinese compared to 1/45 RCTs in English; thereby illustrating the importance of including Chinese manuscripts in the analysis.¹⁰

Our objective is to systematically review the scientific literature for RCTs on astragalus-based Chinese medicines combined with platinum-based chemotherapy and to meta-analyze the pooled data from these RCTs. Should the results be favorable, astragalus-chemotherapy combination treatment may provide an important step forward for new interventions for patients with NSCLC.

Methods

Study inclusion criteria

We included any study that randomized patients with advanced NSCLC, 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, or performance status) with sufficient detail to permit calculation of the risk ratios of each outcome. We excluded pharmacokinetic studies and non-randomized trials. We excluded studies that reported only laboratory values rather than clinical responses. We also excluded direct comparisons of TCM formulations.

Search strategy

PW and EM worked independently, in duplicate, searching the following English electronic databases: MEDLINE (1966 to June 2009), AMED (1985 to June 2009), Alt Health Watch (1995 to June 2009), CINAHL (1982 to June 2009), Nursing and Allied Health Collection: Basic (1985 to June 2009), Cochrane Database of Systematic Reviews (2008). In addition, PW and YL, both fluent in Mandarin and Cantonese, searched the Chinese databases CNKI (1979 to June 2009) and Wan Fang (1994 to June 2009) independently. No language restrictions were placed on the searches.

Three reviewers (PW, EM and YL) assessed eligibility based on the full text papers and conducted data extraction, independently, using a standard pre-piloted form. Disagreements were resolved by consensus or by a third reviewer. If the required information was not available in the published article, we obtained additional information in correspondence with the authors. We included all evaluated outcome measures including: survival at 6, 12, 24, and 36 months, disease stage, Karnofsky performance (KP), and the response evaluation criteria in solid tumors (RECIST). The response is categorized as complete response (CR), partial response (PR) outcomes, stable disease (SD), progressive disease (PD) and as CR + PR as a composite for response rate.

In addition, we extracted data on trial quality, protocol, and outcomes assessed. We assessed quality through the reporting of the following criteria: sequence generation and allocation concealment. We also noted the language in which the paper was written and the setting the studies were conducted. These criteria were not used for weighting covariates in the meta-analysis; instead, these were considered *a priori* explanations for study heterogeneity.

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 NSCLC. Following the example set by D'Addario et al¹⁷ and the Cochrane Collaboration's Non-Small-Cell Lung Cancer Collaborative Group,¹⁸ platinum-based

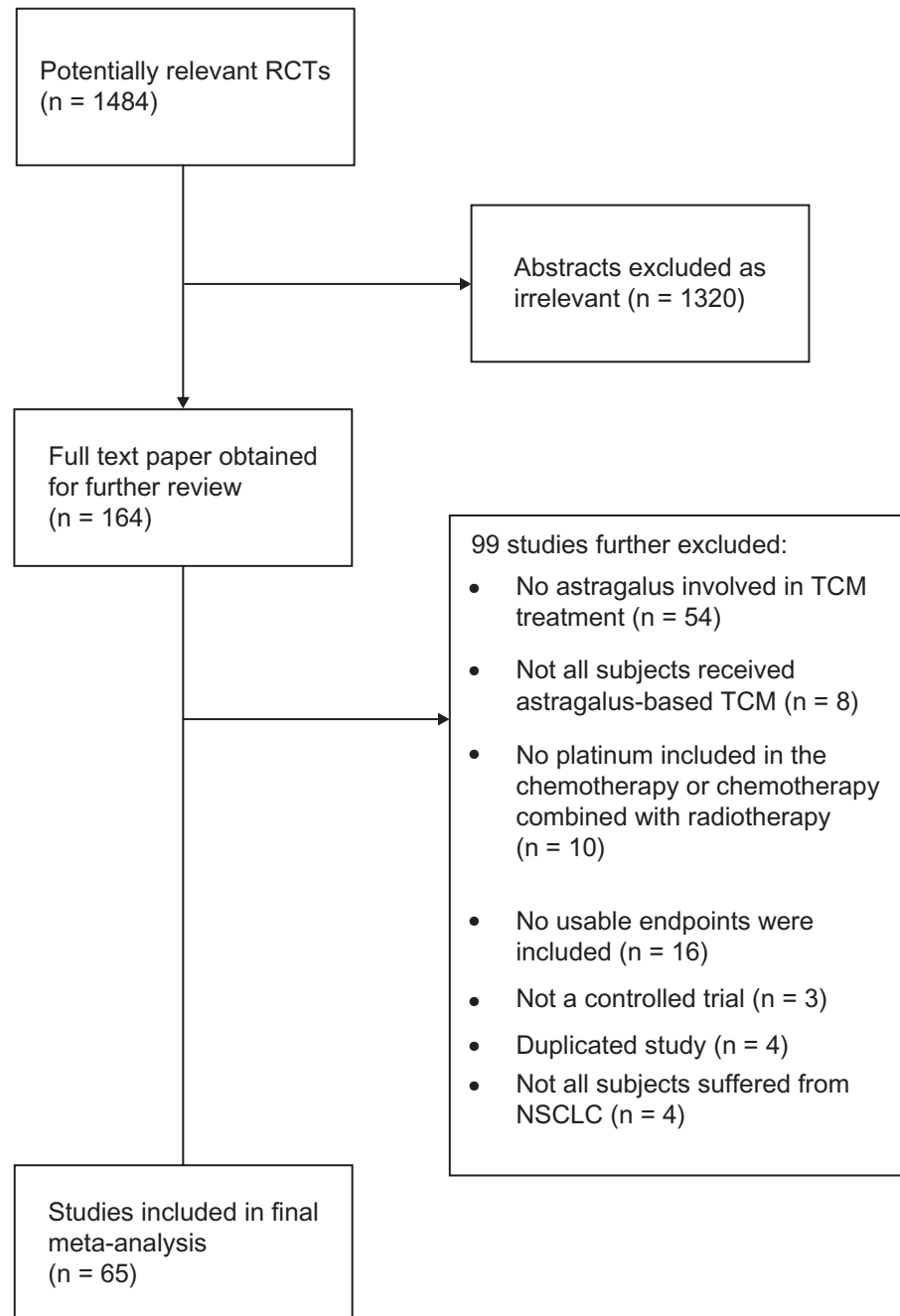


Figure 1 Flow diagram of included studies.

chemotherapy was grouped together as a therapeutic class when assessing efficacy of treatment for NSCLC. Each stage of the planning, design, analysis, and reporting of this meta-analysis was conducted in accordance with the QUOROM Statement guidelines.¹⁹

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.²⁰ 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, compared to the proportion in the platinum-based chemotherapy group. Thus, RR less than 1 favors the combination regimen.

