Highly Agglutinative Staphylococcin Therapy for Malignant Pleural Effusions: A Systematic Literature Review and Meta-analysis

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Abstract

Object: The purpose of our study was to evaluate the therapeutic effect and safety of highly agglutinative staphylococcin (HAS) intreatment of malignant pleural effusion (MPE).

Materials and Methods: A computerized and manual search was performed of scientific studies published before October2016 in the electronic databases. Three categories of treatment comparisons underwent meta-analysis separately for therapeutic effects and safety.

Results: There sults showed that thetherapeutic effect of HAS plus chemotherapy was greater than that of chemotherapy alone (OR, 1.475; 95% CI, 1.14-1.909). The rate of fever was higher in patients treated with HASthan in those treated with lentinan/elemene (OR, 3.791; 95% CI, 1.346-10.687) or chemotherapy (OR, 6.528; 95% CI, 2.331-18.284). The results indicated that the symptom of fever may be a manifestation of HAS stimulating the immune system.

Conclusion: HAS combined with chemotherapy has a better therapeutic effect against MPE compared with chemotherapy alone.

Keywords: Highly Agglutinative Staphylococcin (HAS), Malignant Pleural Effusion (MPE), Chemotherapy, Fever, Quality of life, Meta-Analysis

Introduction

Malignant pleural effusion (MPE) is a common complication in patients with advanced cancer. The estimated annual incidence of MPE in the United States is more than 150,000 cases [1]. Nearly all types of malignant carcinomas have been reported to involve the pleura, butthe most common primary sites that have metastasis to the pleura are the lung in men and the breast in women [2-5]. The main symptom of MPE is progressive dyspnea, followed by cough and chest pain [6]. MPE is a marker of poor prognosis, with median survival in patients with MPE varying from 3 months to 12 months, depending on underlying tumor type [5,7].

Until recently, there has been no standard treatment regimen or reference guide for MPE, making treatment a difficult task. Patients with MPE that is not responding to systemic treatment often require local palliative procedures including thoracentesis, chest tube drainage, pleurodesis, pleuroperitoneal shunting and radiotherapy to relieve dyspnea, and avoid repeated thoracentesis [1,5,8]. Although some treatments are effective in alleviating symptoms, MPE usually recurs within 1 month [9-11]. Furthermore, repeated thoracentesis and pleurodesis bear the risks of pneumothorax, empyema and pleural adhesions, which influence later drainage procedures and thoracoscopy.

Intrapleural chemicals such as cisplatin, carboplatin, or fluorouracil can be administered to patients with MPE to prevent the fluid from coming back, but the overall effect of these drugs has been limited [12,13]. Chemotherapy and radiotherapy also have serious side effects such as fever, chest pain, gastrointestinal adverse reactions, bone marrow suppression, and renal impairment. For patients with MPE, a conservative approach that uses those treatments cautiously is acceptable but can be inadequate [14].

Lentinan and elemene, which are isolated from the fruiting body of shiitake and a variety of plants, are potential alternatives to current treatments for MPE. Lentinan is a host-mediated anti-cancer drug that

has been shown to enhance host defense immune systems. Elemene has anti-proliferative effects on some cancer cell types. Lentinan and elemene reportedly have therapeutic effects against MPE.

Another potential treatment for MPE involves staphylococcal enterotoxin, a bacterial exotoxin produced by *Staphylococcus aureus* that has high levels of biologic activity and super antigenic properties. Staphylococcal enterotoxin stimulates non-specific T-cells differentiated into viable cytotoxic T-cells, profoundly increasing the activity of the immune system. Staphylococcal enterotoxin also activates monocytes of NK cells to release cytokines, including leukocyte interleukin-2, interferon, and tumor necrosis factor, producing significant antitumor effects in animal models of carcinoma, sarcoma, and lymphoma [15-21]. To improve the antitumor potency of staphylococcal enterotoxin, the filtrate of S. *aureus* culture was used to obtain a new form of the serotype staphylococcal enterotoxin C, called highly agglutinative staphylococcin (HAS) [22]. Developed by Xiehe Biopharmaceutical Company (Shenyang, China), HAS inhibits and kills tumor cells, repairs injured tissues and cells, elevates leukocyte levels, and improves immune function by activating T-cells and natural killer cells, enhancing phagocytosis, and directly inhibiting the growth of tumor cells [6]. Since 1998, many clinical trials in China have shown notable efficacy of HAS against cancer, especially MPE [23]. HAS is administered intrapleurally immediately after drainage of the pleural effusion by thoracentesis, has low toxicity, and significantly enhances immunity [24].

Here we present a meta-analysis to evaluate the therapeutic efficacy and safety of immunochemotherapy via intrapleural injection with HAS alone or HAS combined with chemotherapy in the treatment of MPE.

Materials and Methods
Systematic Literature Search
A computerized and manual search was performed for scientific studies published in the electronic databases of PubMed, Medline, the Chinese National Knowledge Infrastructure, and the Wanfang database. We systematically searched the databases independently using the search terms "highly agglutinative staphylococcin", "staphylococcin", "staphylococcale enterotoxin", "superantigen", "pleural effusion", and "pleural fluid". The search included Medical Subject Headings and study text. All the studies that appeared in our search results were examined. Duplication of data was avoided by examining the body of each publication or the names of all authors. To ensure that all relevant studies were included, inquiries were made of the researchers with expertise in MPE and staphylococcin about the possible existence of unpublished related trials. We retrieved studies published before October 2016.

Inclusion and Exclusion Criteria
The studies selected for inclusion satisfied each of the following criteria:
1. The study was a published randomized clinical trial of HAS alone or combined with chemotherapy given as intrapleural perfusion therapy for MPE.
2. The experimental group received HAS alone or combined with chemotherapy, and the control group received chemotherapy or either lentinan or elemene alone.
3. No radiation therapy was given simultaneously with the trial treatment.
4. The full text provided effectiveness and safety indicators

such as objective response rate, adverse reactions, and other outcome indicators.

The exclusion criteria were as follows:
1. The study was a review, case report, animal experiment, basic research, descriptive study, retrospective study, or prospective study.
2. Patient information including gender, age, drugs, therapeutic effect, side effects etc. was not complete.
3. The study was a duplicate of a previously included study.
4. The study was non-random or lacked a control group.

Eligible studies were identified for full review by two authors determining compliance with inclusion and exclusion criteria.

Data Extraction and Quality Assessment
We extracted data from the selected full-length articles using a standardized form. For each study, the data extracted included study name, publication year, country of origin of study, study design, patient inclusion criteria, sample sizes, drugs used in the study, and outcomes including therapeutic effect and side effects. The quality of each selected study was evaluated using the previously validated 0-7 scale described by the Jadad criteria [25]. This scale determines the quality of clinical trials on the basis of study randomization, randomization concealment, the presence of double blinding, the description of withdrawals, and the process of randomization and blinding. Scores of 1-3 indicate low quality, and scores of 4-7 indicate high quality.

