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Original Article

Matrine promotes the efficacy and safety of platinum-based doublet chemotherapy for advanced non-small cell lung cancer

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Abstract: Purpose: Many studies have investigated the efficacy of matrine combined with platinum-based doublet chemotherapy (PBDC) versus PBDC alone for treating advanced non-small cell lung cancer (NSCLC). This study is an analytic value of available evidence. Methods: twenty-two studies reporting matrine combined with PBDC versus PBDC alone for treating advanced NSCLC were reviewed. Pooled odds ratios and hazard ratio with 95% confidence intervals were calculated using either the fixed effects model or random effects model. Results: The overall response rate (ORR) and disease control rate (DCR) of matrine combined with PBDC for treating NSCLC were significantly higher than those of PBDC alone, with 15.1% and 19.7% improvement, respectively ($P < 0.00001$). In addition, the mean survival time (MST) and quality of life (QOL) were improved after the treatment of matrine combined with PBDC ($P < 0.00001$). The main adverse effects found in this review were hematological reactions, nausea and vomiting. Matrine combined with PBDC had a lower incidence of adverse reactions compared with PBDC alone ($P < 0.05$). Conclusions: Matrine combined with PBDC was associated with higher RR, DCR, and MST as well as superior QOL profiles compared with PBDC alone. Matrine combined with PBDC decrease the incidence of adverse reactions compared with PBDC alone.

Keywords: Matrine, lung cancer, first-line chemotherapy, meta-analysis

Introduction

Non-small cell lung cancer (NSCLC) has become the most common disease which threats human health. Chemotherapy can be used for controlling the growth of NSCLC and has received certain curative efficacy, but the side effects of chemotherapeutic drugs limit their application. The current first-line chemotherapy options for patients with advanced NSCLC, such as the combination of platinum-based agents with paclitaxel, gemcitabine, vinorelbine, or docetaxel, have substantial toxicity and seem to have reached a plateau in terms of efficacy [1]. The use of cytotoxic chemotherapy is associated with a response rate (RR) of 20% to 35% and a median survival time of 10 to 12 months among patients with advanced NSCLC. Novel regimens are needed to improve outcome, and the development of more effective therapies remains challenging. Therefore, to discover and develop novel natural compounds that have therapeutic selectivity or that can preferentially kill lung cancer cells without significant toxicity to normal cells is an important tendency for NSCLC therapy. Because of low side toxicity and wide range of biological activities, some natural products have been used as alternative treatments for cancers [2]. Accumulating research evidence suggests that many medicinal plants may be used alone or in combination with common chemotherapeutic agents to prevent the occurrence and metastasis of cancer. Due to their wide range of biological activities and low toxicity in animal models, these products have been used as alternative treatments for lung cancer.

Matrine is a naturally occurring small-molecule compound from Traditional Chinese Medicine

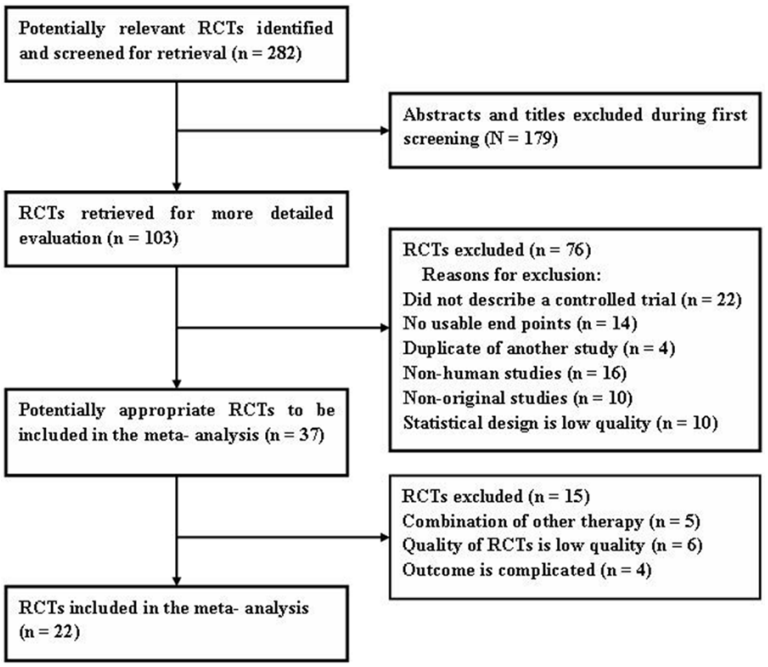

Figure 1. Flow chart of literature search. RCTs = randomized controlled trials.