Objective tumor response

Given that most of the studies identified in our systematic search reported tumor response at conclusion of treatment using RECIST,²¹ 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.²²

Performance status

Many of the studies identified in our systematic search reported performance status using the Karnofsky performance scale,²³ 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 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.

Analysis

We used the random-effects model of DerSimonian and Laird²⁴ 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 I^2 statistic to assess between-study heterogeneity and interpreted the outcome as <50% as non-problematic heterogeneity. To assess publication bias, we used the Begg-Mazumdar 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

We applied the RR and 95% CI as our primary effect measure in this analysis. For analysis examining response, favorable results for the TCM intervention are in the direction greater than 1. In circumstances of zero outcome events in either arm of a trial, we used the Haldane method and added 1 to each arm, as suggested by Sheeche.²⁶ We first pooled studies on all interventions versus all controls using the DerSimonian-Laird random effects method.²⁷ This method recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.²⁸ Forest plots are displayed for the primary analysis, showing individual study effect measures with 95% CIs and the overall DerSimonian-Laird pooled estimate. We conducted a meta-regression analysis using the unrestricted maximum likelihood method to determine if the *a priori* covariates of TCM formulation yielded differing effects. We examined publication bias visually and through the Begg-Mazumdar tests. We calculated the optimal information size (OIS) required to determine adequate power across trials. We used Stats Direct and Comprehensive Meta-Analysis (Version 2) for all statistical procedures. All *P* values are 2-sided and a *P* value < 0.05 was considered significant. PW and EM conducted the analysis.

Results

Included studies

Our systematic search identified 1484 potentially relevant abstracts, of which 164 were identified as requiring full-text article retrieval (Figure 1). Close screening of these 221 studies identified 65 studies that met our inclusion criteria, containing a total of 4751 patients. Most studies were small (median 67, interquartile range 56 to 83). Studies poorly reported methodological issues including sequence generation (25%), allocation concealment (3%), and reporting of adverse events (67%). Table 1 provides the study characteristics.

Survival

We pooled 7 studies^{29–35} (n = 529) reporting on survival at 6 months and found a pooled RR of 0.54 (95% CI, 0.45 to 0.65, $P \leq 0.0001$, $I^2 = 0\%$, 95% CI, 0% to 58%, $P = 0.74$, see Figure 2). We included 20 trials^{30–49} (n = 1520) in our analysis of survival at 12 months and found a pooled RR of 0.65 (95% CI, 0.54 to 0.79, $P \leq 0.0001$, $I^2 = 74\%$, 95% CI, 57% to 82%, $P < 0.0001$, see Figure 3). As 12-month survival was our primary outcome, we applied the publication bias assessment and found no evidence of publication bias (Kendall's tau = -0.157, $P = 0.31$). We included 13 trials^{32,34,35,40–49} (n = 1090) with survival rates reported at 24 months and found a pooled RR of 0.74 (95% CI, 0.66 to 0.84, $P \leq 0.0001$, $I^2 = 64\%$, 23% to 78%, $P = 0.0008$, see Figure 4). We included data from 10 trials^{35,40–46,48,49} (n = 878) reporting on survival at 36 months and found a pooled RR of 0.86 (95% CI, 0.80–0.92, $P \leq 0.0001$, $I^2 = 29\%$, 95% CI, 0% to 65%, $P = 0.17$, see Figure 5).

Tumor response

We were able to include data from 27 trials^{37,39–43,50–70} (n = 1759) reporting on complete responses to treatment and found a pooled RR of 1.43 in the direction of favorable outcomes for herbal-based treatment (95% CI, 0.98 to 2.10, $P = 0.07$, $I^2 = 0\%$, 95% CI, 0% to 42%, $P \leq 0.99$). The same 27 trials reported on partial response to treatment and found a pooled RR of 1.35 favoring herbal treatment (95% CI, 1.19 to 1.53, $P \leq 0.0001$, $I^2 = 0\%$, 95% CI, 0% to 38%, $P = 0.99$). When we applied a composite endpoint of any treatment response we pooled data from 57 trials^{30,32–35,37,39–45,48–50,87–90} and found a pooled RR of 1.35 in favor of herbal treatment (95% CI, 1.26 to 1.44, $P \leq 0.0001$, $I^2 = 0\%$, 0% to 28%, $P = 0.99$, see Figure 6).

Performance status

We included data from 35 trials^{35,37,43,48–53,55,56,58–64,66–72,77,80,84,85,87,88,91–94} (n = 2650) assessing stable or improved

Karnofsky scores and found a pooled RR of 1.58 (95%, 1.39 to 1.81, $P \leq 0.0001$, $I^2 = 69\%$, 55% to 78%, $P \leq 0.0001$, see Figure 7).

Discussion

Our findings should be of interest to cancer researchers and funding agencies. We found consistent evidence of improved survival and tumor response in astragalus-based herbal medicine therapy combined with platinum-based chemotherapy compared with platinum-based chemotherapy alone, the standard of care. While there is reason to be cautious of the quality of the included clinical trials, due to their small sample sizes and inadequate reporting of methodological issues, there has been a consistent direction of treatment effect that warrants further examination by experienced clinical trialists in a transparent manner.

Our study has both strengths and limitations to consider. Strengths include our extensive searching and identification of Chinese clinical trials that few systematic review groups may be able to accomplish. Our analysis used a broad approach that considered all astragalus containing herbal combinations as comparatively similar, thus allowing much greater power to detect an effect over a single trial. It is possible that specific combination exert a differing therapeutic effect; however we were unable to identify such specific formulations. The limitations of our study are predominantly related to the need for caution in interpreting the clinical trials. There is consistent evidence that publication bias may exist in Chinese medical journals and thus, only positive trials are published.⁹⁵ Although we recognize favorable outcomes may be more likely to be published, our analysis actually does not find that only positive trials are published. If one examines the forest plots, on average, most trial are negative, but when pooled, become positive. A recent evaluation, by Wu et al, found that many studies labelled as RCTs with Chinese journals were, in fact, not randomized.⁹⁶ In our own experience, we recognize many Chinese clinical trialists have not been exposed to appropriate clinical epidemiology training. Yet even if our analysis includes predominantly non-randomized studies, the consistency of therapeutic effect warrants further examination. 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.⁹⁷ We assessed publication bias in our primary outcome (survival at 12 months) and did not find statistical evidence of bias, although funnel plots and statistical tests cannot identify the absence of publication bias.