The therapeutic effect of HAS was evaluated according to the World Health Organization (WHO) standard. Complete remission was considered to mean that the MPE completely disappeared and that the symptoms were completely relieved for 4 weeks. Partial remission meant that the MPE was reduced by 50% or more and that the symptoms obviously improved for 4 weeks. No change meant that the effusion reduction failed to meet the above criteria or that effusion increased again in 4 weeks. The remission rate was calculated as the sum of the complete remission and partial remission rates. Major adverse reactions in the process of treatment were defined as fever, chest pain, gastrointestinal tract reaction, bone marrow suppression, liver and kidney damage. The quality of life assessment was based on changes in Karnofsky Performance Status score (KPS) after treatment. Improved quality of life meant that KPS increased by ≥10 points after treatment; no change in quality of life meant that KPS changed by <10 points; decreased quality of life meant that KPS decreased by ≥10 points.

Statistical Analysis
The meta-analysis was performed using STATA 11.0 software provided by the Cochrane collaboration network. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a fixed-effects or random-effects model. Statistical heterogeneity was assessed by an I2 test, with a value greater than 50% recognized as indicative of substantial heterogeneity [26]. If substantial heterogeneity was observed, random-effects models were used. Three categories of trials - HAS compared with lentinan or elemene, HAS compared with chemotherapy, and HAS plus chemotherapy compared with chemotherapy alone - underwent meta-analysis separately to compare therapeutic effects and adverse effects between regimens. Therapeutic effects, adverse effects, and life quality were respectively quantified by the pleural fluid remission rate, the proportion of patients who had adverse effects after treatment, and the ratio of patients whose

KPS increased. Meta-regression was performed to find sources of heterogeneity. A funnel plot was applied to assess publication bias visually, and the Egger test was used to evaluate publication bias statistically, $p < 0.05$ was considered statistically significant [27].

Results
Trial Screening
Our search yielded 28 study reports, of which three were excluded because those studies mainly assessed toxic shock syndrome caused by a pleural cavity S. aureus infection. Another three studies were excluded because one was a review, one was a letter to the editor, and one was basic research, as determined on the basis of the titles and abstracts (Fig. 1). Twenty-two studies were then retrieved for full text review. Four studies were excluded because the study aims were to compare different therapy administration methods rather than different therapeutic agents. Two studies were excluded because they lacked a control group or lacked complete curative data for the control group. One study was excluded because the patients in the control group were treated with talc poudrage. After this detailed evaluation, 15 clinical trials were included in the final analysis.
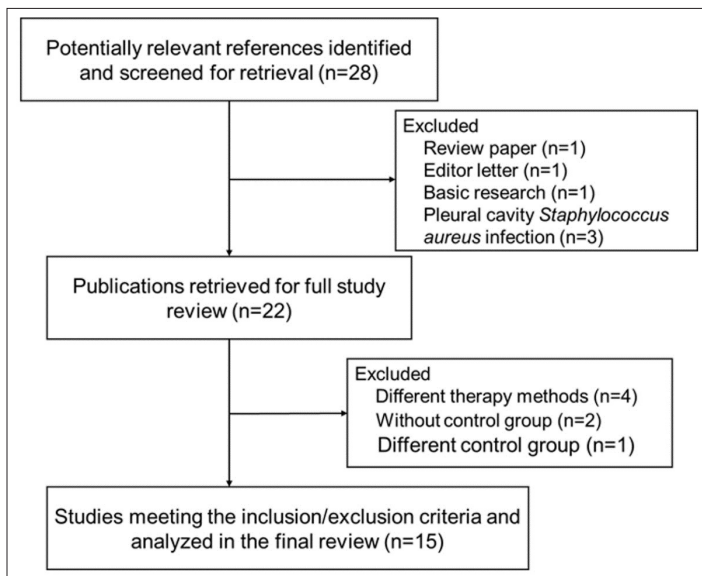

Figure 1: Flow chart of the studies included in the meta-analysis

Study Characteristics and Quality Assessment
The characteristics of most included studies were fairly similar. Fifteen clinical trials that included a total of 827 patients qualified for inclusion. All of the clinical trials were conducted in China and were published from 1998 through 2013. The baseline characteristics of the 15 included trials are listed in Table 1. Among these, three trials compared HAS with lentinan/elemene, four trials compared HAS with chemotherapy, and 11 trials compared HAS plus chemotherapy with chemotherapy alone [23,28-41].

Overall, the quality of the included studies was good. All included studies were randomized, had randomization concealment, were

double blinded, and had dropouts or withdrawals. Four studies - by Liang L *et al*., Ding H *et al*., Song X *et al*., and Liu Y *et al*. -were randomized in a manner deemed appropriate by the Jadad criteria and received a score of 5; the rest received a score of 4.

Table 1: Characteristics of the 15 studies of MPE included in the meta-analysis.

Study and References	Study location	Study period	Study Size	Cancer type
Gao Z *et al.* [23]	Shanghai	1992-1998	40	All Cancer
Gao H *et al.* [28]	Nanjing	2009-2012	40	NSCLC
Tong W *et al.* [29]	Shanghai	2003-2010	104	Lung Cancer
Zhou L *et al.* [30]	Shanghai	2008-2010	52	All Cancer
Cheng J *et al.* [31]	Liaoning	2003-2009	90	NSCLC
Liu Y *et al.* [32]	Shenyang	1997-2002	35	All Cancer
Li L *et al.* [33]	Nanjing	2009-2012	30	NSCLC
Liang J *et al.* [34]	Henan	2002-2004	38	All Cancer
Ding H *et al.* [35]	Huhzou	2003-2006	45	NSCLC
Pan Y *et al.* [36]	Wuhan	2000-2004	48	Lung Cancer
Li X *et al.* [37]	Baotou	1998-1999	76	All Cancer
Song X *et al.* [38]	Shanxi	2001-2003	66	All Cancer
Liu Q. [39]	Chongqing	2005-2008	47	All Cancer
Xiao Y *et al.* [40]	Chongqing	1999-2002	56	NSCLC
Zhou Y *et al.* [41]	Wuhan	2006-2008	60	NSCLC

Note: NSCLC = Non Small Cell Lung Cancer

Meta-analysis
HAS vs. lentinan/elemene
For the first category of trials, we compared the therapeutic effect of HAS with that of lentinan/elemene. Three studies involving 148 patients compared the efficacy of HAS with that of lentinan/elemene [28-30]. Our meta-analysis revealed that HAS was not more effective than the lentinan/elemene (OR, 1.054; 95% CI, 0.635-1.747; $p = 0.84$; fixed-effects model; Fig. 2 A).