Sophora flavescens Ait. In China, matrine as a clinical drug has been used to treat cancer as well as other diseases such as viral hepatitis, cardiac arrhythmia and skin inflammations. Matrine induced the apoptosis of murine hepatoma cells in vitro and in vivo as well as inhibited tumor growth [3]. Matrine also inhibited the invasiveness and metastasis of human malignant melanoma cell line A375 [4]. Some studies reported that matrine induced gastric cancer MKN45 cell apoptosis [5] and reduced Hela cell adhesion and migration [6]. However, the effects of matrine on human NSCLC as well as the mechanisms of action are largely unknown. Whether or not matrine has the potential therapeutic and/or adjuvant therapeutic application in the treatment of human NSCLC is unclear. Matrine was approved by the China State Food and Drug Administration (SFDA) for the treatment of cancer in 1992. To date, some studies discuss the efficacy and safety of murine in treating advanced NSCLC. Authentic assessment of matrine treatment in NSCLC is important and urgent. The current study presents a systematic study to quantify the toxicities and clinical benefits of matrine combined with platinum-based doublet chemotherapy (PBDC) versus chemotherapy alone for treating advanced NSCLC.

Methods

Search strategy and data extraction

An electronic search of scientific literature published in the databases of MEDLINE/PubMed, EMBASE, Cochrane Library, Science Citation Index, Current Controlled Trials, and CNKI was performed using free text and Medical Subject Heading terms such as “non-small cell lung cancer”, “NSCLC”, “lung adenocarcinoma”, “lung cancer”, “lung squamous carcinoma”, “matrine”, “oxymatrine”, “matrine injection”, “kushenzongjian zhusheye”, “fufang kushen zhusheye”, “chemotherapy”, “sophora flavescens ait”, and “shrubby sophora extract”. The search period was from the start of each database up to July 2014 without language restrictions. Moreover, a manual revision of the bibliographical references of the selected articles was done. In addition to the database search, papers were also identified by personal contact with the authors using E-mail and telephone as necessary. The extracted data are summarized as follows: (i) general information, including the title, author, publication date, and literature sources; (ii) design and implementation, including the type of design, research and follow-up time, interventions, measurement indicator, the number of lost and processed samples; and (iii) outcome indicators, including RR, disease control rate (DCR), one-year survival rate (OYS), mean survival time (MST), time to progression (TTP), quality of life (QOL), and adverse effects (AEs).

Criteria for inclusion and exclusion

Meta-analysis inclusion criteria were as follows: (i) trials must compare matrine combined with PBDC to PBDC alone for treating advanced NSCLC; (ii) patients in the studies meeting the first inclusion criteria must be diagnosed and confirmed by cytology and pathology; (iii) age and gender must not be restricted; (iv) must report on at least one of the outcome measures