Table 1 Included study characteristics

Study	No of patients	Protocol ^a	Ingredients	Disease stage ^b
Cao ⁸⁶	76	CAP/NP + astragalus combination	<i>Adenophora verticillata</i> , <i>Ophiopogon japonicus</i> , <i>Schisandra chinensis</i> , <i>Astragalus membranaceus</i> (<i>astragalus</i>), <i>Oldenlandia diffusa</i> , <i>Eriobotrya japonica</i> , <i>Fritillaria cirrhosa</i> , <i>Arisaema amurense</i>	III/IV
Chen ³²	43	CAP + astragalus combination	<i>Codonopsis pilosula</i> , <i>Astragalus membranaceus</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Pinellia ternata</i> , <i>Citrus reticulata</i> , <i>Dioscoreae opposita</i> , <i>Oldenlandia diffusa</i> , <i>Houttuynia cordata</i> , <i>Patrina villosa</i> , <i>Scutellaria barbata</i> , <i>Agrimonia pilosa</i> , <i>Ziziphus jujube</i>	III/IV
Chen ⁵⁸	56	NP + Yi Qi Yan Yin	<i>Adenophora</i> , <i>Liriope</i> , <i>Rehmanniae praeparatum</i> , <i>astragalus</i> , <i>Radix pseudostellariae</i> , <i>Poria</i> , <i>Ligustrum</i> , <i>hawthorn</i> , <i>Chinese sage</i> , <i>Oldenlandia diffusa</i>	III/IV
Cheng ⁷⁵	60	FDH + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris sichoi</i>	III/IV
Chu ^{80,a}	128	EAP + radiation + astragalus combination	<i>Astragalus</i> , <i>Panax ginseng</i> , <i>Atractylodes macrocephala</i> , <i>Psoralea corylifolia</i> , <i>Asparagus cochinchinensis</i> , <i>Ophiopogon japonicus</i> , <i>Scrophularia ningpoensis</i> , <i>Rehmannia glutinosa</i> , <i>Sparganium stoloniferum</i> , <i>Curcuma zedoria</i> , <i>Manis pentadactyla</i> , <i>Ostrea gigis</i> shell, <i>Trichosanthes kirilowii</i> , <i>Arisaema amurense</i> , <i>Scutellaria barbata</i> , <i>Oldenlandia diffusa</i>	III/IV
Fan ⁶⁵	112	CAP + astragalus combination	<i>Codonopsis pilosulae</i> , <i>Atractylodes macrocephala</i> , <i>Glycyrrhiza uralensis</i> , <i>Astragalus</i> , <i>Ligustrum lucidum</i> , <i>Poria cocos</i> , <i>Salvia miltiorrhiza</i> , <i>Prunus persica</i>	III/IV
Fei ⁹⁰	68	MVP + astragalus combination	<i>Astragalus</i> , <i>Codonopsis pilosulae</i> , <i>Rehmannia glutinosa</i> , <i>Asparagus cochinchinensis</i> , <i>Ophiopogon japonicus</i> , <i>Scrophulariae ningpoensis</i> , <i>Cimicifuga foetida</i> , <i>Houttuynia cordata</i> , <i>Smilax glabra</i> , <i>Aloe vera</i>	III/IV
Feng ⁶³	60	GP + Feiliping II	<i>Astragalus</i> , <i>American ginseng</i> , <i>peach seed</i> , <i>safflower</i> , <i>petiole paris</i> [root], <i>Oldenlandia diffusa</i>	III/IV
Gao ⁸⁹	96	MVP/CAP + astragalus	<i>Astragalus</i>	III/IV
Gao ⁷²	67	GCN + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris sichoi</i>	III/IV
Hong ³⁸	47	NP + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris sichoi</i>	III/IV
Jia ⁸⁷	68	MVP/NP + astragalus combination	<i>Curcuma longa</i> , <i>Curcuma aromatica</i> , <i>Snake</i> , <i>Prunellae vulgaris</i> , <i>Concha ostrea</i> , <i>Oldenlandia diffusa</i> , <i>astragalus</i> , <i>Panax quinquefolium</i>	III/IV
Jin ⁴⁶	90	MVP + astragalus combination	<i>Astragalus</i> , <i>Polygonatum chinense</i> , <i>Ligustricum lucidum</i> , <i>Ganoderma lucidum</i> , <i>Salvia chinensis</i> , <i>Paris polyphylla</i> , <i>Drynaria fortunei</i> , <i>Citrus reticulata</i>	III/IV
Kong ⁶⁶	52	GP + Zhenqifuzhen capsule	<i>Astragalus</i> , <i>Ligustrum</i>	III/IV
Li ⁸¹	114	CE/CAP + astragalus combination	<i>Astragalus</i> , <i>Polygonatum chinense</i> , <i>Panax ginseng</i> , <i>Agrimonia pilosa</i> , <i>Houttuynia cordata</i> , <i>Rheum palmatum</i> , <i>Polyporus umbellatus</i> , <i>Lobelia chinensis</i> , <i>Oldenlandia diffusa</i> , <i>Arisaema amurense</i> , <i>Coix lachryma</i> , <i>Prunus persica</i> , <i>Trichosanthes kirilowii</i> , <i>Prunella vulgaris</i>	III/IV
Li ⁷⁸	90	CE/CAP + astragalus combination	<i>Astragalus</i> , <i>Adenophora verticillata</i> , <i>Lilium brownii</i> , <i>Ophiopogon japonicus</i> , <i>Coix lachryma</i> , <i>Scutellaria barbata</i> , <i>Akebia trifoliata</i> , <i>Selaginella doederleinii</i> , <i>Agrimonia pilosa</i> , <i>Polistes japonicus</i> , <i>Fritillaria thunbergii</i> , <i>Houttuynia cordata</i> , <i>Pinellia ternata</i> , <i>Glycyrrhiza</i>	III/IV
Li ⁵⁴	35	NP + Jian Pi Wen Shen	<i>Astragalus</i> , <i>Atractylodes</i> , <i>Poria</i> , <i>Epimedium</i> , <i>cistanche</i> , <i>greater selaginella</i> , <i>Chinese sage</i>	II-IV
Li ⁵⁶	70	NP + Jian Pi Yi Shen	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Poria</i> , <i>Atractylodes</i> , <i>dry orange peel</i> , <i>amomum fruit</i> , <i>Red peony root</i> , <i>Ligustrum</i> , <i>Cuscuta</i> , <i>eclipta</i> , <i>babchi seed</i> , <i>Encornimiae ulmoide</i> , <i>Epimedium</i> , <i>Wolfberry</i> , <i>Polygonatum</i> , <i>hawthorn</i> , <i>gizzard lining</i> , <i>liquorice root</i>	III, IV

