Systematic Review and Meta-Analysis

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Evaluation of the efficacy and safety of elemene in treating malignant pleural effusion caused by tumors

A PRISMA guided meta-analysis

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Abstract

Objective: Elemene is widely used to treat malignant pleural effusion in China. This meta-analysis aimed to evaluate the efficacy and safety of elemene in treating malignant pleural effusion.

Methods: Electronic databases including Pubmed, the Cochrane Library, Embase and Chinese biomedical literature database were searched until March 2017. Clinical controlled trials (CCTs) assessing the efficacy and safety of elemene in the treatment of malignant pleural effusion were included. The quality of the included studies was evaluated using the quality evaluation criteria of the Cochrane Handbook version 5.1.0.

Results: A total of 46 CCTs were included, with 2992 patients. Results of meta-analysis showed that elemene significantly improved the overall response rate (ORR) in controlling malignant pleural effusion (risk ratio [RR] = 1.16; 95% CI: 1.08–1.23; $P < .05$). Subgroup results showed that the ORR of elemene in the treatment of lung cancer patients with malignant pleural effusion (RR = 1.20, 95% CI: 1.07–1.34; $P < .05$) was higher than that of other cancers (RR = 1.14, 95% CI: 1.05–1.23; $P < .05$). Meanwhile, elemene did not significantly increase the incidences of chest pain and fever ($P > .05$).

Conclusion: Elemene is suggested to have the ability of improving the treatment outcome of malignant pleural effusion with acceptable safety.

Abbreviations: BLM = bleomycin, CBM = Chinese Biomedical Literature Database, CCTs = clinical controlled trials, CI = confidence interval, CR = complete response, DDP = cisplatin, OR = odds ratio, ORR = overall response rate, PR = partial response, QOL = quality of life, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: cancer, elemene, malignant pleural effusion, meta-analysis, traditional Chinese medicine ;

1. Introduction

Malignant pleural effusion is often diagnosed based on aggressive pleural effusion or pleural biopsy.[1] The occurrence of malignant pleural effusion is almost associated with advanced malignant tumors, affecting quality of life (QOL) and representing high mortality.[2,3] Massive pleural effusions may occasionally cause significant lung mediastinal compression, resulting in respiratory and circulatory failure, which often need emergency treatments.[2,3]

The characteristics mentioned above suggest a palliative treatment regimen, as the survival of these patients ranges from 4 months to 1 year, despite considerable advances achieved in recent years.[2,3] Recurrence of malignant pleural effusions is common following initial thoracentesis. Besides, repeated extraction of pleural effusion will accelerate the loss of albumin and cause electrolyte imbalance in cancer patients.[4,5] Therefore, effective control of malignant pleural effusion can improve the general condition of patients, and thus it is the main focus of therapy for advanced cancer patients with malignant pleural effusion.[6] At present, the commonly used clinical treatment of malignant pleural effusion includes systemic chemotherapy, diuretic, and thoracic injection of drugs (such as cisplatin (DDP), bleomycin [BLM] and traditional Chinese medicine preparations) for pleurodesis after thoracic closed drainage.[6,7]

Elemene, 1 of the Chinese medicine extracts, is extracted from the ginger plant temperature turmeric, exhibiting anti-cancer activity.[8] According to the drug instruction of Elemene Injection, it contains a mixture of β-,γ-, and δ-Elemene. Basic and clinical experimental results showed that elemene has a wide range of anti-tumor spectrum, with curative effect, mild adverse reactions and other prominent advantages.[8–10] In recent years, there have been several reports of elemene alone or combined with chemotherapy and/or hyperthermia in the treatment of malignant pleural effusion, however, the results are not entirely consistent.[8,11] In 2014, Chen et al performed a meta-analysis to evaluate the clinical efficacy of elemene intrapleural injection in

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lung cancer patients with malignant pleural effusion.[8] Two years later, Wang et al conducted another meta-analysis to evaluate the clinical efficacy of elemene versus DDP in treating malignant pleural effusion caused by lung cancer.[12] These 2 meta-analyses only included lung cancer patients with malignant pleural effusion. In addition, elemene was mainly compared with DDP in limited number of clinical trials. However, whether elemene versus other controls has the similar efficacy and safety in the treatment of pleural effusion caused by lung cancer or other cancers, there is lack of sufficient evidence.

In this study, we searched the electronic databases including PubMed, the Cochrane library, EMbase, and Chinese Biomedical Literature Database (CBM), screened the eligible randomized controlled trials (RCTs), extracted data of efficacy and safety, and conducted this meta-analysis to assess the efficacy and safety of elemene versus other controls in treating malignant pleural effusion caused by several different types of cancers, aiming to provide evidence-based medicine for application of elemene.

2. Methods

This study was performed under the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This study was not registered.

2.1. Search strategy

Electronic databases including PubMed, the Cochrane library, EMbase, and CBM were searched to identify clinical controlled trials (CCTs) comparing the efficacy and safety of elemene versus other agents in treating malignant pleural effusion. Relevant literatures indicated by the initial reference on the same topic were also searched. The search period was from the establishment of the database to March 2017. The language of the references was limited to Chinese or English. The search terms used in various combinations were as follows: elemene, elemenum emulsion, delta-elemene, elemene injection, chemotherapy, DDP, BLM, tumor pleural effusion, cancer pleural effusion, and malignant pleural effusion.

2.2. Inclusion and exclusion criteria

Subjects: patients with malignant pleural effusion diagnosed by pathology or cytology. Study types: CCT presenting adequate definition of efficacy (such as complete response (CR), partial response (PR) and overall response rate [ORR]), adverse events and evaluating the efficacy and safety of elemene alone or combined with DDP or BLM or hyperthermia versus DDP or BLM or hyperthermia in the treatment of malignant pleural effusions. Interventions: experimental group used elemene based regimen, the control group used elemene free regimen. Exclusion criteria:

(1) non-malignant pleural effusion;
(2) incomplete or insufficient data of efficacy and safety;
(3) reviews and animal studies.

This study did not need ethical approval as it was a meta-analysis. All the grades of disease described in our included studies are advanced disease. The concentration of elemene was 0.1 g/20 mL (5 mg/mL) as stated in the drug instruction of elemene.

2.3. Endpoints

Primary endpoints were CR rate, PR rate and ORR. As mentioned above, there were adequate definitions of the primary endpoints in the eligible studies. Secondary endpoints included adverse events and QOL.

2.4. Screening for eligible CCTs and data extraction

The processes of screening and identifying the potential literature and filling the designed form were done by 2 reviewers, independently. When it is uncertain about data or study, a third reviewer was employed. If the interested information was incomplete, the authors of the original publications were contacted to obtain essential data. Otherwise, the article was dropped. The basic characteristics of the studies including title, publication year, primary diseases, diagnosis of malignant pleural effusion, number of the patients, age of the patients, the time of follow-up, and interventions were extracted by 2 reviewers, independently. The outcomes of the included studies, such as CR, PR, ORR, QOL and safety of elemene versus other medications were also extracted and used for the meta-analysis.

2.5. Quality assessment of included studies

The quality of the included studies was evaluated according to the Cochrane Handbook 5.1.[13] The evaluated items are mainly as following:

(1) randomization: it contains 3 categories: correct and adequate, inadequate, and not clear, based on whether random methods are used and their use is reasonable;
(2) allocation concealment: it has 4 categories: correct and sufficient, inadequate, unclear, and not used;
(3) blinding: it can be divided into single blind, double blind, and triple blind according to whether the blind is rationally used;
(4) loss to follow-up;
(5) incomplete reporting;
(6) selective reporting;
(7) other sources of biases.

The quality of the studies can be divided into three degrees. Grade A: mild bias with full compliance with the above quality standards, and smallest possibility of various bias. Grade B stands for moderate bias. It is defined as only 1 or more of the criteria are fulfilled, and the probability of occurrence of bias is moderate. Grade C means high bias. It is defined as completely unsatisfied with any 1 or more of the standards, with the highest probability of bias.