We also compared the rates of side effects of HAS with those of lentinan/elemene, including fever, chest pain, and gastrointestinal adverse reactions. The rate of fever in patients treated with HAS was higher than that in patients treated with lentinan/elemene (OR, 3.791; 95% CI, 1.346-10.687; $p = 0.012$; Fig. 2 B). The rates of chest pain (OR, 0.751; 95% CI, 0.157-3.579; $p = 0.719$) and gastrointestinal adverse reactions (OR, 1.786; 95% CI, 0.309-3.579; $p = 10.337$) were similar between in patients treated with HAS and those treated with lentinan/elemene. The Begg test (z=0, p=1.00) and the Egger test (t=1.6, p=0.356) indicated that there was no publication bias (Fig.3A).
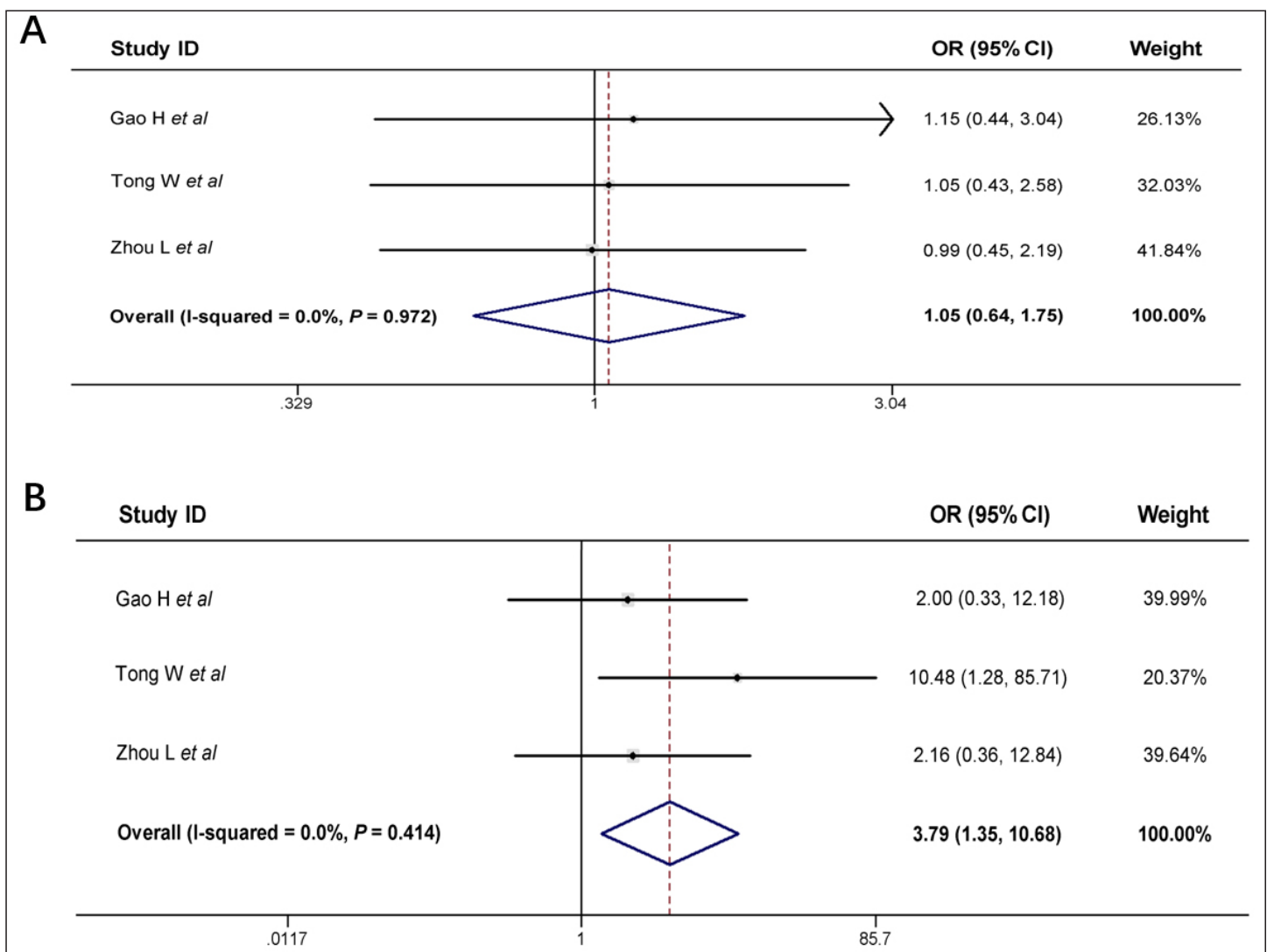
Figure 2: Forest plot for odds ratios and corresponding 95% confidence intervals of therapeutic effect (A) and fever (B) in patients treated with of HAS compared with lentinan/elemene.