Li ⁶¹	83	NP + TCM	Astragalus, <i>Atractylodes</i> , <i>Adenophora</i> , <i>dendrobium</i> , <i>ligustrum</i> , <i>Wolfberry</i> , <i>ily</i> , Chinese <i>angelica</i> , <i>rehmanniae vaporata</i> , <i>hemlock parsley</i>	III/IV
Li ⁶⁵	40	NP/VP + Yi Qi Hua Tan	<i>Campanumaea pilosula</i> , <i>astragalus</i> , <i>Trichosanthes</i> rind, <i>fritillary</i>	III/IV
Lin ⁵²	202	NP/MVP + Shan-dan capsule	Ginseng, <i>astragalus</i> , <i>Atractylodes</i> , <i>gizzard lining</i> , <i>Trichosanthes</i> , <i>Pinella</i> , <i>magnolia</i> , <i>Hovenia dulcis</i> , <i>Curcuma</i> , <i>salvia</i>	I-IV
Li ³⁴	77	MAP + Jin Fu Kang	<i>Astragalus</i> , <i>Adenophora verticillata</i> , <i>Ophiopogonis japonicus</i> , <i>Ligustricum lucidum</i> , <i>Selaginella doederleinii</i> , <i>Paris polyphylla</i>	II, III or IV
Li ^{88*}	190	CAP/MVP + Jin Fu Kang	<i>Astragalus</i> , <i>Adenophora verticillata</i> , <i>Ophiopogonis japonicus</i> , <i>Ligustricum lucidum</i> , <i>Selaginella doederleinii</i> , <i>Paris polyphylla</i>	III/IV
Li ³⁵	144	MAP + Jin Fu Kang	<i>Astragalus</i> , <i>Adenophora verticillata</i> , <i>Ophiopogonis japonicus</i> , <i>Ligustricum lucidum</i> , <i>Selaginella doederleinii</i> , <i>Paris polyphylla</i>	III/IV
Li ⁷⁹	65	EAP/CAP + astragalus combination	<i>Astragalus</i> , <i>Pseudostellaria heterophylla</i> , <i>Adenophora verticillata</i> , <i>Atractylodes macrocephala</i> , <i>Rehmannia glutinosa</i> , <i>Coix lachryma</i> , <i>Poria cocos</i> , <i>Curcuma zeodaria</i> , <i>Salvia miltiorrhiza</i> , <i>Panax notoginseng</i> , <i>Citrus aurantium</i> , <i>Cremastra variabilis</i> , <i>Prunus armeniaca</i>	III/IV
Li ⁴⁸	78	CAP/MVP/CE + astragalus combination	<i>Pseudostellaria heterophylla</i> , <i>astragalus</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Ophiopogonis japonicus</i> , <i>Oldenlandia diffusa</i> , <i>Scutellaria barbata</i> , <i>Taraxicum mongolicum</i> , <i>Paris polyphylla</i> , <i>Fritillaria thunbergii</i> , <i>Ligustricum lucidum</i> , <i>Buthus martensi</i> , <i>Scolopendra subspinipes</i> , <i>Hirudo nipponica</i> , <i>Coix lachryma</i> , <i>Glycyrrhizae uralensis</i>	III/IV
Li ⁵⁹	40	NP/GP + Yi Qi Yan Yin	<i>Astragalus</i> , <i>Adenophora</i> , <i>asparagus</i> , <i>Liriope</i> , <i>Ligustrum</i> , greater <i>selaginella</i> , Chinese <i>sage</i> , <i>paris</i> [root]	III/IV
Li ⁶⁹	60	NP + Fuzhenguben	American <i>ginseng</i> , <i>astragalus</i> , <i>Salvia</i> , Chinese <i>angelica</i> , <i>Heartleaf Houத்துය්න</i> Herb, dry orange peel, <i>Thunberg fritillary bulb</i>	III/IV
Lu ⁷⁴	73	NP + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Lu ⁴²	96	PAC + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Lu ⁷⁰	58	NP + Zhongyao Zengmian	Black ant, <i>Acanthopanax</i> , raw oyster shell, <i>astragalus</i> , <i>polygonatum</i> [root], <i>Epimedium</i> herb, mulberry, <i>Barbary wolfberry fruit</i> , <i>Campanumaea pilosula</i> , <i>atractylodes</i> , <i>Poria</i> , <i>Salvia</i>	III/IV
Luo ⁶²	50	TAX + DDP + Shenqifuzhen injection	<i>Campanumaea pilosula</i> , <i>astragalus</i>	III/IV
Luo ⁴³	108	EP + TCM	<i>Astragalus</i> , <i>Atractylodes</i> , Dried longan pulp, <i>Rehmanniae praeparatum</i> , white peony root, <i>Radix rehmanniae</i> , dry orange peel, <i>costustoot</i> , <i>hemlock parsley</i>	III/IV
Mao ³²	60	MVP + TCM	<i>Astragalus</i> , Chinese <i>angelica</i> , <i>Atractylodes</i> , <i>Poria</i> , <i>polygonatum</i> , <i>Ligustrum</i> , <i>paris</i> [root], <i>ornus</i> , dried orange peel	I-II
Shen ³⁶	80	NP + TCM	<i>Stragalus</i> , <i>Atractylodes</i> , <i>Adenophora</i> , <i>asparagus</i> , <i>Liriope</i> , almond, <i>Radix stemonae</i> , <i>Trichosanthes</i> rind, raw <i>arisaema</i> [root], <i>Shizandra berry</i> , Chinese <i>sage</i> , <i>Oldenlandia diffusa</i> , <i>prunella</i> , raw oyster shell, <i>Bulbus Fritillariae</i>	IIIb/IV
Shen ⁴¹	72	NP + TCM	<i>Astragalus</i> , <i>Atractylodes polygonatum</i> , <i>Adenophora</i> , <i>Liriope</i> , <i>umbilicaria</i> , <i>ligustrum</i> , <i>babchi seed</i> , <i>Spatholobus stem</i> , <i>Oldenlandia diffusa</i>	III/IV

(Continued)

Table 1 (Continued)