Table 1. Patient characteristics of the clinical trials reviewed

Study	N	F/M	Age (Mean)	Histology (N)	TNM Stage (N)	Quality of Life	Invention Group (N)	Group 1 (N)	Group 2 (N)	End point
Jun L 2008 [10]	100	60/40	32-72	SCC (58) LAC (28) Others (14)	III (61) IV (39)	KPS	NPM versus NP	60	40	RR, DCR, MST, SI, AEs
Qinhuai Z 2008 [17]	96	51/55	35-75	SCC (66) LAC (26) Others (4)	IIB (7) III(62) IV (27)	KPS	M + RT versus RT	55	41	RR, DCR, SI, AEs
Ping D 2009 [18]	143	88/54	36-69	SCC (47) LAC (69) Others (27)	IIIA (36) IIIB (47) IV (60)	KPS	GPM versus GP	72	71	RR, DCR, SI, AEs
Qiuyan F 2009 [14]	126	82/44	60-79	SCC (69) LAC (50) Others (7)	IIIA (48) IIIB (54) IV (24)	KPS	GPM versus GP	64	62	RR, DCR, SI
Zeyu Z 2009 [11]	108	74/34	42-78	SCC (62) LAC (42) Others (4)	III (51) IV (57)	KPS	PPM versus PP	54	54	RR, DCR, SI, AEs
Leyuan W 2009 [20]	90	58/32	27-72	SCC (45) LAC (38) Others (7)	III (64) IV (26)	KPS	NPM versus NP	45	45	RR, DCR, SI, AEs
Xiaorong Y 2010 [15]	109	62/47	63-79	SCC (39) LAC (41) Others (29)	IIIA (48) IIIB (54) IV (24)	KPS	GPM versus GP	53	56	RR, DCR, SI, AEs
Chen W 2010 [27]	112	72/40	45-70	SCC (57) LAC (49) Others (6)	IIIB (47) IV (65)	KPS	TPM versus TP	56	56	RR, DCR, SI, AEs
Yan W 2010 [19]	143	95/48	45-75	SCC (47) LAC (73) Others (23)	IIIA (38) IIIB (48) IV (57)	KPS	NCM versus NC	72	71	RR, DCR, SI, AEs
Haiying Z 2011 [13]	80	42/38	34-76	SCC (32) LAC (46) Others (2)	III (34) IV (46)	ECGO	GPM versus GP	40	40	RR, DCR, OYS, SI, AEs
Haisheng Z 2011 [25]	80	54/26	70-86	SCC (34) LAC (46)	IIIA (39) IIIB (36) IV (5)	KPS	M + RT versus RT	40	40	RR, DCR, SI, AEs
Liming Z 2011 [12]	182	104/78	42-75	SCC (94) LAC (71) Others (17)	IIIA (57) IIIB (77) IV (48)	KPS	NPM versus NP (58) TPM versus TP (62) GPM versus GP (61)	92	90	RR, DCR, MST, SI, AEs

Huai K 2011 [16]	377	248/129	34-75	SCC (115) LAC (219) Others (43)	IIIA (139) IIIB (120) IV (118)	KPS	NPM versus NP	183	186	RR, DCR, MST, OS, SI, AEs
Jinyun X 2012 [9]	369	192/177	34-75	SCC (158) LAC (172) Others (39)	III (200) IV (169)	KPS	NPM versus NP	183	186	RR, DCR, MST, OS, SI, AEs
Xinwen S 2012 [26]	106	65/41	31-73	SCC (43) LAC (63)	IIIB (47) IV (59)	KPS	NPM versus NP	54	52	RR, DCR, SI, AEs
Zhengang Y 2012 [21]	90	55/35	40-78	SCC (58) LAC (32)	IIIB (57) IV (33)	KPS	GCM versus GC	50	40	RR, DCR, SI, AEs
Peng X 2012 [22]	112	68/44	41-72	NA	NA	KPS	GPM versus GP	53	50	RR, DCR, MST, OS, SI, AEs
Guohui L 2012 [23]	120	98/22	36-73	SCC (38) LAC (80) Others (2)	IIIB (26) IV (94)	KPS	GPM versus GP	60	60	RR, DCR, SI, AEs
Xiangming K 2012 [24]	88	58/30	36-77	SCC (42) LAC (46)	III (55) IV (33)	KPS	GPM versus GP	45	43	RR, DCR, SI, AEs
Yanru L 2013 [30]	88	51/37	36-74	SCC (26) LAC (43) Others (19)	III (52) IV (36)	ECGO	GCM versus GC	44	44	RR, DCR, SI, AEs
Jianning C 2014 [29]	86	45/41	65-85	NA	NA	ECGO	TPM versus TP	43	43	RR, DCR, SI, AEs
Yiwei S 2014 [28]	96	65/31	45-78	SCC (54) LAC (36) Others (6)	III (45) IV (51)	KPS	GPM versus GP	48	48	RR, DCR, SI, AEs

N = number of patients; F/M = female/male; Group 1 = matrine combined with PBDC; Group 2 = PBDC alone; SCC = squamous cell carcinoma; LAC = lung adenocarcinoma; SCLC = small cell lung cancer; ECGO = eastern cooperative oncology group; KPS = karnofsky physical status score; NPM = vinorelbine + cisplatin + matrine; NP = vinorelbine + cisplatin; TPM = docetaxel + cisplatin + matrine; TP = docetaxel + cisplatin; PPM = paclitaxel + cisplatin + matrine; PP = paclitaxel + cisplatin; GPM = gemcitabine + cisplatin + matrine; GP = gemcitabine + cisplatin; Pe + M = pemetrexed + matrine; Pe = pemetrexed; NCM = vinorelbine + carboplatin + matrine; NC = vinorelbine + carboplatin; GCM = gemcitabine + carboplatin + matrine; GC = gemcitabine + carboplatin; M + RT = matrine + radiotherapy; RT = radiotherapy; RR = response rate; DCR = disease control rate; OYS = one-year survival rate; MST= median survival time; OS = overall survival; SI = symptom improvement; AEs = adverse effects; NA = not available.

mentioned in the succeeding portion of this study; (v) randomized phase II and III studies were eligible if fully published; and (vi) the total number of cases must be greater than or equal to 80.