HAS vs. chemotherapy

For the second category of trials, we compared the therapeutic effect of HAS with that of chemotherapy such as cisplatin and mitomycin in four studies involving 189 patients [23,29,31,32]. HAS was not more effective than chemotherapy (OR, 1.192; 95% CI, 0.738-1.925; $p = 0.472$; Fig. 4 A). Forthe side effects of HAS with those of chemotherapy, three studies including 149 patients were used to compare the rates of fever [29,31,32]. The rate of fever in patients treated with HAS was significantly higher than that in patients treated with chemotherapy (OR, 6.528; 95% CI, 2.331-18.284; $p < 0.001$; Fig. 4 B). No significant difference was observed between the patients treated with HAS and those treated with chemotherapy for the rates of chest pain (n = 114; OR, 2.305; 95% CI, 0.77-6.899; $p = 0.135$) or gastrointestinal adverse reactions (n = 114; OR, 0.159; 95% CI, 0.011-2.335; $p = 0.18$). The funnel plots for publication bias showed no asymmetry. The Begg test (z = 1.02, $p = 0.308$) and the Egger test (t = 1.71, $p = 0.23$) indicated no publication bias (Fig. 3 B).
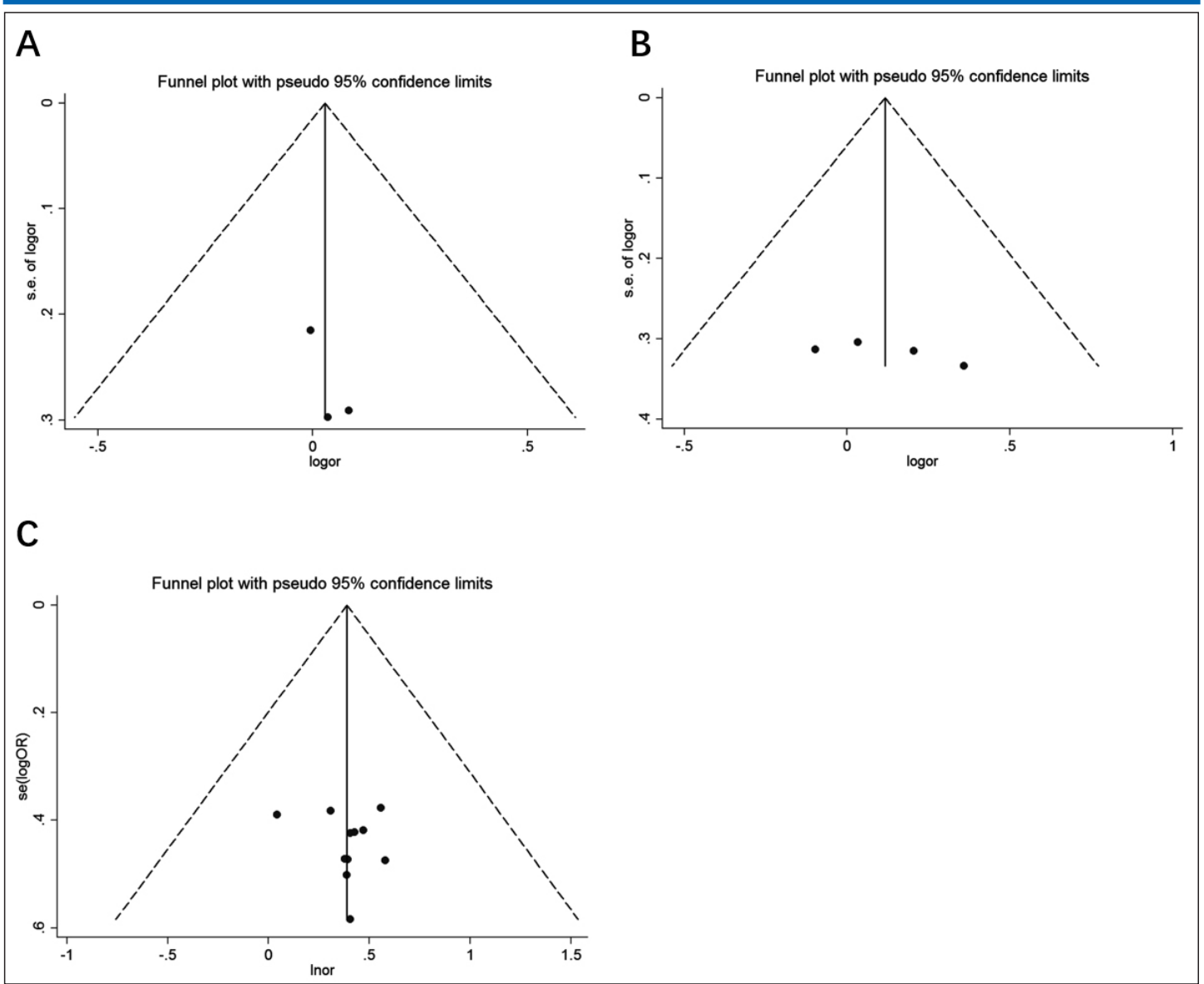
Figure 3: Funnel plot for assessment of publication bias in each category of trials. A. HAS compared with lentinan/elemene. B. HAS compared with chemotherapy. C. HAS plus chemotherapy compared with chemotherapy.
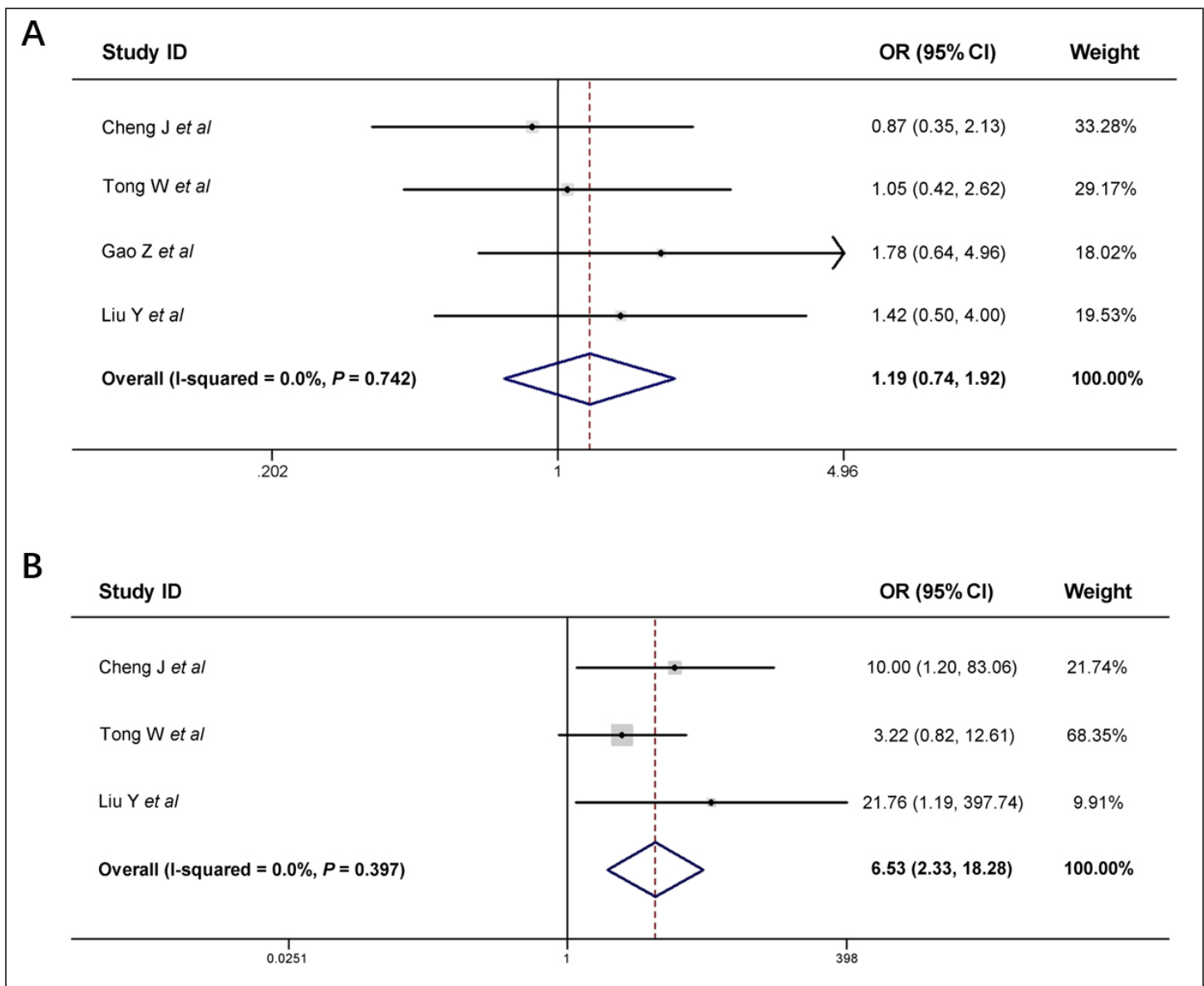
Figure 4: Forest plot for odds ratios and corresponding 95% confidence intervals for therapeutic effect (A) and fever (B) in patients with HAS compared with chemotherapy.
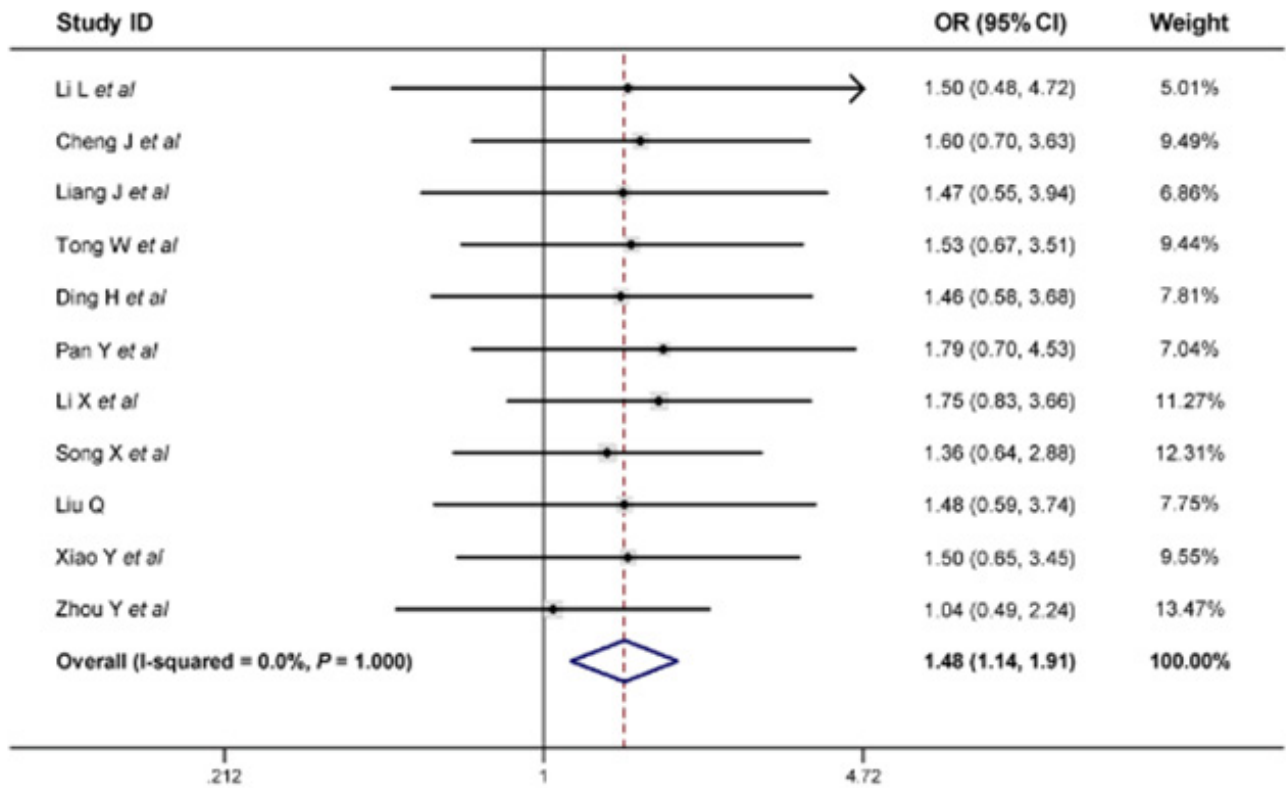
HAS plus chemotherapy vs. chemotherapy alone