Study	No of patients	Protocol ^a	Ingredients	Disease stage ^b
Sui ^{33*}	80	MVP + Astragalus combination	<i>Lilium brownii</i> , <i>Rehmannia glutinosa</i> , <i>Scrophularia ningpoensis</i> , <i>Angelicae sinensis</i> , <i>Ophiopogonis japonicus</i> , <i>Paeonia lactiflora</i> , <i>Adenophora verticillata</i> , <i>Astragalus</i> , <i>Ligustricum lucidum</i> , <i>Paris polyphylla</i> , <i>Oldenlandia diffusa</i> , <i>Houttuynia cordata</i> , <i>Fritillaria cirrhosa</i> , <i>Crematista variabilis</i> (with individualized additions)	II, III or IV
Sui ⁶²	74	CE-CAP/MVP/TC + Astragalus combination	<i>Ganoderma lucidum</i> , <i>Pseudostellaria heterophylla</i> , <i>Coix lachryma</i> , <i>Atractylodes macrocephala</i> , <i>astragalus</i> , <i>Lycium chinense</i> , <i>Curcuma zedoaria</i> , <i>Scolopendria subspinipes</i> , <i>Smilax glabra</i>	III/IV
Tian ⁸³	40	NP + Fu Zhen Jie Du	<i>Astragalus</i> , <i>Adenophora</i> , <i>asparagus</i> , <i>Liriope</i> , <i>Ligustrum</i> , <i>epimedium</i> , <i>Oldenlandia diffusa</i>	III/IV
Wang ⁷¹	32	NP/MVP + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Wang ⁷⁷	98	NP + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Wang ⁴⁴	93	MOP + astragalus combination	<i>Adenophora verticillata</i> , <i>Asparagus cochinchinensis</i> , <i>Ophiopogonis japonicus</i> , <i>Pseudostellaria heterophylla</i> , <i>Astragalus</i> , <i>Curcuma zedoaria</i> , <i>Atractylodes macrocephala</i> , <i>C. aromatica</i> , <i>Paeonia rubra</i> , <i>Paeonia lactiflora</i> , <i>Oldenlandia diffusa</i> , <i>Scutellaria barbata</i>	III/IV
Wang ³¹	58	Cisplatin + astragalus combination	<i>Astragalus</i> , <i>Panax ginseng</i> , <i>Lilium brownii</i> , <i>Adenophora verticillata</i> , <i>Ophiopogonis japonici</i> , <i>Fritillaria cirrhosa</i> , <i>Morus alba</i> , <i>Trichosanthes kirilowii</i> , <i>Scutellariae baicalensis</i> , <i>Paris polyphylla</i> , <i>Scutellaria barbata</i> , <i>Solanum nigrum</i> , <i>Lepidium apetalum</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Phaseolus carcaratus</i> , <i>Ziziphus jujube</i>	III/IV
Wang ⁸³	58	CAP/MVP + astragalus combination	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Asparagus cochinchinensis</i> , <i>Ophiopogonis japonicus</i> , <i>Adenophora verticillata</i> , <i>Angelicae sinensis</i> , <i>Dioscoreae opposita</i> , <i>Dendrobium nobile</i> , <i>Polygonatum chinense</i> , <i>Schisandra chinensis</i> , <i>Ziziphus spinosa</i> , <i>Glycyrrhizae uralensis</i> , <i>Citrus reticulata</i>	III/IV
Wang ³⁰	60	NP + Ai Di injection	<i>Panax ginseng</i> , <i>astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Wang ⁴⁰	46	GP/TP + TCM	<i>Astragalus</i> , <i>polygonatum</i> , <i>umbilicaria</i> , <i>babchi seed</i> , <i>Atractylodes</i>	II–IV
Wen ⁶⁷	78	NP + TCM	<i>Astragalus</i> , <i>Campanumaea pilosula</i> , <i>Polygonatum</i> , <i>Ligustrum</i> , <i>Spatholobus stem</i> , <i>ass hide glue (melt)</i> , <i>Pinellia</i>	II–IV
Weng ²⁰	34	CAP + astragalus combination	<i>Codonopsis pilosulae</i> , <i>astragalus</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , <i>Pinellia ternata</i> , <i>Citrus reticulata</i> , <i>Dioscorea opposita</i> , <i>Oldenlandia diffusa</i> , <i>Houttuynia cordata</i> , <i>Patrina villosa</i> , <i>Scutellaria barbata</i> , <i>Agrimonia pilosa</i> , <i>Ziziphus jujube</i>	III/IV
Xie ⁶⁸	60	NP + TCM	<i>Ginseng</i> , <i>Atractylodes</i> , <i>Poria</i> , <i>liquorice root</i> , <i>astragalus</i> , <i>Chinese angelica</i> , <i>Spatholobus stem</i> , <i>Pyrosia [leaf]</i> , <i>Barbed skullcap herb</i>	III/IV
Xu ⁵⁷	40	TP + Ke Liu Wan	<i>Curcuma</i> , <i>Mylabris</i> , <i>Gecko</i> , <i>Vietnamese Sophora Root</i> , <i>leech</i> , <i>ground beetle</i> , <i>astragalus</i>	II–IV
Xu ⁶⁰	72	GP/TP + TCM	<i>Astragalus</i> , <i>Adenophora</i> , <i>Liriope</i> , <i>apricot kernel</i> , <i>Thunberg Fritillary Bulb</i> , <i>wild buckwheat rhizome</i> , <i>curcuma</i> , <i>Chinese honeylocust fruit</i> , <i>coix seed</i> , <i>Oldenlandia diffusa</i>	IV
Xue ³⁷	72	GP + TCM	<i>Astragalus</i> , <i>Pseudostellaria root</i> , <i>Atractylodes</i> , <i>Poria</i> , <i>Pinellia</i> , <i>dry orange peel</i> , <i>mulberry root bark</i> , <i>Rehmanniae vaporata</i> , <i>heartleaf Houttuynia herb</i> , <i>Oldenlandia diffusa</i>	IIIb/IV
Yang ⁵¹	56	GP + Ai Di injection	<i>Panax ginseng</i> , <i>Astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Yang ⁶⁴	40	GP + Ke Liu Wan	<i>Astragalus</i> , <i>Mylabris</i> , <i>leech</i>	III/IV
Yu ^{47†}	92	MAP + radiation + astragalus combination	<i>Astragalus</i> , <i>Pseudostellaria heterophylla</i> , <i>Poria cocos</i> , <i>Amomum xanthioides</i> , <i>Salvia miltiorrhiza</i> , <i>Paeonia rubra</i> , <i>Spatholobus suberectus</i> , <i>Schisandra chinensis</i> , <i>Glycyrrhizae uralensis</i> (with individualized additions)	III/IV
Zhang ⁷⁶	50	NP + Ai Di injection	<i>Panax ginseng</i> , <i>Astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV
Zhang ⁷³	98	NP + Ai Di injection	<i>Panax ginseng</i> , <i>Astragalus</i> , <i>Eleutherococcus senticosus</i> , <i>Mylabris cichoi</i>	III/IV