2.6. Statistical analysis

Meta-analysis was performed using the stata 12.0 software. The RR and its 95% confidence interval (CI) were used to represent the overall effect of the combined data. The weighted mean difference (WMD) and its 95% CI were used to represent the pooled effect of continuous variable. The heterogeneity between the included studies was analyzed by Cochran Q statistic and the I^2 statistic (0.25, 0.50, and 0.75 suggesting low, moderate, and high degrees of heterogeneity, respectively). When $P < .05$ and $I^2 > 50\%$, the random effect model was used for meta-analysis. Otherwise, the fixed effect model was used for analysis. The bias of publication was assessed by the Egger regression asymmetry test and the funnel plot. If there was no clinical homogeneity between the studies, the sub-group analysis was introduced. It was considered as statistically significant when the $P < .05$.

3. Results

3.1. Search results

A total of 1820 relevant articles were obtained after primary search. After reading the title and abstract, the literatures that did not meet the inclusion criteria were excluded, and 122 articles left. After further reviewing of the full text, studies with interventions, subjects, or other aspects that did not meet the inclusion criteria were excluded, resulting in 46 clinical trials.[11,14–58] 2992 cancer patients were included, 1499 of them were in the elemene group, and the rest were in the control group. The baseline data of the 2 groups were comparable. The specific process of searching and identifying the literatures is shown in Figure 1.

3.2. Baseline characteristics and overall quality of included studies

In summary, 89% were RCTs and the rest was retrospective trials (Table 1). The age of patients participated in these studies ranged from 18 to 82 years. This population was diagnosed with advanced cancers. The primary diseases were lung cancer, breast cancer, gastric cancer, ovarian cancer and other types of malignant tumors. The diagnostic methods of malignant pleural effusion included B-ultrasound, computed tomography scan, Magnetic Resonance Imaging scan, and effusion extraction. Elemene, DDP, BLM, interleukin-2 (IL-2), and other medications were used as interventions for these cases. The duration and dose of elemene varied across included trials, with a range of 200 mg/m^2 to 300 mg/m^2, q.w., for 2 W to 3 W. The reported outcomes were mainly focused on efficacy of controlling malignant pleural effusion, improving QOL, and incidences of adverse events.

The quality of included studies was assessed according to the Cochrane Handbook 5.1. Overall, the quality of these trials was considered as moderate risk of bias. Though most of the studies reported utilization of randomization, the specific details and methods of randomization were presented in only few trials. Risk of allocation was evaluated as moderate to

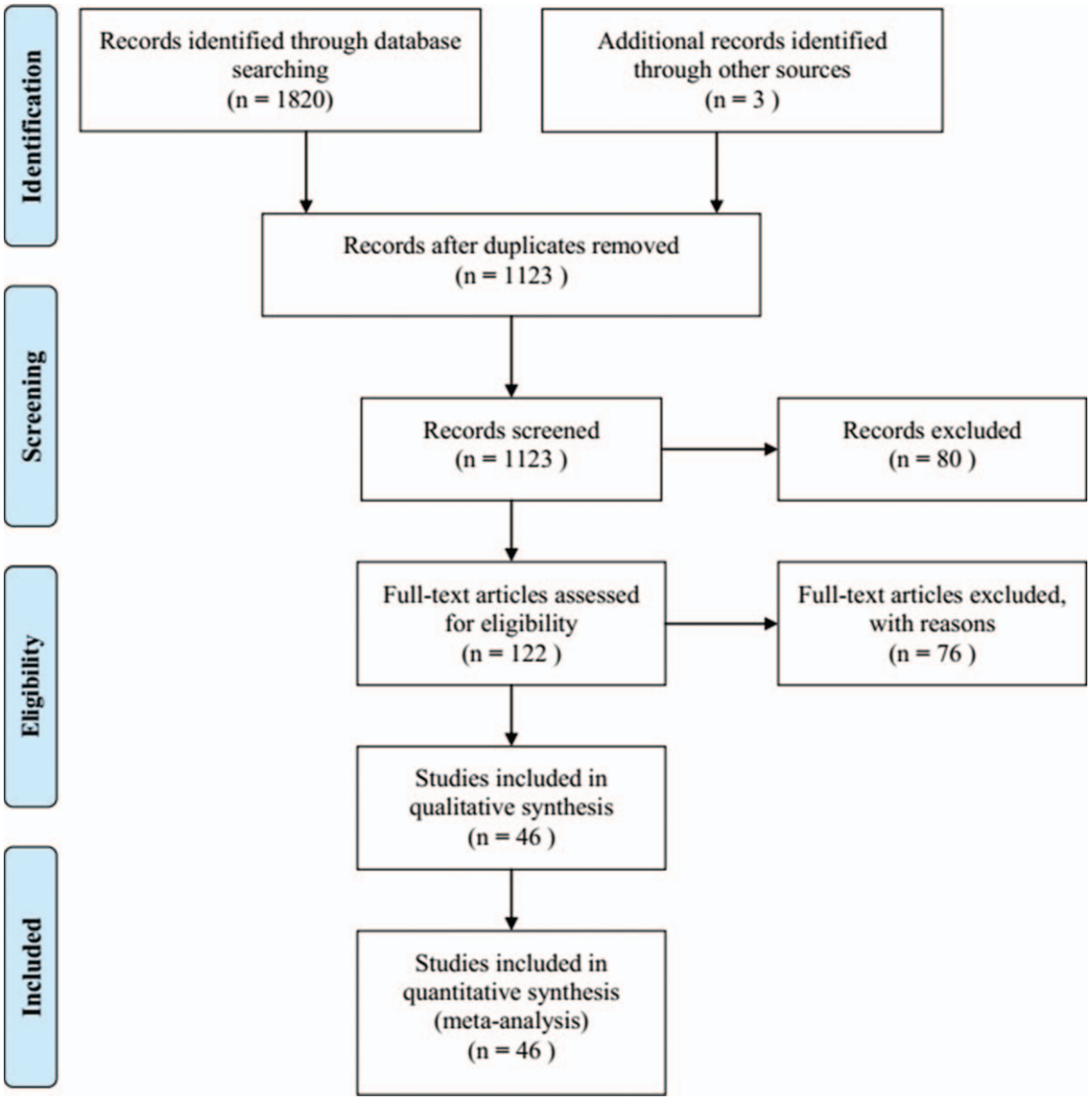

Figure 1. Study flow diagram.

Table 1

Baseline characteristics of included studies.