Abstracts, letters, editorials and expert opinions, reviews without original data, and case reports were excluded. The following studies were also excluded: (i) those with no clearly reported outcomes of interest; (ii) those evaluating patients with other types of malignant tumors and did not contain a distinct group of patients with NSCLC; and (iii) studies lacking control groups.

Type of trial design, interventions, and indicators to determine efficacy

Trial design: randomized controlled trials of matrine combined with PBDC versus PBDC for treating advanced NSCLC. Type of interventions: (i) matrine + PBDC vs. PBDC; (ii) matrine substituted one or more drugs of PBDC vs. PBDC; (iii) matrine + PBDC A vs. PBDC B; and (iv) matrine + PBDC + radiotherapy vs. PBDC + radiotherapy. Efficacy indicators: ORR, DCR, OYS, TTP, QOL, and AEs (according to the toxicity criteria of WHO).

Methodological quality assessment

The methodological quality for RCTs was assessed using the criteria from the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.1). The quality of trials was categorized into low risk of bias, unclear risk of bias, or high risk of bias. This categorization was according to the risk for each important outcome within included trials, including adequacy of the generation of allocation sequence, allocation concealment, blinding, and the presence of incomplete outcome data, selective outcome, or other sources of bias. The intention-to-treat (ITT) analysis was also assessed for the randomized controlled trials included into the present meta-analysis [7, 8].

Statistical analysis

To assess the efficacy and safety of matrine combined with PBDC versus PBDC alone for treating advanced NSCLC, two different meta-analysis approaches were used: a fixed effects model and a random effects model. Dichotomous variables were analyzed using estimation of odds ratios (OR) and hazard ratio (HR) with a 95% confidence interval (95% CI). The overall effect was tested using Z-scores, with significance being set at $P < 0.05$. Pooled effect was calculated using either the fixed effects model or random effects model. Heterogeneity was evaluated through chi-square and I^2. In the absence of statistically significant heterogeneity, the fixed effects method was used to combine the results. When heterogeneity was confirmed, the random effects method was used. Meta regression was done to evaluate whether results were different between two groups. Sensitivity was analyzed by omitting each study from the estimated pool conducted at each step. Finally, publication bias was evaluated using funnel plots, the Egger's test, and the Begg's test. Statistical analyses were performed using SPSS (SPSS Institute, version 15.0, Chicago, USA), RevMan 4.2 (The Cochrane Collaboration), and Stata version 12.0 (Stata Corporation, TX, USA). All *p*-values were two-sided, and $P < 0.05$ was considered to indicate statistical significance.

Results

Selection of studies

Our systematic search identified 282 potentially relevant abstracts, of which 103 were identified as requiring full-text article retrieval. Close screening of these 103 studies excluded 76 because of the following reasons: limited cases, non-human studies, and some received matrine therapy without a parallel control. Finally, 22 studies published between 2006 and 2014 matched the inclusion criteria and were therefore included [9-30] (**Figure 1**). A database was established according to the extracted information from each selected paper. **Table 1** shows the baseline demographic factors of the patients. The eligible studies included 2901 patients, of whom 1123 were women and 1787 were men. The sample sizes oscillated between 80 [13, 25] and 377 [16] patients, and the age of the patients mainly concentrated at the range of 40 to 70 years old, with the youngest at 27 years old [20] and the oldest at 86 [25] years old.