For the third category of trials, we analyzed the therapeutic effect of HASplus chemotherapy such as cisplatin, carboplatin, mitomycin and hydroxycamptothecin compared with that of chemotherapy alone in 11 studies involving 574 patients [29,31,33-41]. The treatments with HAS combined with chemotherapy were done by local intracavitary injection after pleural drainage except in the study by Zhou Yet al., in which chemotherapy was given by intravenous injection and HAS was given by local intracavitary injection. The therapeutic effect of HAS combined with chemotherapy for MPE was significantly greater than that of chemotherapy alone (OR, 1.475; 95% CI, 1.14-1.909; p = 0.003; Fig. 5 A).

Furthermore, we compared the side effects of HAS plus chemotherapy with those of chemotherapy alone. Eight studies including 452 patients were used to compare the rates of fever [29,31,34,36-38,40,41]. The results showed that threat of fever in patients treated with HAS plus

chemotherapy was significantly higher than that in patients treated with chemotherapy alone (OR, 1.559; 95% CI, 1.05-2.317; p = 0.028; fixed-effects model; Fig. 5 B).We found no significant differences between these two groups with regard to gastrointestinal adverse reactions (n = 376; OR, 0.546; 95% CI, 0.362-0.825; p = 0.004; Fig.5 C), chest pain (n = 396; OR, 1.000; 95% CI, 0.637-1.569; p = 0.999), bone marrow suppression (n = 376; OR, 0.712; 95% CI, 0.447-1.134; p = 0.153), or renal impairment (n = 108; OR, 1.835; 95% CI, 0.238-14.144; p = 0.56).