Studies	N		Sex		Age		Interventions		Cancers	Outcomes
	T	C	M	F	T	C	T	C		
Fang Zhao,et al 2015	17	17	17	17	42–75	42–75	Elemene 300 mg, QW, 3 W	bleomycin 45 mg, QW, 3 W	Lung cancer	Efficacy, AEs
Jingbo Sun, et al 2014	15	15	20	10	24–80	23–79	Elemene, 400 mg, QW, 2 W	DDP 60 mg, QW, 2 W	Lung cancer, breast cancer and other cancers	Efficacy
Jianpeng Li, et al 2014	40	41	NA	NA	60–82	60–82	Elemene 200 mg/m^2 in 40 ml saline + IL-2 2MU, QW, 3 W	DDP 40 mg/m^2, IL-2 2MU, QW, 3 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Jinna Wang, et al 2015	40	40	45	35	34–70	33–71	elemene 300mg/m^2, QW, 2W	DDP 40-60 mg, QW, 2W	Lung cancer	Efficacy
Bianrong Wu, et al 2015	29	27	31	25	42–76	45–78	Elemene 400 mg, QW, 3W	DDP80 mg, QW, 3W	Lung cancer	Efficacy, AEs, QOL
Yihe Zhang, et al 2016	32	31	27	36	55.5	56	Elemene 200mg/m^2, QW, 3W	epirubicin 50mg/m^2, QW, 3W	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jing Su, et al 2014	23	22	25	20	29–74	30–75	Elemene 200 mg in 40 ml Saline, QW, 3W	DDP 40 mg/m^2, QW, 3W	Lung cancer, breast cancer and other cancers	Efficacy
Ke Dong, et al 2015	35	35	41	29	54.6 ± 4.5	55.2 ± 4.4	Elemen, 600 mg, DDP40mg/m^2, QW	DDP40mg/m^2, QW	Lung cancer	Efficacy, AEs
Zhuangwei Li, et al 2016	30	30	35	25	38–70	40–70	Elemene 400 mg in 250 ml saline + IL-2	Elemene 400 mg in 250 ml saline	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Zan Liu, et al 2016	26	26	32	20	34–78	34–78	Elemene 200mg/m^2 + DDP40mg/m^2 + Fluorouracil 750mg/m^2, QW	DDP 40 mg/m^2 + Fluorouracil 750 mg/m^2, QW	Lung cancer, breast cancer and other cancers	Efficacy, KPS
Hong Wang, et al 2007	32	41	41	32	38–78	34–76	Elemene 300 mg	bleomycin 45 mg	Lung cancer	Efficacy, AEs
Zhihong Feng, et al 2015	40	40	37	43	35–70	35–72	IL-2 2MU + elemene 300 mg, QW, 3 W	IL-2 2MU,QW, 3 W	Lung cancer	Efficacy, AEs, QOL
Lianping Jiang, et al 2009	26	26	30	22	43–76	48–73	Elemene 300 mg, QW	bleomycin 30 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Fangfang Si, et al 2015	20	20	22	18	45–72	51–78	DDP, 30 mg + elemene 200 mg/m^2, QW, 3 W	DDP 30 mg, QW, 3 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Siming Chen, et al 2012	23	23/23	41	28	61.2 ± 5.2	61.2 ± 5.2	IL-2 2MU + elemene 300 mg, QW	IL- 2 2MU, DDP 60 mg	Lung cancer	Efficacy, AEs, QOL
Zhijie Li, et al 2006	38	40	48	30	42–77	42–77	Elemene 600~800 mg	DDP 60~80 mg	Lung cancer	Efficacy, AEs
Yan Gao, et al 2010	35	35	35	35	18–75	18–75	DDP 40 mg/m^2, elemene 600 mg	DDP, 40 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Lidan Wang, et al 2012	50	50	57	43	54.3 ± 3.4	54.7 ± 3.6	DDP 20 mg/m^2, elemene 400 mg/m^2, QW, 2 W	DDP40 mg/m^2,QW, 2 W	Lung cancer	Efficacy, AEs
Yiming Kong, et al 2012	30	30	NA	NA	50–72	46–71	Elemene, 500 mg in 100 ml saline, QW, 3 W	DDP60 mg,qw	Lung cancer	Efficacy, AEs
Hongsong Wu, et al 2011	30	30	30	30	45–69	43–70	elemene 300 mg/m^2	DDP 50 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jichun Zhong, et al 2011	46	50	34	62	38–72	38–72	Elemene 500 mg in 100 ml saline	DDP 80 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jianbin Zhang, et al 2013	45	45	52	58	62.74 ± 6.8	61.5 ± 6.7	Elemene 400 mg in 80 ml saline	Bleomycin 60 mg	Lung cancer	Efficacy, AEs, QOL
Aifen Wang, et al 2011	18	18	19	17	66	65	elemene 300 mg	Bleomycin, 30 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Boquan Yang, et al 2000	30	30	38	22	28–75	29–74	Elemene 200–300 mg	DDP 60–80 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Jin Qi, et al 2011	24	26	NA	NA	NA	NA	Elemene 200 m g/m^2	DDP 50 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jinsheng Yu, et al 2015	81	61	78	64	50–72	50–72	Elemene 300 mg/m^2, QW, 4 W + thermal therapy, TIW	Elemene 300 mg/m^2, QW, 4 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Chang Liu, et al 2011	69	69	65	73	38–75	39–77	DDP 30 mg + elemene 300 mg, QW, 4 W	DDP 60 mg, QW, 4 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Lanying Sun, et al 2012	32	32	44	20	43–75	43–75	Elemene 300 mg/m^2, QW, 2 W	DDP 40–60 mg, QW, 2 W	Lung cancer	Efficacy, AEs, QOL
Liujie Gao, et al 2013	34	34	43	25	65.1 ± 12.2	64.2 ± 12.4	Elemene 200 mg/m^2 + thermal therapy	Elemene 200 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Chang Liu, et al 2011	38	37	49	26	70.3 ± 2.4	69.5 + 2.6	Elemene 300 mg +DDP 30 mg, thermal therapy	Elemene 300 mg + DDP30 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Ling Zhou, et al 2012	27	25	27	25	26–82	26–82	elemene 400 mg	Staphylococcal enterotoxin 40 mL	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Yonghua Hu, et al 2016	50	50	NA	NA	40–75	40–75	DDP + elemene	DDP	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Xiaoying Yao, et al 2002	30	30	52	8	18–75	18–75	elemene 400 mg, QW, 3 W	DDP 60 mg, QW, 3 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jianqing Chen, et al 2004	32	32	40	24	26–70	26–71	Elemene 200 mg/m^2 +DDP 50 mg/m^2, QW, 3 W	DDP 50 mg/m^2, QW, 3 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Jianming Lu, et al 2011	30	30	35	25	34–74	41–76	Elemene 500 mg	DDP 50 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Ping Huang, et al 2000	30	30	36	24	32–70	32–70	Elemene 500 mg + DDP60 mg	DDP 60 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Ping Wang, et al 2002	30	20	34	16	58.25 ± 20.12	59.16 ± 19.67	Elemene 500 mg	DDP 80 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs

(*continued*)

Table 1

(continued).

Studies	N		Sex		Age		Interventions		Cancers	Outcomes
	T	C	M	F	T	C	T	C		
Guoqiang Shi, et al 2007	25	25	30	20	58 ± 10	59 ± 12	Elemene 300 mg	DDP50 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs, QOL
Ming Li, et al 2008	26	26	30	22	45–69	43–70	Elemene 300 mg	DDP60 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Yanjun Wang, et al 2009	43	32	45	30	34–78	38–78	Elemene 400 mg	hyperosmotic glucose 40 ml	Lung cancer	Efficacy, AEs
Aihe Ye, et al 2001	46	50	64	32	40–70	42–68	Elemene 400∼ 600 mg	DDP 60 ∼ 80 mg	Lung cancer	Efficacy, AEs
Lixin Gu, et al 2003	20	20	25	15	32–71	34–70	Elemene 400 mg, QW, 2 W	DDP 40 mg/m^2, QW, 2 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Shuntong Lin, et al 1996	11	10	11	10	37–70	37–70	Elemene 100–300 mg	DDP 40 mg	Lung cancer	Efficacy, AEs
Youjuan Jiang, et al 1997	17	17	28	6	40–72	44–71	Elemene 200–300 mg	DDP 40 mg	Lung cancer, breast cancer and other cancers	Efficacy, AEs
Haibin Li, et al 2007	30	29	36	23	48–69	48–69	Elemene 200 mg	DDP 100 mg/m^2	Lung cancer, breast cancer and other cancers	Efficacy
Xianli Bai, et al 2005	24	23	30	17	56 ± 12	60 ± 13	Elemene 200 mg/m^2, QW, 2 W	DDP 40 mg/m^2, QW, 2 W	Lung cancer, breast cancer and other cancers	Efficacy, AEs

AEs = adverse events; C = control group; DDP = cisplatin; F = female; KPS = Karnofsky Performance Status Scale; M = male; MU = million units; NA = not available; QOL = quality of life; QW = once per week; T = treatment group; TIW = three times a week; W = week.

high. Blinding was not detailed in these studies. The risks of selective reporting were regarded to be low in these studies. The detailed information of quality assessment is presented in Table 2.