Quality of study design

The studies were appraised independently by three authors (Liu H, Zhao CC and Gao WL) based on the criteria from the Cochrane

Table 2. Raw data and methodological quality of included trials

Studies	Region	Sequence generation	Allocation concealment	Blind	Outcome data	Selective out-come reporting	Other sources of bias	ITT	Risk of bias
Jun L 2008 [10]	Single center	Random number table (SAS)	Insufficient	Clear	No	No	Unclear	Yes	Low risk of bias
Qinhuai Z 2008 [17]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	NO	Unclear	No	Unclear risk of bias
Ping D 2009 [18]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	No	Unclear	No	Low risk of bias
Qiuyan F 2009 [14]	Single center	unclear	Clear	Clear	Yes	No	Unclear	No	Low risk of bias
Zeyu Z 2009 [11]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	No	Unclear	No	Unclear risk of bias
Leyuan W 2009 [20]	Single center	Random number table (SPSS)	Unclear	Clear	Yes	No	Unclear	No	Low risk of bias
Xiaorong Y 2010 [15]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	NO	Clear	No	Unclear risk of bias
Chen W 2010 [27]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	Yes	Clear	No	Unclear risk of bias
Yan W 2010 [19]	Single center	Random number table (SAS)	Clear	Unclear	Yes	No	Clear	No	Unclear risk of bias
Haiying Z 2011 [13]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	No	Clear	No	Low risk of bias
Haisheng Z 2011 [25]	Single center	Random number table (SPSS)	Unclear	Clear	Yes	No	Unclear	No	Low risk of bias
Liming Z 2011 [12]	Multi-center	Random number table (SPSS)	Insufficient	Clear	Yes	No	Unclear	No	Unclear risk of bias
Huai K 2011 [16]	Multi-center	Random number table (SPSS)	Insufficient	Clear	Yes	No	Unclear	No	Unclear risk of bias
Jinyun X 2012 [9]	Multi-center	Random number table (SAS)	Unclear	Unclear	Yes	No	Unclear	No	Unclear risk of bias
Xinwen S 2012 [26]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	No	Unclear	No	Unclear risk of bias
Zhengang Y 2012 [21]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	No	Unclear	No	Unclear risk of bias
Peng X 2012 [22]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	NO	Clear	No	Low risk of bias
Guohui L 2012 [23]	Single center	Random number table (SAS)	Clear	Unclear	Yes	No	Clear	No	Low risk of bias
Xiangming K 2012 [24]	Single center	Random number table (SPSS)	Clear	Clear	Yes	No	Clear	No	Unclear risk of bias
Yanru L 2013 [30]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	No	Clear	No	Unclear risk of bias
Jianning C 2014 [29]	Single center	Random number table (SPSS)	Clear	Unclear	Yes	No	Clear	No	Unclear risk of bias
Yiwei S 2014 [28]	Single center	Random number table (SPSS)	Unclear	Unclear	Yes	NO	Unclear	No	Unclear risk of bias

SAS = SAS software; SPSS = SPSS software; ITT = intention-to-treat.