Finally, three studies including 138 patients were selected to analyze quality of life in patients treated with HAS plus chemotherapy or with chemotherapy alone [29,31,33]. The results indicated that the rate of quality of life improvement was significantly better in patients treated with HAS plus chemotherapy than inpatients treated with chemotherapy alone (OR, 1.879; 95% CI, 1.087-3.247; p=0.012; Fig. 5 D).
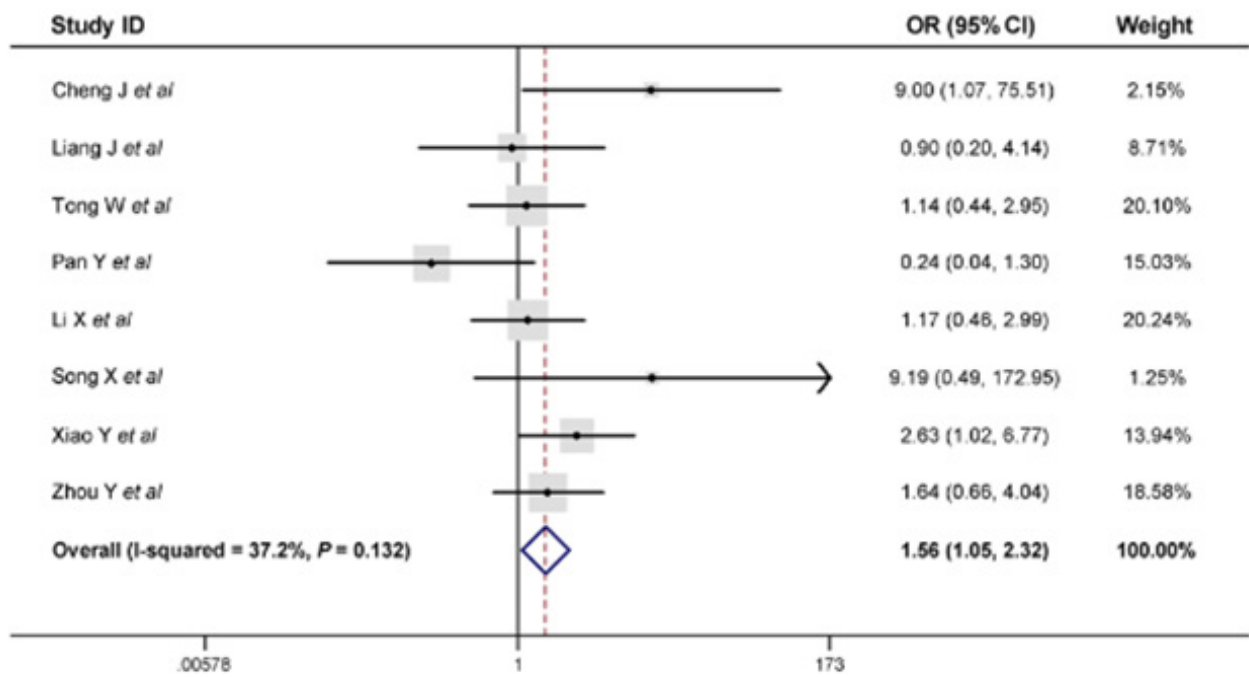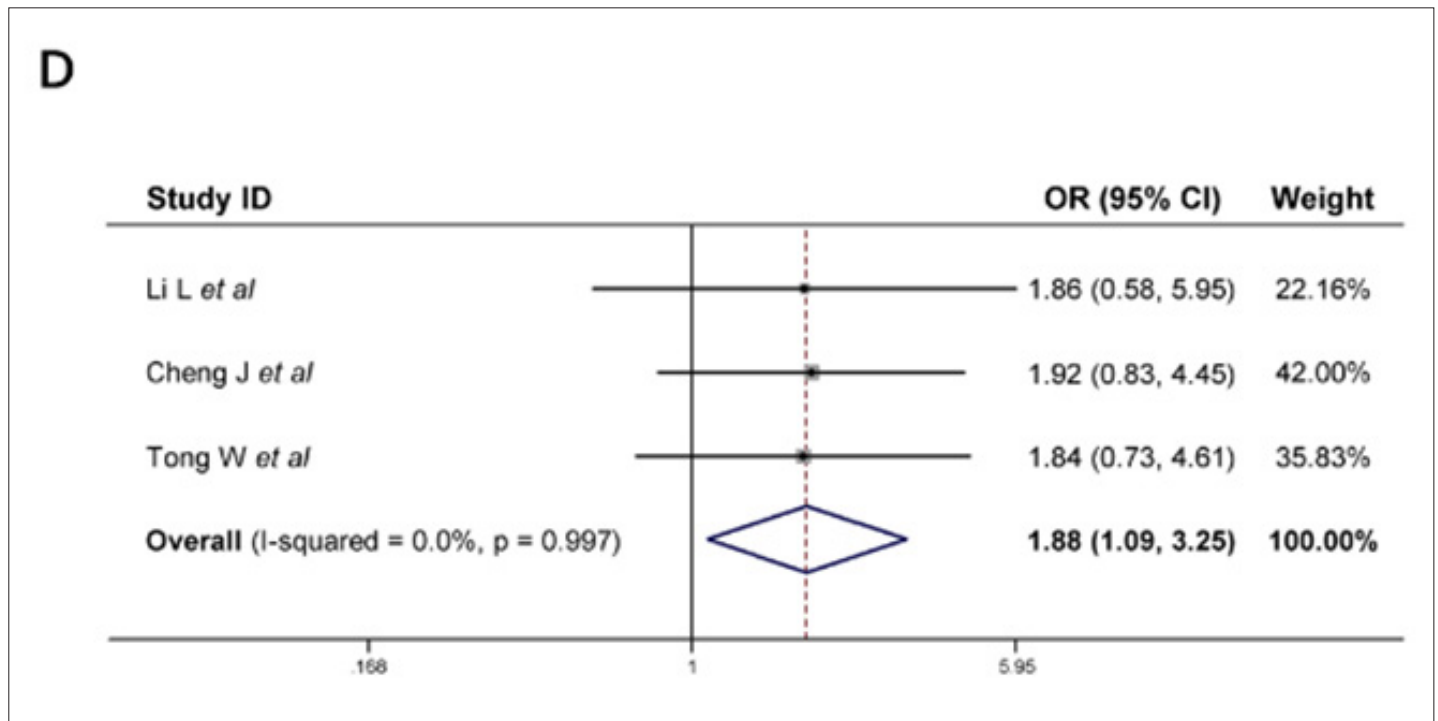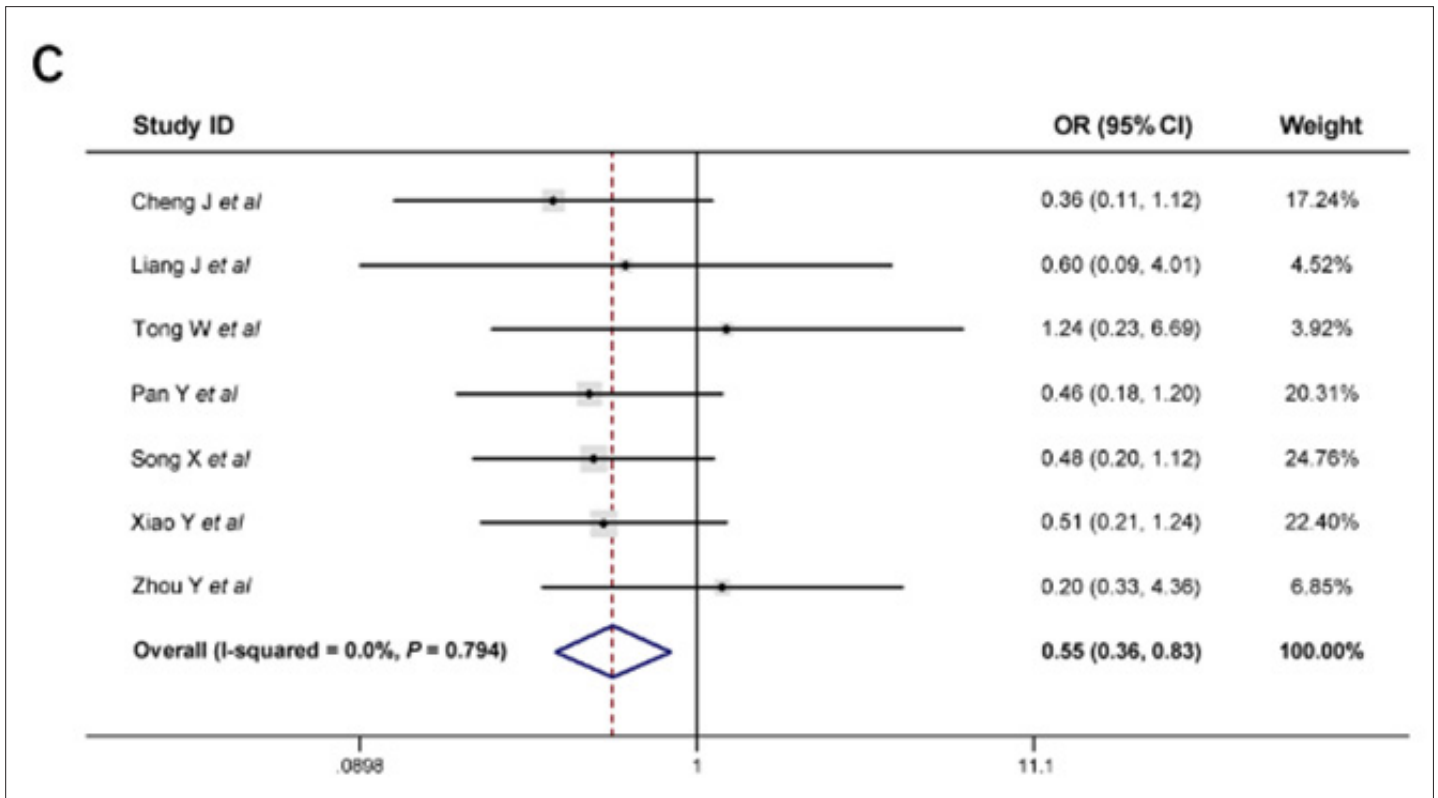
Figure 5: Forest plot for odds ratios and corresponding 95% confidence intervals for therapeutic effect (A), fever (B), gastrointestinal adverse reactions (C), and Karnofsky Performance Status score (D) in patients treated with HAS plus chemotherapy compared with chemotherapy.