3.3. Results of meta-analysis

3.3.1. Efficacy of controlling malignant pleural effusion.

3.3.1.1. CR. Forty-six clinical studies reported outcomes of complete resolution of the pleural effusion. As there was no

Table 2

Methodological quality evaluation of included studies.

Studies	Random	Allocation	Blinding	Selective reporting	Other bias
Fang Zhao,et al 2015	Y	N	N	N	NR
Jingbo Sun, et al 2014	Y	N	N	N	NR
Jianpeng Li, et al 2014	Y	N	N	N	NR
Jinna Wang, et al 2015	Y	N	N	N	NR
Bianrong Wu, et al 2015	Y	N	N	N	NR
Yihe Zhang, et al 2016	Y	N	N	N	NR
Jing Su, et al 2014	Y	N	N	N	NR
Ke Dong, et al 2015	Y	N	N	N	NR
Zhuangwei Li, et al 2016	Y	N	N	N	NR
Zan Liu, et al 2016	Y	N	N	N	NR
Hong Wang, et al 2007	Y	N	N	N	NR
Zhihong Feng, et al 2015	Y	N	N	N	NR
Lianping Jiang, et al 2009	N	N	N	N	NR
Fangfang Si, et al 2015	Y	N	N	N	NR
Siming Chen, et al 2012	Y	N	N	N	NR
Zhijie Li, et al 2006	Y	N	N	N	NR
Yan Gao, et al 2010	Y	N	N	N	NR
Lidan Wang, et al 2012	Y	N	N	N	NR
Yiming Kong, et al. 2012	Y	N	N	N	NR
Hongsong Wu, et al 2011	Y	N	N	N	NR
Jichun Zhong, et al 2011	Y	N	N	N	NR
Jianbin Zhang, et al 2013	Y	N	N	N	NR
Aifen Wang, et al 2011	NA	N	N	N	NR
Boquan Yang, et al 2000	NA	N	N	N	NR
Jin Qi, et al 2011	NA	N	N	N	NR
Jinsheng Yu, et al 2015	Y	N	N	N	NR
Chang Liu, et al 2011	Y	N	N	N	NR
Lanying Sun, et al 2012	Y	N	N	N	NR
Liujie Gao, et al 2013	Y	N	N	N	NR
Chang Liu, et al 2011	Y	N	N	N	NR
Ling Zhou, et al 2012	Y	N	N	N	NR
Yonghua Hu, et al 2016	Y	N	N	N	NR
Xiaoying Yao, et al 2002	Y	N	N	N	NR
Jianqing Chen, et al 2004	NA	N	N	N	NR
Jianming Lu, et al 2011	Y	N	N	N	NR
Ping Huang, et al 2000	Y	N	N	N	NR
Ping Wang, et al 2002	Y	N	N	N	NR
Guoqiang Shi, et al 2007	Y	N	N	N	NR
Ming Li, et al 2008	Y	N	N	N	NR
Yanjun Wang, et al 2009	Y	N	N	N	NR
Aihe Ye, et al 2001	Y	N	N	N	NR
Lixin Gu, et al 2003	Y	N	N	N	NR
Shuntong Lln, et al 1996	Y	N	N	N	NR
Youjuan Jiang, et al 1997	Y	N	N	N	NR
Haibin Li, et al 2007	Y	N	N	N	NR
Xianli Bai, et al 2005	Y	N	N	N	NR

N = no; NA = not available; NR = not reported; Y = yes.

Table 2 Risk of bias: review authors' judgements about each risk of bias item for each included study.

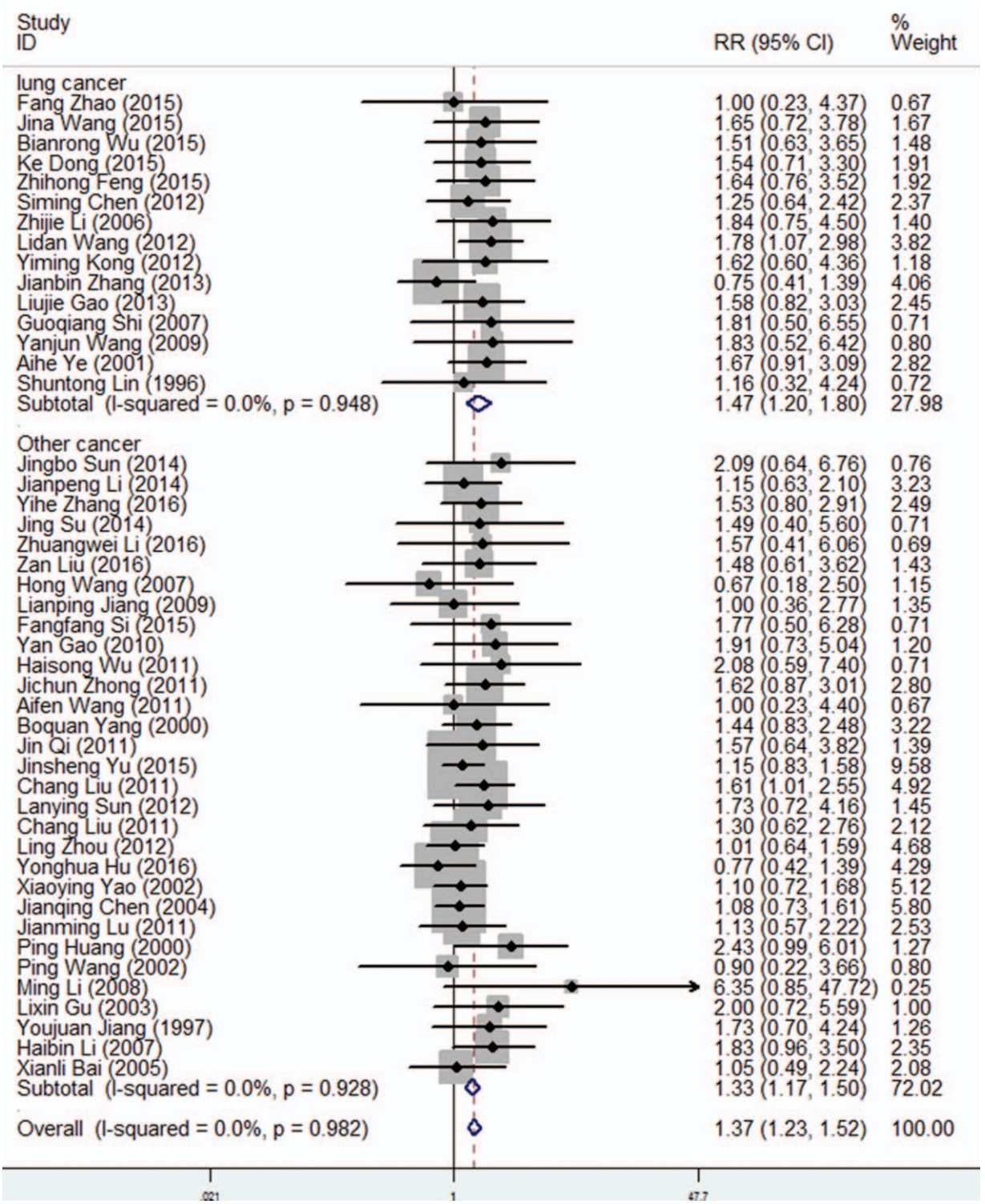

Figure 2. Forest plot of comparison: elemene versus other medications, outcome: complete response.

significant heterogeneity among the pooled studies, the fixed effect model was used. The results showed that the complete control of the pleural effusion in the experimental group was higher than that of the control group, and the difference was statistically significant [RR=1.37, 95% CI: 1.23–1.52; $P < .05$]. Sub-group analysis was also performed based on different types of treatment and diseases. With regards to different types of cancer, the results showed that the rate of CR was significantly higher than that of the control group in lung cancer patients [RR=1.47, 95% CI:1.20–1.80; $P < .05$]. The RR was 1.47 in lung cancer patients and it was 1.33 in various cancers (Fig. 2). For different types of treatments, elemene was proved to be superior to other medications including DDP, BLM, and IL-2, and the differences were statistically significant (Supplemental Figure 1, http://links.lww.com/MD/C555).