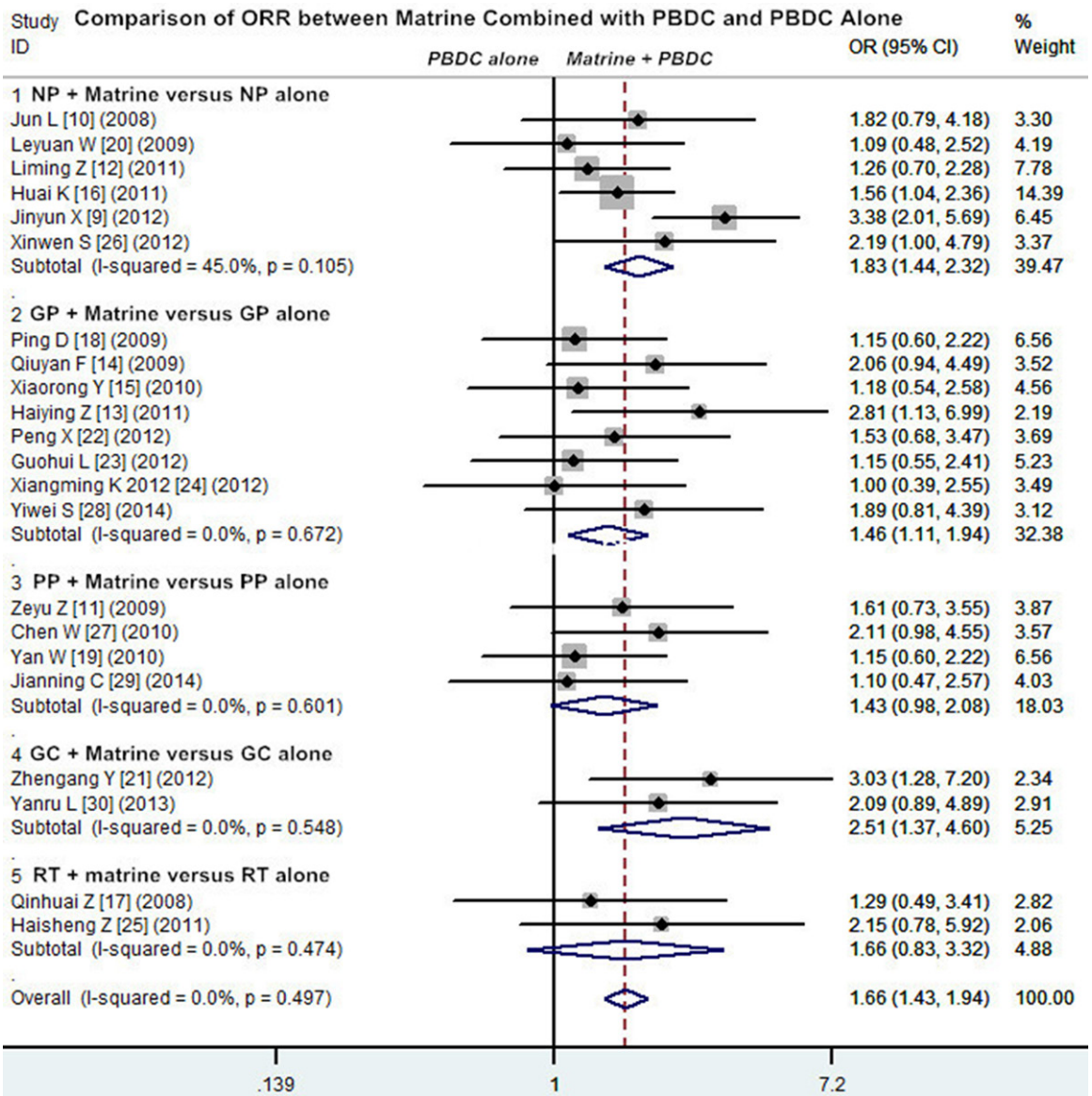

Figure 2. ORR of matrine combined with PBDC versus PBDC alone for treating NSCLC. PBDC = platinum-based doublet chemotherapy; ORR = overall response rate; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

Handbook for Systematic Reviews of Interventions (Version 5.0.1). According to our predefined quality assessment criteria, 8 of the 22 trials (36%) were evaluated as having a low risk of bias, and another 14 included trials were evaluated as having an unclear risk of bias (64%). **Table 2** shows the quality of each study included in the present systematic review.

Comparison of ORR between matrine combined with PBDC and PBDC alone

Twenty-two studies compared the ORR between matrine combined with PBDC and PBDC alone. The results of the fixed effects model showed that OR = 1.34 (95% CI 1.17 to 1.54; test for heterogeneity = 12.04; I^2 = 0%), test for overall effect: Z = 4.18, P < 0.0001. The ORR of matrine combined with PBDC for treating NSCLC was significantly higher than that of PBDC alone. The subgroup analyses showed that ORR favored the following five matrine combinations with the overall effect Z-value and p-values as follows: NP + matrine versus NP alone (Z = 4.92, P = 0.0001), GP + matrine versus GP alone (Z = 2.68, P = 0.007), PP + matrine versus PP alone (Z = 1.86, P < 0.063), GC + matrine versus GC alone (Z = 2.98, P =