Zhang ⁹¹	60	EP + Ai Di injection	Panax ginseng, Astragalus, Eleutherococcus senticosus, Mylibirs cichoi	III/IV
Zhang ⁵⁵	70	GP + Jian Pi Zi Yin	Astragalus, Atractylodes, Poria, cinnamonvine, coix seed, mix-fried licorice, pseudostellaria root, Adenophora, Liriope, Ligustrum, dry toad's skin, Thunberg Fritillary Bulb, Buthus, notoginseng, Curcuma	II-IV
Zhang ³⁹	60	MVP + Bu Qi Huo Xue	Astragalus, Radix pseudostellariae, Atractylodes, amomum fruit, Poria, salvia, Spatholobus stem, earthworm, red peony root, ligustrum, Oldenlandia diffusa, bulbus fritilariae, mix-fried licorice	III/IV
Zhong ²⁴	48	GP + Yi Fei Jian	Poria, astragalus, Atractylodes, Pinellia, Hovenia dulcis, sweetflag, Hovenia dulcis, Platycodon root, greater selaginella, dry toad's skin, Wolfberry, ligustrum, epimedium, mix-fried turtle shell, Shizandra berry	III/IV
Zhou ³³	60	NP + Fu Zhen Bu Xu	Astragalus, Campanumaea pilosula, Poria, Atractylodes, Dioscoreae, Chinese angelica, white peony root, ass hide glue, wolfberry, Ligustrum, Semen psoraleae, cinnamon, Rehmanniae, Liriope, Adenophora, Dendrobium, Pinellia, dried orange peel, unibract fritillary bulb, liquorice root	II-IV
Zhou ⁸⁴	63	CAP + astragalus combination	Panax ginseng, Atractylodes macrocephala, Poria cocos, astragalus, Polygonatum chinense, Ophiopogonis japonicus, Cordyceps chinensis, Lycium chinense, Ephedra sinica, Prunus armeniaca, Trionyx sinensis, Prunellae vulgaris, Oldenlandia diffusa, Scutellaria barbata, P. notoginseng	III/IV
Zhou ⁴⁵	91	Cisplatin + astragalus combination	Adenophora verticillata, Ophiopogonis japonicus, Pseudostellaria heterophylla, Paris Polyphylla, astragalus, Scutellaria barbata, Curcuma zeodaria, Atractylodes macrocephala, Paeonia rubra, Paeonia lactiflora, Oryza sativa, Hordeum vulgare, Massa fermenta, Crataegus pinnatifida, Cremastra variabilis, Curcuma aromatica, Citrus reticulata	III/IV
Zou ⁴⁹	60	MAP + astragalus	Astragalus	III/IV

⁹¹In studies that included stage II patients, all patients received systemic therapy and no patients received surgery.

⁹¹In 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.

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.

Relative risk meta-analysis plot (random effects)

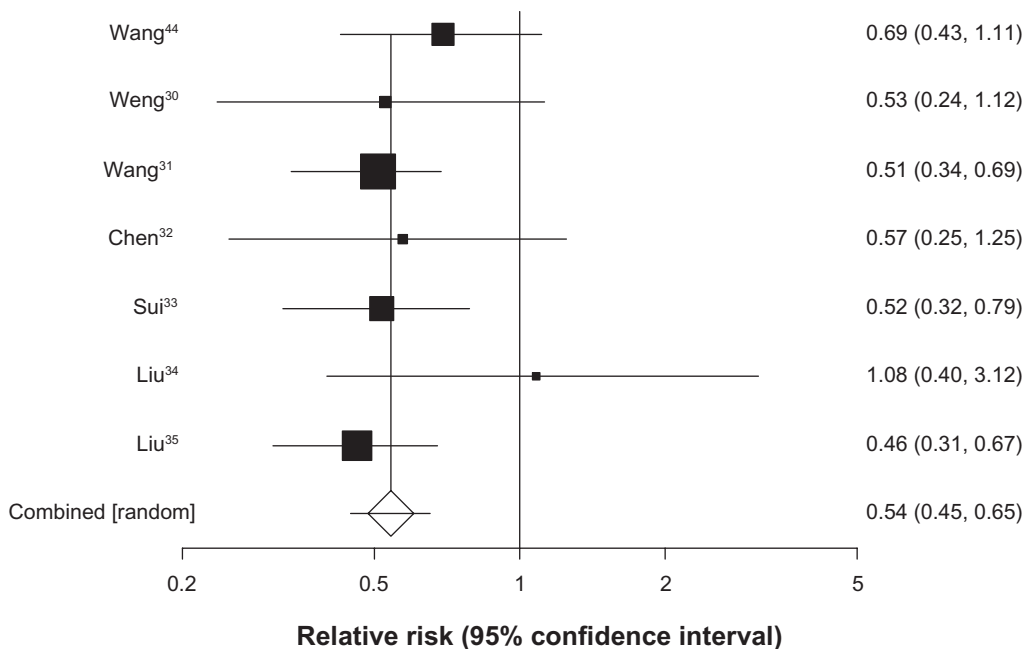


Figure 2 Six-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

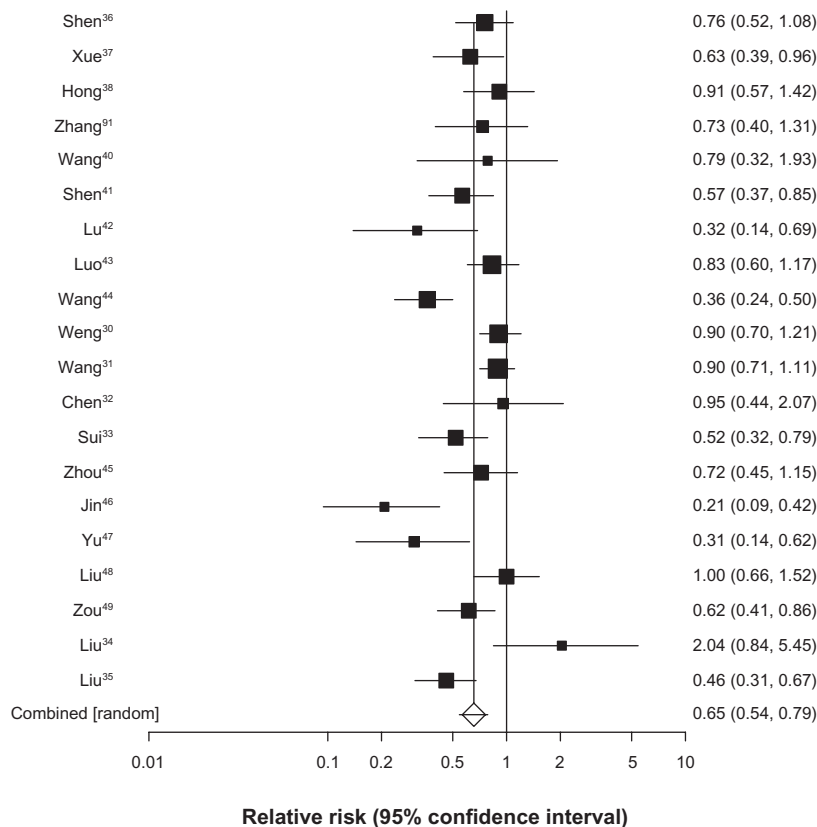


Figure 3 Twelve-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

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Relative risk meta-analysis plot (random effects)