Publication bias and study heterogeneity

The funnel plots for publication bias showed no asymmetry. The Begg test (z=0.16, p=0.876) and the Egger test (t=0.62, p=0.548; Fig.3 C) indicated that there was no publication bias. We also performed a meta-regression to determine sources of heterogeneity, but none were identified. Publication year, proportion of male to female, and age were not sources of heterogeneity.

Discussion

MPE is a common but serious clinical problem, especially in patients with neoplasms, and is associated with poor quality of life, morbidity, and mortality. Our meta-analysis comparing various therapies for patients with MPE revealed no significant difference between the therapeutic effects of HAS and of lentinan/elemene or chemotherapy (Figs. 2 A and 4 A), indicating that although HAS could reduce MPE, it is not superior to lentinan/elemene or chemotherapy in that regard. Furthermore, our analysis of the therapeutic effect of HAS plus chemotherapy compared with the therapeutic effect of chemotherapy alone revealed that HAS plus chemotherapy had a significantly greater therapeutic effect than chemotherapy alone (Fig. 5 A), indicating that HAS exerts synergistic effects with chemotherapy in the treatment of MPE.

We also compared the rates of serious side effects, including fever, chest pain, and gastrointestinal adverse reactions, after treatment with HAS compared with lentinan/elemene and chemotherapy. HAS resulted in fever more frequently than lentinan/elemene and chemotherapy did. HAS plus chemotherapy also resulted in fever more frequently than chemotherapy alone. This tendency to produce fever may be due to the mechanism of HAS.

HAS is filtrated from S. *aureus* and related super antigenic toxins produced by myriad microbes that are potent stimulators of the immune system. These protein toxins directly bind to the specific Vβ regions of T-cell receptors and major histocompatibility complex class II on antigen-presenting cells, resulting in hyper activation of T lymphocytes and monocytes/macrophages. Activated host cells produce excessive amounts of proinflammatory cytokines and chemokines, especially tumor necrosis factor α, interleukin 1, interleukin 2, interferon γ, interleukin 6, and macrophage chemoattractant protein 1, causing symptoms such as fever, hypotension, and shock [42,43]. Therefore, fever may be a manifestation of HAS acting to stimulate the immune system and may play an important role in monitoring the treatment of MPE.

The results also revealed that intrapleural combination therapy with HAS and chemotherapy led to a relatively lower rate of gastrointestinal adverse reactions compared with chemotherapy alone. This may due to gastrointestinal mucosa cells belong to proliferative cells, with high growth activity, and so they are sensitive to chemotherapy drugs. Even more the gastrointestinal adverse reactions may be caused by the drug's inhibition of mucosal repair. However, HAS perform its antitumor effects by stimulate T cells which can targeted kill tumor cells, and protect gastrointestinal mucosa cells from injury.

It has been reported that HAS tremendously activates natural killer cells and stimulates T lymphocyte differentiation into CD4+ and CD8+ subpopulations, which can kill tumor cells directly. In addition, HAS can induce T helper cells and cytotoxic T-cells to secreteinterferon γ, which is known to have direct anti-proliferative properties that lead to the death of cancer cells from a variety of origins [44-46]. These mechanisms suggest that HAS is a super antigen-processing drug with the potential for synergetic effects in combination with chemotherapy in the treatment of cancer. Our study proved that HAS combination with chemotherapy have obvious therapeutic effects and less side effects in treatment of pleural effusion caused by malignant tumor.

This study collected the related clinical trials of HAS on the therapy of MPE, and systematic analysis the therapeutic effects of HAS compared with chemotherapy or *lentinan/elemene*, and the effects of HAS plus chemotherapy versus chemotherapy alone. HAS plus chemotherapy recognized as a superior clinical treatment compared with chemotherapy for patients with MPE, which prove an optional treatment strategy for patients with MPE. However, there are some limitations in our meta-analysis. Firstly,the meta-analysis used the pooled data which was extracted from heterogeneous studies, not original data from the individual patients. The number of patients from each involved study was relatively small. Second, the randomization methods in most studies were not very detailed, we can't judge whether randomizations are appropriate. At last, all the clinical trials collected in our study were performed in China, whether the therapeutic effects of HAS for patients with MPE varies between races need further study.

In conclusion, there is evident that HAS combined with chemotherapy yields superior therapeutic effects compared with chemotherapy in the treatment of patients with MPE. The symptom of fever may indicate that HAS works and stimulates the immune system. However, HAS did not alleviate the symptoms of chest pain, bone marrow suppression, and renal impairment in patients with MPE in this analysis. Regardless, our meta-analysis indicates that HAS combined with chemotherapy effectively controls MPE in patients with malignant tumors, alleviates gastrointestinal adverse reactions, and improves quality of life better than chemotherapy alone. Further investigations are needed to study the antineoplastic effects of HAS in patients with MPE and elucidate the mechanisms underlying these effects.

References

1. Kastelik JA (2013) Management of malignant pleural effusions. Lung 191: 165-175.
2. Mongardon N, Pinton-Gonnet C, Szekely B, Michel-Cherqui M, Dreyfus JF, et al. (2011) Assessment of chronic pain after thoracotomy: a 1-year prevalence study. Clin J Pain 27: 677-681.
3. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT (2016) Malignant pleural effusion: from bench to bedside. Editorial comment in Eur Respir Rev 25: 189-198.
4. DiBonito L, Falconieri G, Colautti I, Bonifacio D, Dudine S (1992) The positive pleural effusion. A retrospective study of cytopathologic diagnoses with autopsy confirmation. Acta Cytologica 36: 329-332.
5. Roberts ME, Neville E, Berrisford RG, George Antunes, Nabeel J Ali, et al. (2010) Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax 65: 32-40.

6. Martinez-Moragon E, Aparicio J, Sanchis J, Menendez R, Cruz Rogado M, et al. (1998) Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. Respiration 65: 108-113.

7. Lui M, Fitzgerald D, Lee Y (2016) Phenotyping malignant pleural effusions. Curr Opin Pulm Med. 22: 350-355.

8. Khaleeq G, Musani AI (2008) Emerging paradigms in the management of malignant pleural effusions. Respir Med 102: 939-948.

9. Burrows CM, Mathews WC, Colt HG (2000) Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. Chest 117: 73-78.

10. Ozyurtkan MO, Balci AE, Cakmak M (2010) Predictors of mortality within three months in the patients with malignant pleural effusion. Eur J Intern Med. 21: 30-34.

11. Xia H, Wang X-J, Zhou A, Shi H-Z, Tong Z-H (2014) Efficacy and safety of talc pleurodesis for malignant pleural effusion: a meta-analysis. Plos One 9: 1-9.

12. Walker-Renard PB, Vaughan LM, Sahn SA (1994) Chemical pleurodesis for malignant pleural effusions. Ann Intern Med 120: 56-64.