3.3.1.2. Overall response. There were 46 clinical trials presented the data of overall response. As there was no significant heterogeneity ($I^2\% < 50\%$), the fixed effect model was used in this meta-analysis. The pooled results showed that the ORR of the experimental group was higher than that of the control group, and the difference was statistically significant [RR=1.16, 95% CI: 1.08–1.23; $P < .05$]. This result indicated that patients received elemene could have a better overall response. The subgroup analysis showed that the lung cancer patients treated with elemene had a 1.20 times chance of controlling malignant pleural effusion, while it was 1.14 times for all other included cancer patients (Fig. 3). As for different treatments, the elemene

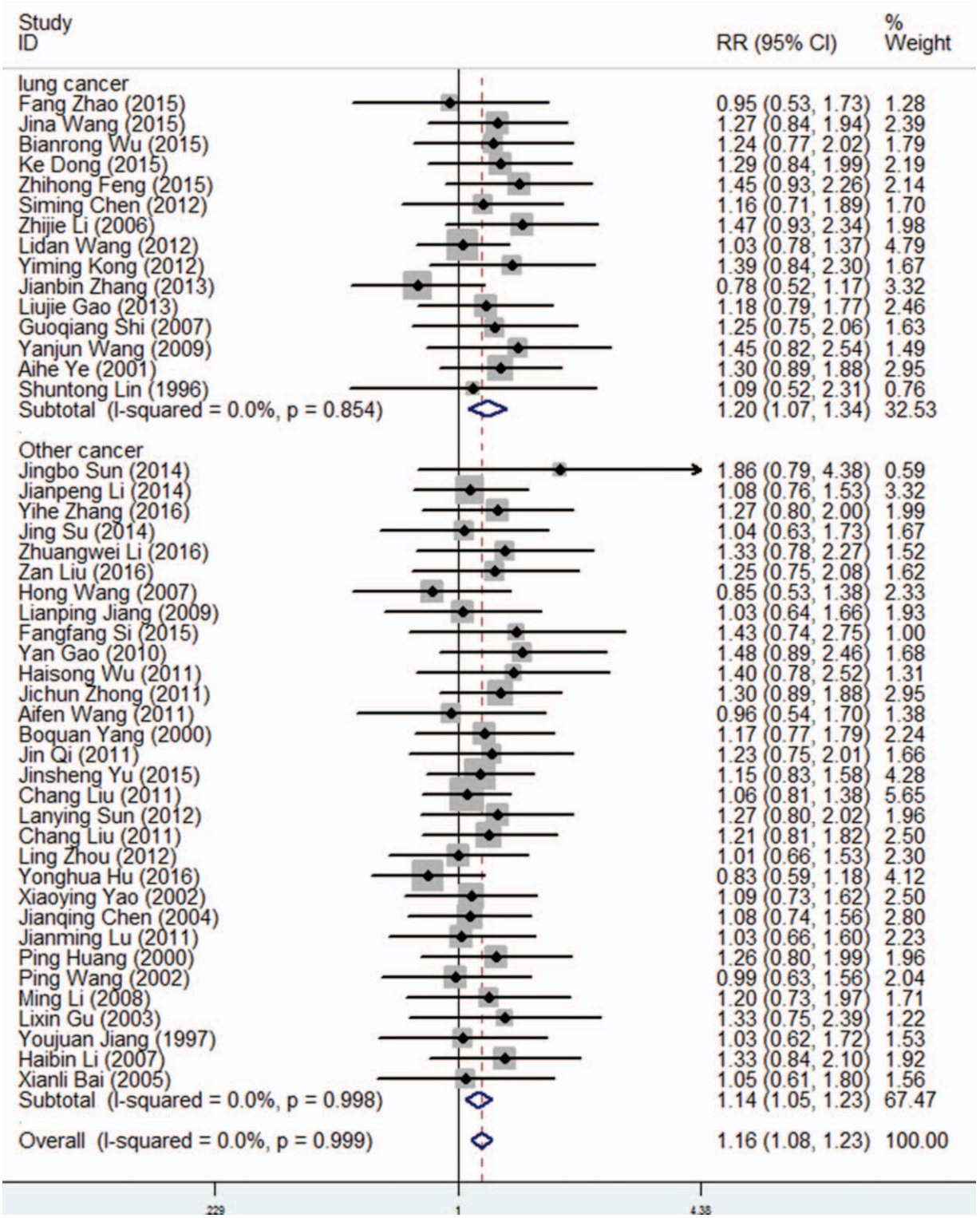

Figure 3. Forest plot of comparison: elemene versus other medications, outcome: overall response.

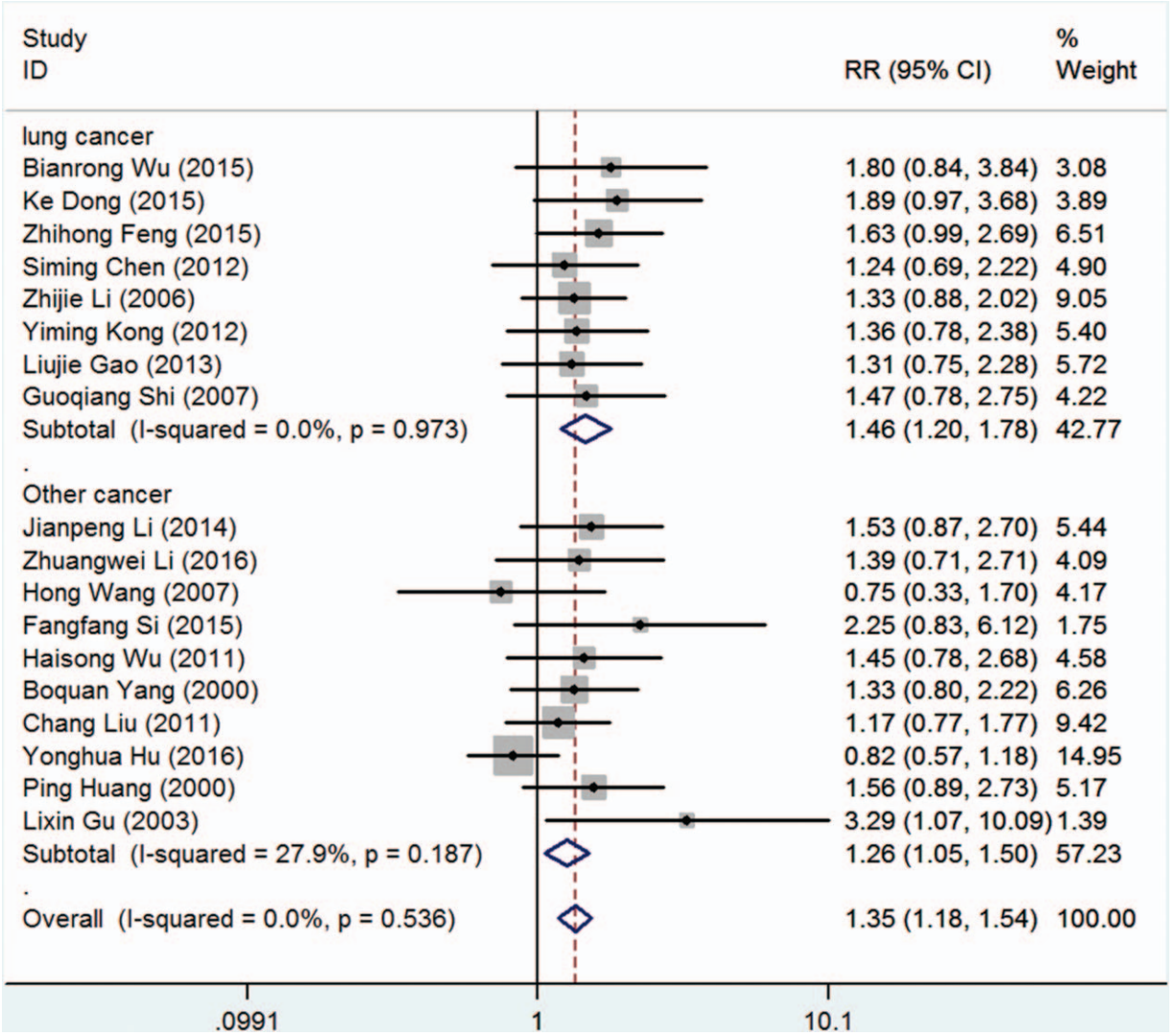

Figure 4. Forest plot of comparison: elemene versus other medications, outcome: quality of life.

had a 1.16 times chance in achieving overall response than other interventions (Supplemental Figure 2, http://links.lww.com/MD/C555).