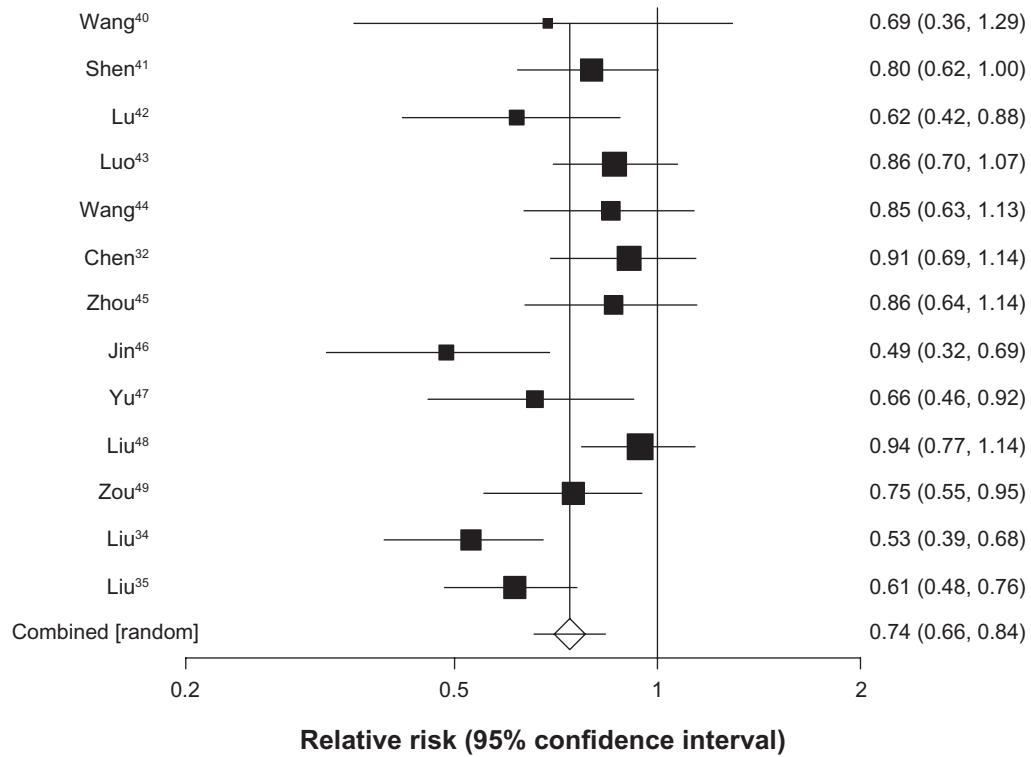


Figure 4 Twenty-four-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

Relative risk meta-analysis plot (random effects)

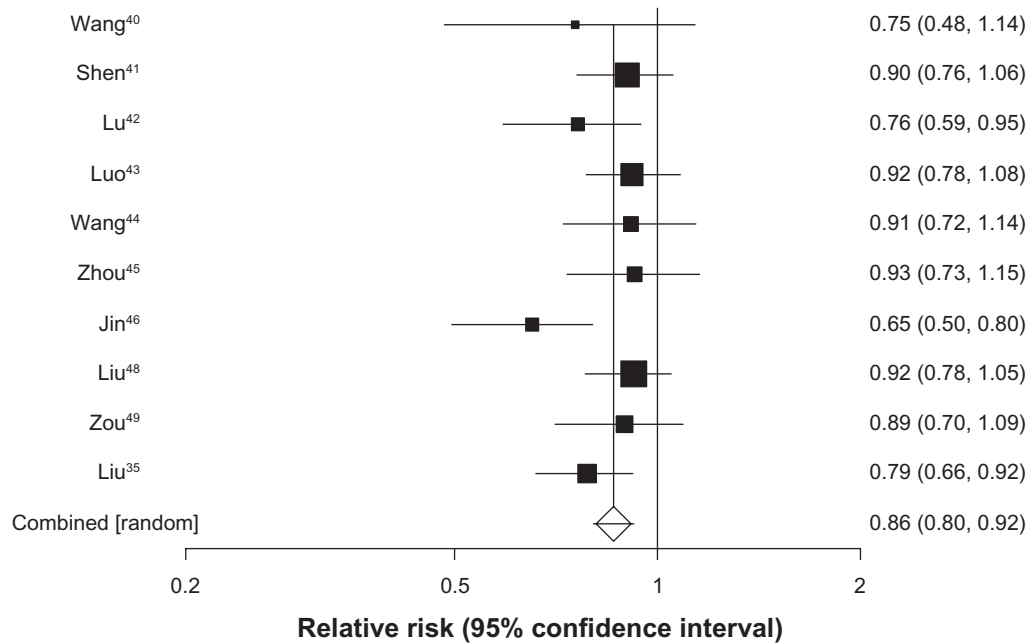


Figure 5 Thirty-six-month survival with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

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Relative risk meta-analysis plot (random effects)