13. Walker S, Bibby AC, Maskell NA (2017) Current best practice in the evaluation and management of malignant pleural effusions. Ther Adv Respir Dis. Ther Adv Respir Dis 11: 105-114.

14. Thomas R, Francis R, Davies H, Lee Y (2014) Interventional therapies for malignant pleural effusions: the present and the future. Respirology 19: 809-822.

15. Dohlsten M, Sundstedt A, Björklound M, Hedlund G, Kalland T (1993) Superantigen-induced cytokinessuppress growth of human colon-carcinoma cells. Int J Cancer 54: 482-488.

16. D'orazio JA, Burke GW, Stein-Sterilein J (1995) Staphylococcal enterotoxin B activated purified NK cells to secrete IFN-γ but required T lymphocytes to augment NK cytotoxicity. J Immunol 154: 1014-1023.

17. Terman DS, Bohach G, Vandenesch F, Etienne J, Lina G, et al. (2006) Staphylococcal superantigens of the enterotoxin gene cluster (egc) for treatment of stage IIIb non-small cell lung cancer with pleural effusion. Clin Chest Med 27: 321-334.

18. Kalland T, Dohlsten M, Lind P, Sundstedt A, Abrahmsén L, et al. (1993) Monoclonal antibodies and superantigen: a novel therapeutic approach. Med Oncol Tumor Pharmacother 10: 37-47.

19. Penna C, Dean PA, Nelson H (1994) Antitumor X anti-CD3 bifunctional antibodies redirect T-cells activated in vivo with staphylococcal enterotoxin to neutralize pulmonary metastases. Cancer Res 54: 2738-2743.

20. Hansson J, Ohlsson L, Persson R, Gunnar Andersson, Nils-Gunnar Ilbäck, et al. (1997) Genetically engineered superantigens as tolerable antitumor agents. Proc Natl Acad Sci 94: 2489-2494.

21. Persson B, Persson R, Weiner LM, Alpaugh RK (1998) Overview of clinical trials employing antibody-targeted superantigens. Adv Drug Deliv Rev 31: 143-152.

22. Pan YQ, Ding D, Li DX, Chen SQ (2007) Expression and bioactivity analysis of Staphylococcal enterotoxin M and N. Protein Expr Purif 56: 286-292.

23. Gao Z, Zhang W, Mao A, Wang Y, Zhang L (1999) The treatment of carcinomatous pleural effusion by cannula perfusion of biological products. Chinese Journal of Coal Industry Medicine 2: 9-10.

24. Xu M-K, Zhang C-G, Chen Y, Guo W, Cai Y-M, et al. (2008) Research advances on immunopharmacology and cancer therapy of Staphylococcal enterotoxins. Asian Journal of Pharmcodynamics and Pharmacokinetics 8: 83-108.

25. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, et al. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1-12.

26. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21: 1539-1558.

27. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BM 315: 629-634.

28. Gao H, Zhang X, Yang J (2013) Comparison of lentinan and staphylococcin in treatment of lung cancer induced pleural effusion. Chinese Journal of Medicinal Guide 15: 285-287.

29. Tong W, Zhuo A, Cao Y (2011) Clinical effect of highly agglutinative staphylococcin and lentinan combined with cisplatin in treatment of malignant pleural effusion caused by lung cancer. Modern Oncology 19: 2239-2242.

30. Zhou L, Ye W, Zhang W, Pan H (2012) Radiofrequency hyperthermia combined with interapleural infusion of elemene emulsion or staphyloccin in the treatment of malignant pleural effusion. Chinese Journal of Clinical Medicine 19: 25-26.

31. Cheng J, An Y, Zhang X, Wang Y, Liu W, et al. (2010) Clinical Observation on treatment of malignant hydrothorax with locally administered highly agglutinative staphylococcin and Cisplatin. China Pharmacy 21: 1130-1131.

32. Liu Y, Chang J, Li Y (2004) The comparative Analysis of Curative Effect of HAS and DDP Treating Malignant Pleural Effusion (35 example clinical reports). Journal of Shenyang Medical College 6: 9-13.

33. Li L, Qian X (2013) Clinical effect of highly agglutinative staphylococcin combined with cisplatin in treatment of malignant pleural effusion. Modern Oncology 21: 1762-1764.

34. Liang J, Zhang R, Lan J (2001) Clinic study on treatment of malignant thoracic hydrops by carboplatin combined with HAS. Journal of Medicine Forum 26: 34-37.

35. Ding H, Xie Y, Nie S (2006) Clinical effects of highly agglutinated staphylococcin on malignant pleural effusion. Journal of Clinical and Experimental Medicine 5: 919.

36. Pan Y, Tang Y, Pan T, Xu X (2006) Clinical observation of highly agglutinative staphylococcin combined with cisplatin in treatment of malignant hydrothorax. China Journal of Modern Medicine. 16: 410-412.

37. Li X, Wang Y, Wu Y (2000) Clinical observation on malignant pleural effusion treated by intrapleural catheterization and infusion of Highly agglutinative staphylococcin (a report of 40 cases). Chinese Journal of Clinical Oncology 27: 359-361.

38. Song X, Su W, Zhu H, Guo W, Tian R, et al. (2004) Clinical study on hydroxycamptothecin (HCPT) combined with staphylococcin aureus filtrate preparation in treatment of refractory malignant pleural effusions. Chinese Journal of Clinical Oncology 31: 640-642.

39. Liu Q (2010) Curative effect observation of highly agglutinative staphylococcin plus cisplatin in treatment of malignant hydrothorax. Laboratory Medicine and Clinic 7: 1700-1701.

40. Xiao Y, Peng J (2003) Effect of highly agglutinative

staphylococcin combined with the chemotherapy of cisplatin in the treatment of thoracic cavity. Journal of Clinical Pulmonary Medicine 8: 117-118.

41. Zhou Y, Gong S, Ni J (2008) Study of highly agglutinative staphylococcin or lentinan combined with chemotherapy on malignant pleural effusion of non-small cell lung cancer. Modern Journal of Integrated Traditional Chinese and Western Medicine 17: 5561-5562.

42. Krakauer T, Pradhan K, Stiles BG (2016) Staphylococcal superantigens spark host-mediated danger siginals. Front Immunol 7: 1-14.

43. Yoshioka T, Imura K, Hikita I, Hirasawa T, Sakata T, et al. (2007) Synergistic production of interleukin-13 caused by staphylococcal enterotoxin C and peptide glycans from Staphylococcus aureus. Blackwell Publishing Ltd, Immunology 121: 51-61.

44. Mahlknecht U, Herter M, Hoffmann MK, Niethammer D, Dannecker GE (1996) The toxic shock syndrome toxin-1 induces anergy in human T cells in vivo. Hum Immunol 45: 42-45.

45. Kominsky SL, Johnson HM, Bryan G, Tanabe T, Hobeika AC, et al. (1998) IFN- inhibition of cell growth in glioblastomas correlates with increased levels of p21WAF1/CIP1. Oncogene 17: 2973-2979.

46. Hobeika AC, Etienne W, Torres BA, Johnson HM, Subramaniam PS (1999) IFN- induction of p21WAF1 is required for cell cycle inhibition and suppression of apoptosis. J Interferon Cytokine Res 19: 1351-1361.