3.3.1.3. Improvement in QOL. 18 clinical trials reported data of improvement in QOL. Because of the homogeneity of included studies (P=.536, I^2%=0%), the fixed effect model was used. As shown in Figure 4, the meta-analysis results showed that patients in the experimental group had a better chance in improving QOL than those in the control group [RR=1.35, 95% CI:1.18–1.54; $P<.05$]. Subgroup-analysis suggested that patients with lung cancer seemed to benefit most from the treatment of elemene [RR=1.46, 95% CI:1.20–1.78; $P<.05$].

3.4. Adverse events

3.4.1. Chest pain. Thirty-three clinical studies reported the incidence of chest pain due to the treatment. As it was heterogeneous (P=.019, I^2%=51.9%), so the random effect model was used for meta-analysis. Overall results showed that the incidence of chest pain in the experimental group was significantly higher than that in the control group [RR=1.39, 95% CI (1.18–1.64)]. Subgroup analysis based on the type of disease was performed. As shown in Figure 5, the results showed no significant difference in the incidences of chest pain between the experimental group and control group in lung cancer studies [RR=1.10, 95% CI (0.89–1.34)]. In the 21 studies of various malignancies, the incidence of chest pain in the treatment group was significantly higher than that in the control group [RR=1.95, 95% CI (1.47–2.57)].

3.4.2. Fever. 30 clinical controlled studies reported the incidence of fever, and the fixed effect model was used as there was no significant heterogeneity across the studies. The overall results showed that the incidence of fever in the treatment group was higher than that in the control group, with a statistically significant difference [odds ratio (OR)=1.43, 95% CI (1.17–1.74)]. As shown in Figure 6, subgroup analysis based on the type of disease showed that the incidence of fever in the treatment group was not significantly higher than that in the control group (OR=1.19, 95% CI (0.93–1.53)] in lung cancer patients, but not for various malignancies [OR=1.80, 95% CI (1.31–2.46)].

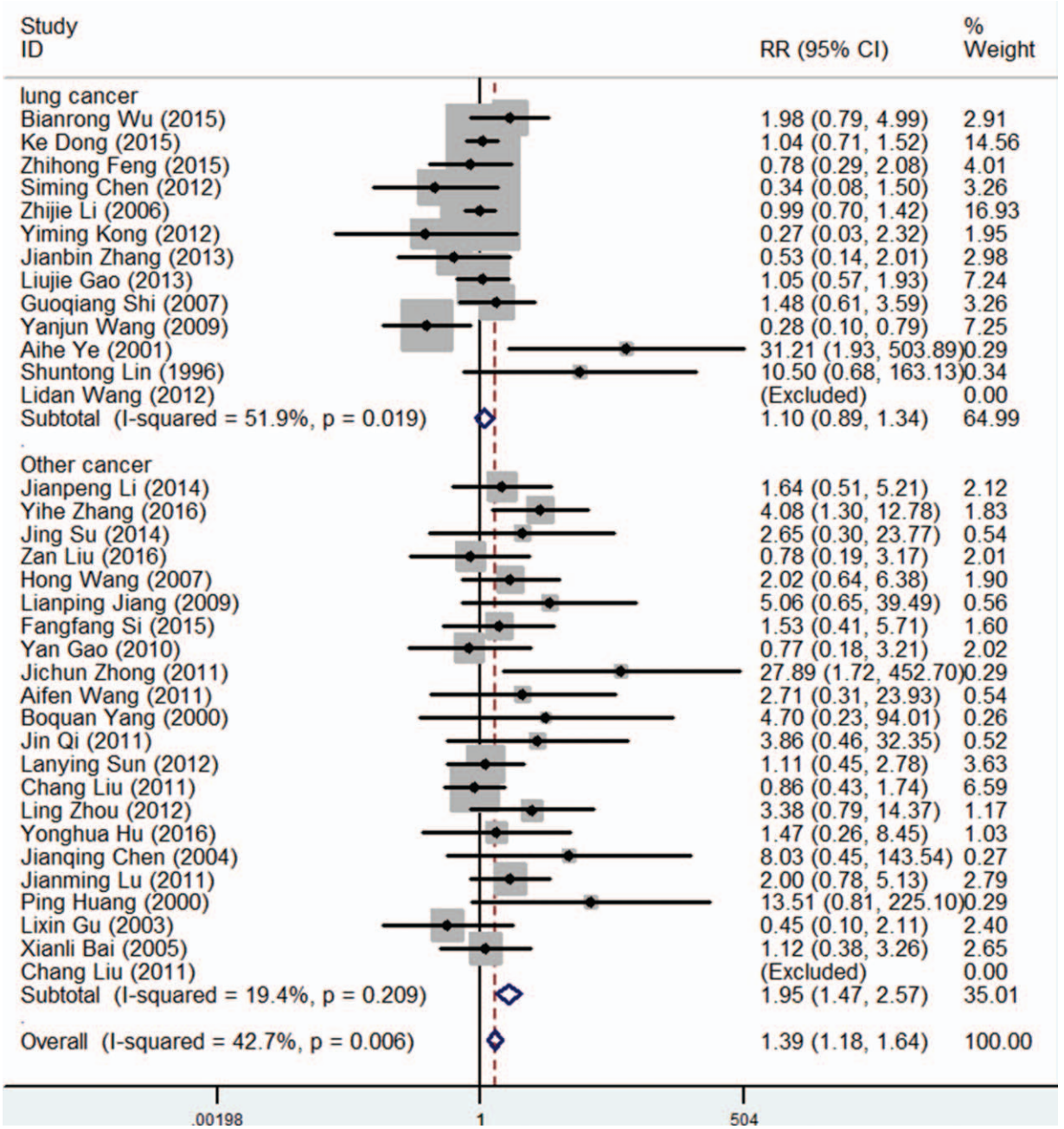

Figure 5. Forest plot of comparison: elemene versus other medications, outcome: chest pain.

3.4.3. Myelosuppression. Seventeen clinical controlled studies provided the rates of myelosuppression. Due to homogeneity across the studies, the fixed effect model was used. The overall results showed that the incidence of myelosuppression in the treatment group was significantly lower, when compared with the control group [OR = 0.40, 95% CI (0.33–0.49)]. As illustrated in Figure 7, the subgroup analysis was done based on different cancers. There was significant difference in the incidence of myelosuppression [OR = 0.47, 95% CI (0.35–0.64)] in patients with lung cancer.

3.4.4. Gastrointestinal adverse reactions. Thirty-five clinical studies reported the incidence of gastrointestinal reactions. The fixed effect model was used for this meta-analysis. As shown in Figure 8, the overall results showed that the incidence of gastrointestinal reactions in the treatment group was statistically significantly lower when compared with that of the control group [OR = 0.50, 95% CI (0.41–0.60)]. Results from the sub-group analysis showed that there was significant difference in the incidence of gastrointestinal reactions between the 2 groups in lung cancer patients [OR = 0.56, 95% CI (0.43–0.75)].