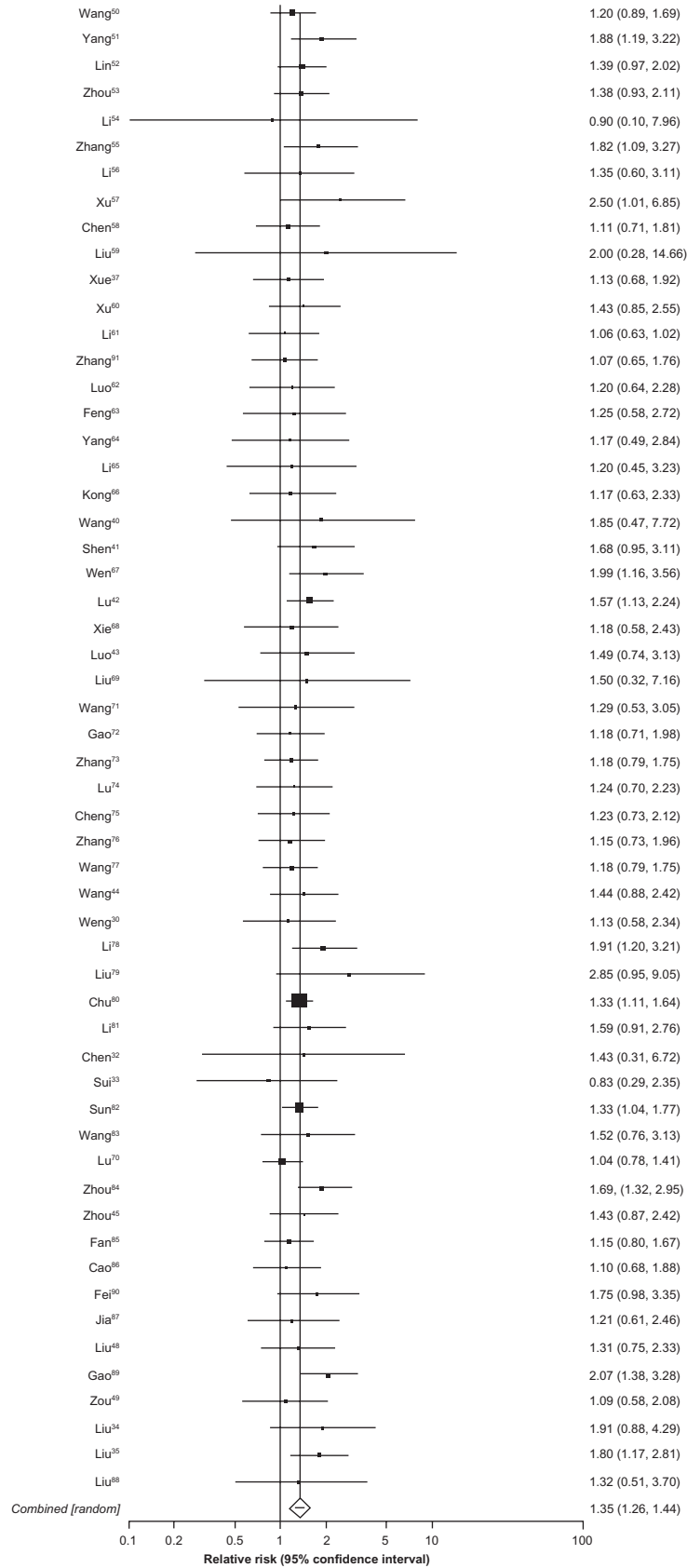


Figure 6 Tumor response with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

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Relative risk meta-analysis plot (random effects)

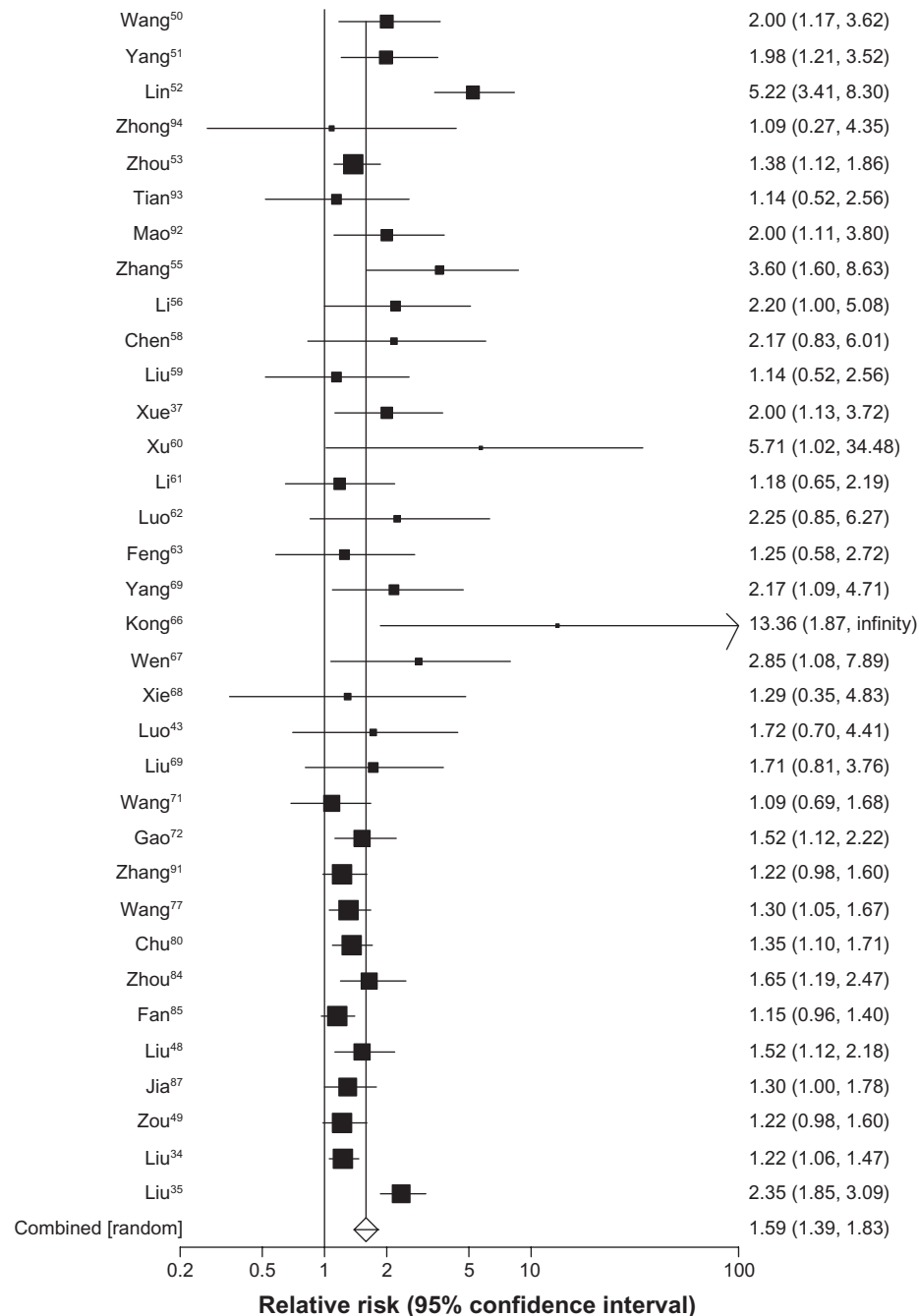


Figure 7 Stable/improved Karnofsky performance status with astragalus-based herbs and platinum-based chemotherapy versus platinum-based chemotherapy alone.

The reporting of quality features including how trials were randomized and how allocation concealment was achieved adds further caution to our study interpretation. While the inadequate reporting of these items is undesirable, there is, as yet, conflicting evidence that the reporting of these issues affects the magnitude of treatment effect.^{98–100}

Given the consistency of treatment effect, large number of trials, importance of the disease and the caution about

study quality it seems only reasonable that a clinical trial should be conducted in a Western setting that can ensure adequate sample size and concealed allocation to study arms. Such a clinical trial would provide strong inferences into the believability of our meta-analysis findings and could massively impact drug development. However, until a trial is conducted, we recommend counseling interested patients to maintain cautious optimism on any treatment effect and

discuss with their oncology physician about potential costs and harms.

Our study builds on an existing collaboration between researchers in China and in North America. We recognize that important and effective drugs have been discovered by examining the Chinese medical literature for existing clinical trials. Artemisin-based therapy for malaria and oseltamivir (Tamiflu®) for influenza are two compelling examples.^{101,102} We have previously used this approach for examining potentially effective interventions for hepatocellular cancers and found evidence of existing interventions that have never been evaluated in the West, despite compelling evidence of effectiveness. We believe that this approach represents a low-cost approach to identifying potentially effective new opportunities for drug development.

Additional research is needed to further understand the specific immunologic and cytotoxic mechanisms that astragalus may affect as an adjunct to chemotherapy for the treatment of advanced NSCLC.

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Disclosure

The authors declare no potential conflicts of interest.

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