3.4.5. Publication bias assessment. The data of efficacy was used to detect the publication bias. Begg test was used to calculate the significance of publication bias. As illustrated by the funnel plot, the figure is basically symmetrical, suggesting no significant risk of bias ($P > .05$) and indicating that the meta-analysis results

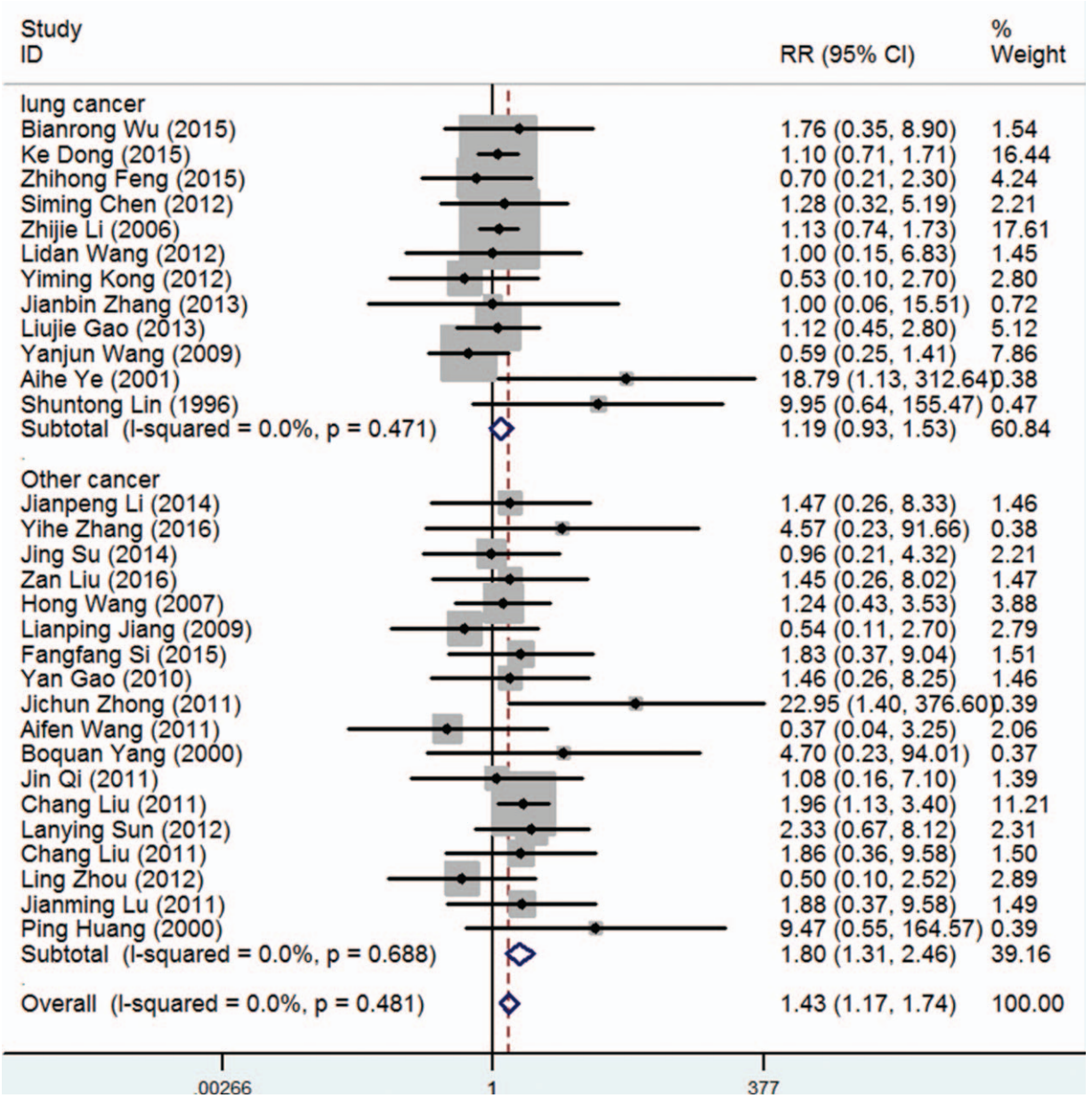

Figure 6. Forest plot of comparison: elemene versus other medications, outcome: fever.

are stable and reliable (Supplemental Figure 3, http://links.lww.com/MD/C555).

4. Discussion

Elemene has been widely used in the treatment of cancer, including complications of cancer.[59] In recent years, several publications supporting elemene in the treatment of malignant pleural effusion have been reported, but their findings are established based on limited number of patients.[8,12] In this meta-analysis, we found that elemene could significantly improve the short-term control of malignant pleural effusion. Subgroup results showed that the effective rate of elemene in the treatment of malignant pleural effusion was significantly higher than that of the DDP group. Meanwhile, elemene did not significantly increase the incidence of adverse events.

Meta-analysis results of this study showed that, elemene alone or combined with DDP or BLM could improve the CR rate [OR = 1.55, 95% CI (1.34, 1.79)] when compared with DDP, BLM. Subgroup analysis showed that elemene combined with DDP or BLM or hyperthermia could improve complete control of the pleural effusion in lung cancer patients [OR = 1.67, 95% CI (1.28, 2.17)]. In term of QOL improvement, elemene alone or combined with DDP or BLM could improve QOL [OR = 1.58, 95% CI (1.29, 1.93)]. Subgroup analysis showed that this beneficial effectiveness existed in both lung cancer and other malignant tumors.

A few meta-analyses[8,12] have been published to evaluate the efficacy and safety of elemene in treating various types of tumors, including lung cancer. Xu et al[60] performed a study to assess the efficacy of elemene in cancer treatment. A total of 11 trials were included after their search of several databases. The results

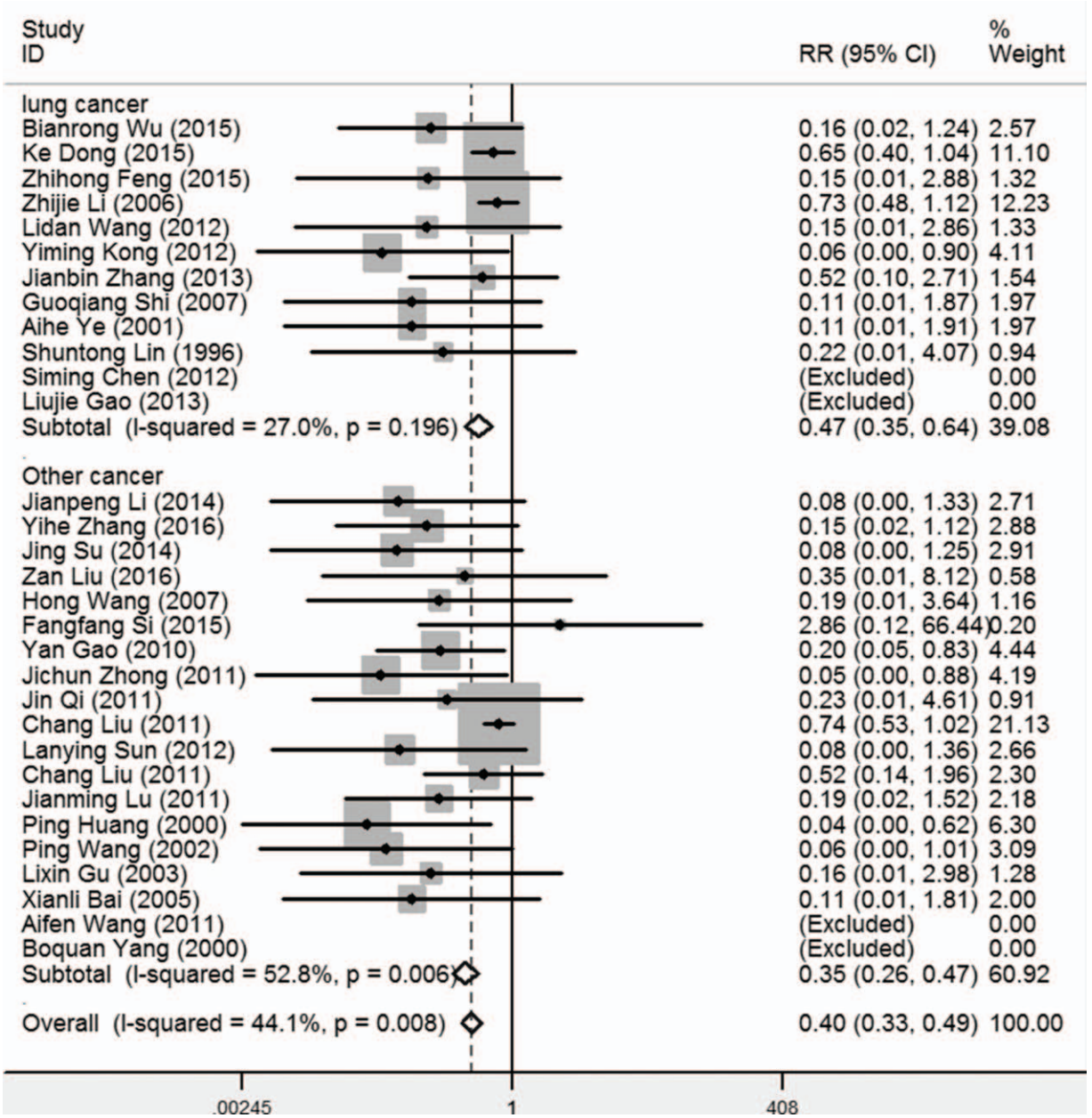

Figure 7. Forest plot of comparison: elemene versus other medications, outcome: myelo-suppression.

showed that elemene combined with chemotherapy had a significant rise in the number of patients who achieved treatment response, associated with low risk of adverse events. However, their findings failed to prove elemene was better in improving survival rate. Another study by Chen et al[8] evaluated the clinical efficacy of elemene in treating lung cancer patients with malignant pleural effusion. They included a total of 14 RCTs with 1298 cancer patients for the meta-analysis and the results showed that the objective response rate of the elemene was significantly higher than that of the control group, especially when compared with DDP. Recently, Wang et al[12] performed another meta-analysis to assess the clinical efficacy of elemene versus DDP in treating malignant pleural effusion caused by lung cancer. They included 14 studies with a total of 732 lung cancer patients. Their findings suggested that the ORR in elemene group was significantly higher than that of the DDP group. These results are in accordance with our findings. Our results showed that elemene was not only exhibiting the ability of controlling malignant pleural effusion, but also improving QOL with tolerable adverse events. With regard to adverse reactions, we also found that the incidences of chest pain and fever in elemene group were increased when compared with control group, but the rates of myelo-suppression and gastrointestinal reaction were similar or even decreased when compared with other medications. These may be caused by the varied types of cancer, different combination of treatment and other aspects. The subgroup analyses showed that elemene was most effective in treating pleural effusion caused by lung cancer.

Though the results of our meta-analysis show beneficial clinical outcomes and safety when using elemene for cancer patients with malignant pleural effusion, several limitations exist in our study. First, the overall qualities of the included studies are moderate,

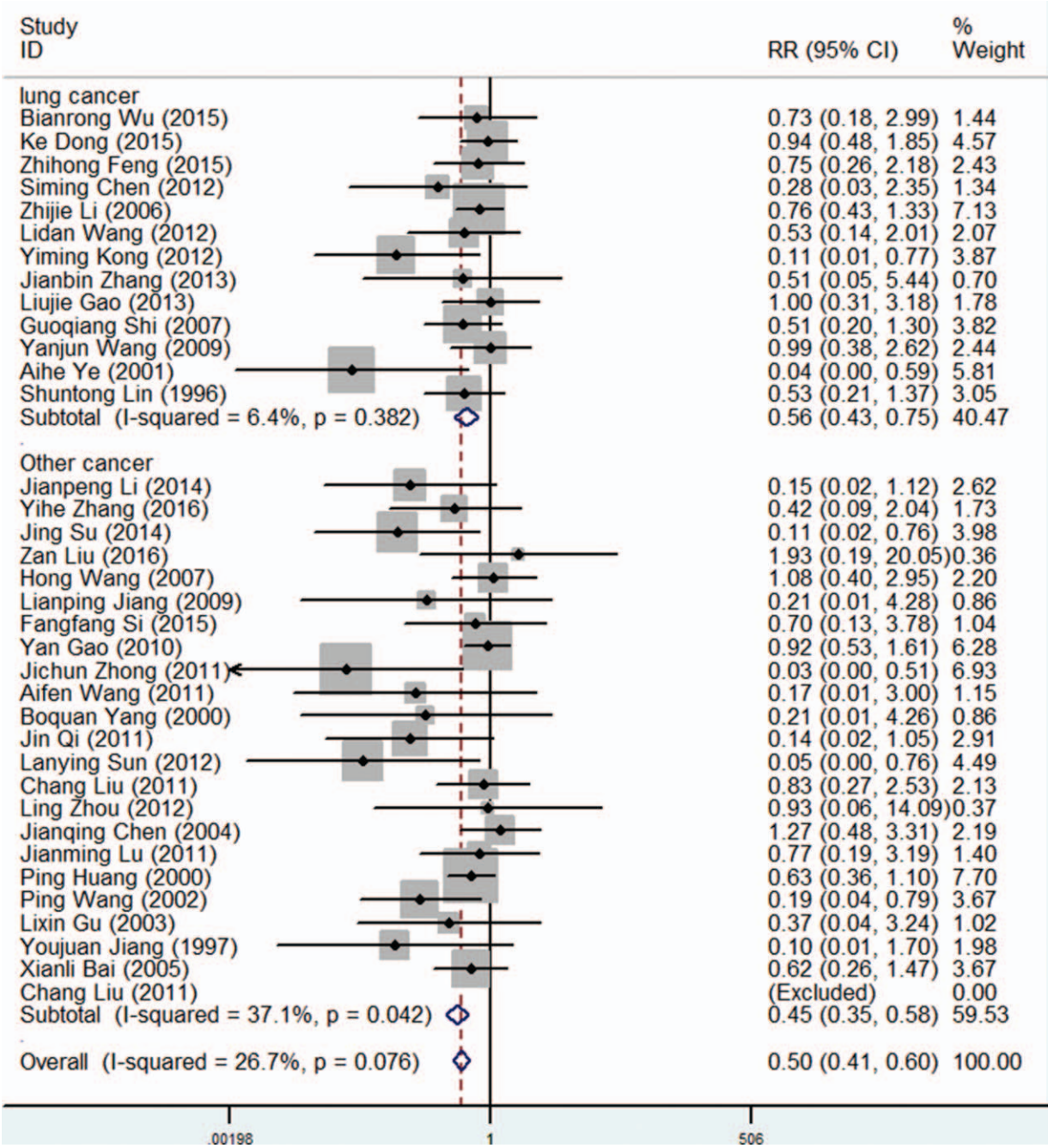

Figure 8. Forest plot of comparison: elemene versus other medications, outcome: gastrointestinal adverse reactions.

with moderate risk of bias. Though most of the included studies are RCTs, few of them reported details of randomization, blinding, indicating potential selection and detection bias may exist. Besides, the number of sample varies across studies. Second, though there is no significant heterogeneity across these eligible studies, the characteristics of patients and study design are different. All the included studies did not report the overall survival rate, making the total survival of patients with malignant pleural effusion still inconclusive. These inherent differences may increase the risk of bias. Overall, the findings of our meta-analysis are reliable, but it should be carefully viewed.

In conclusion, the results of this study show that elemene treatment can improve clinical control of malignant pleural effusion, QOL, with tolerable adverse events. Large scale, randomized, controlled, clinical trials are required to verify our findings.

Author contributions

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Validation: Ya-fei Wang.
Writing – original draft: Qing-tao Wang, Jian Liang.
Writing – review & editing: Ze-lin Zhang.

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