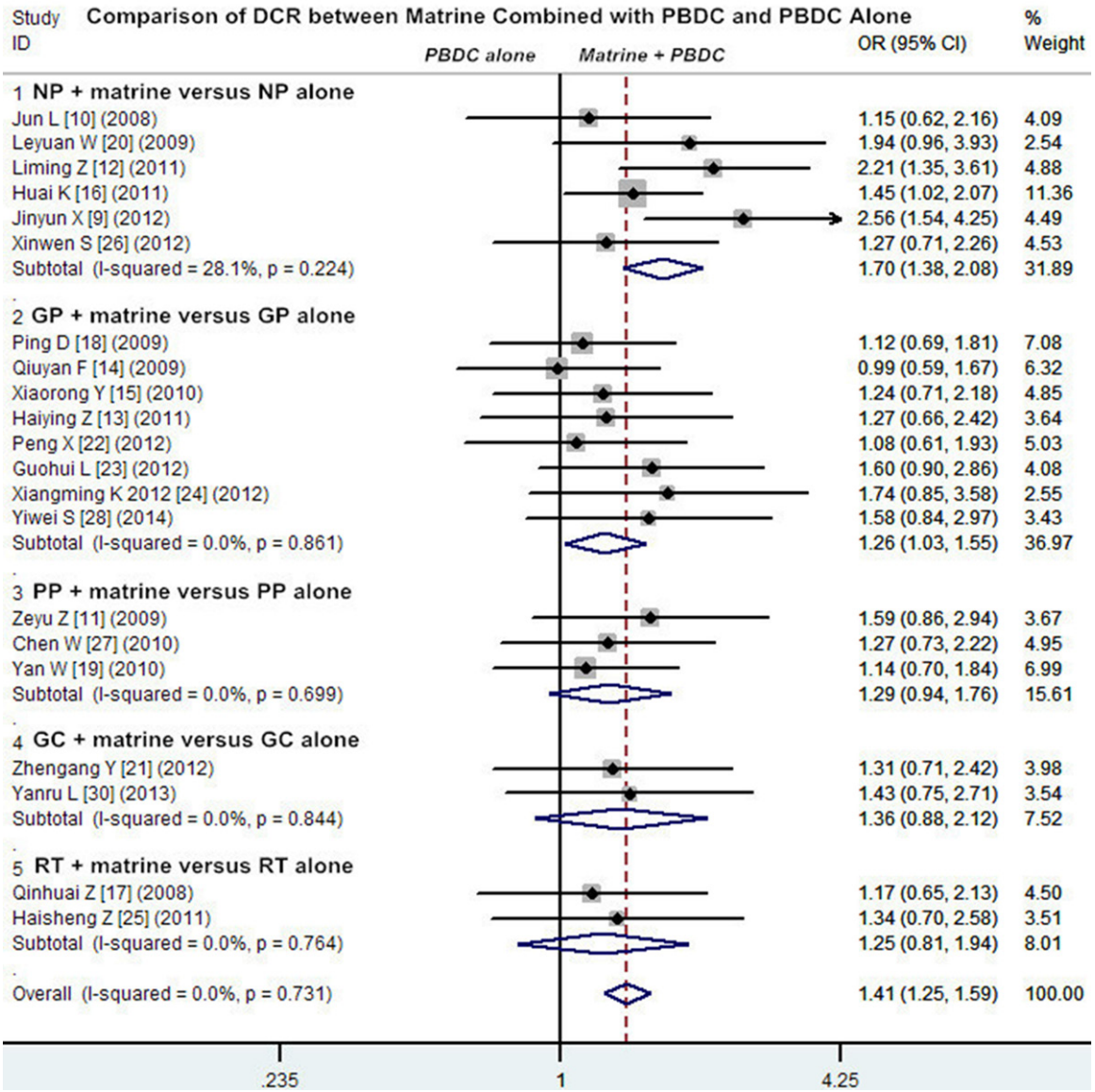

Figure 3. DCR of matrine combined with PBDC versus PBDC alone for treating NSCLC. PBDC = platinum-based doublet chemotherapy; ORR = overall response rate; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

0.003), and radiotherapy + matrine versus radiotherapy alone (Z = 1.42, *P* = 0.156) (**Figure 2**). Sensitivity analyses showed that the RR and 95% CI did not alter substantially by removing any one trial (data not shown), with an OR pool oscillating between 1.00 and 3.38.

Comparison of DCR between matrine combined with PBDC and PBDC alone

Twenty-one studies compared the DCR between matrine combined with PBDC and PBDC alone. The results of the fixed effects model showed that the OR was 1.41 (95% CI 1.25 to 1.59; Z = 5.60, P < 0.0001). The DCR of matrine combined with PBDC for treating NSCLC was significantly higher than that of PBDC alone. The subgroup analyses showed that DCR favored the following four Endostar combinations with the overall Z-value and *p*-values as follows: NP + matrine versus NP alone (Z = 5.06, *P* < 0.0001), GP + matrine versus GP alone (Z = 2.23, *P* = 0.026), PP + matrine versus PP alone (Z = 1.59, *P* = 0.011), GC + matrine versus GC alone (Z = 1.37, *P* = 0.017), and radiotherapy + matrine versus radiotherapy alone (Z =0.99, *P* = 0.32) (**Figure 3**). Sensitivity analyses showed that the RR and 95% CI did not alter substantially by

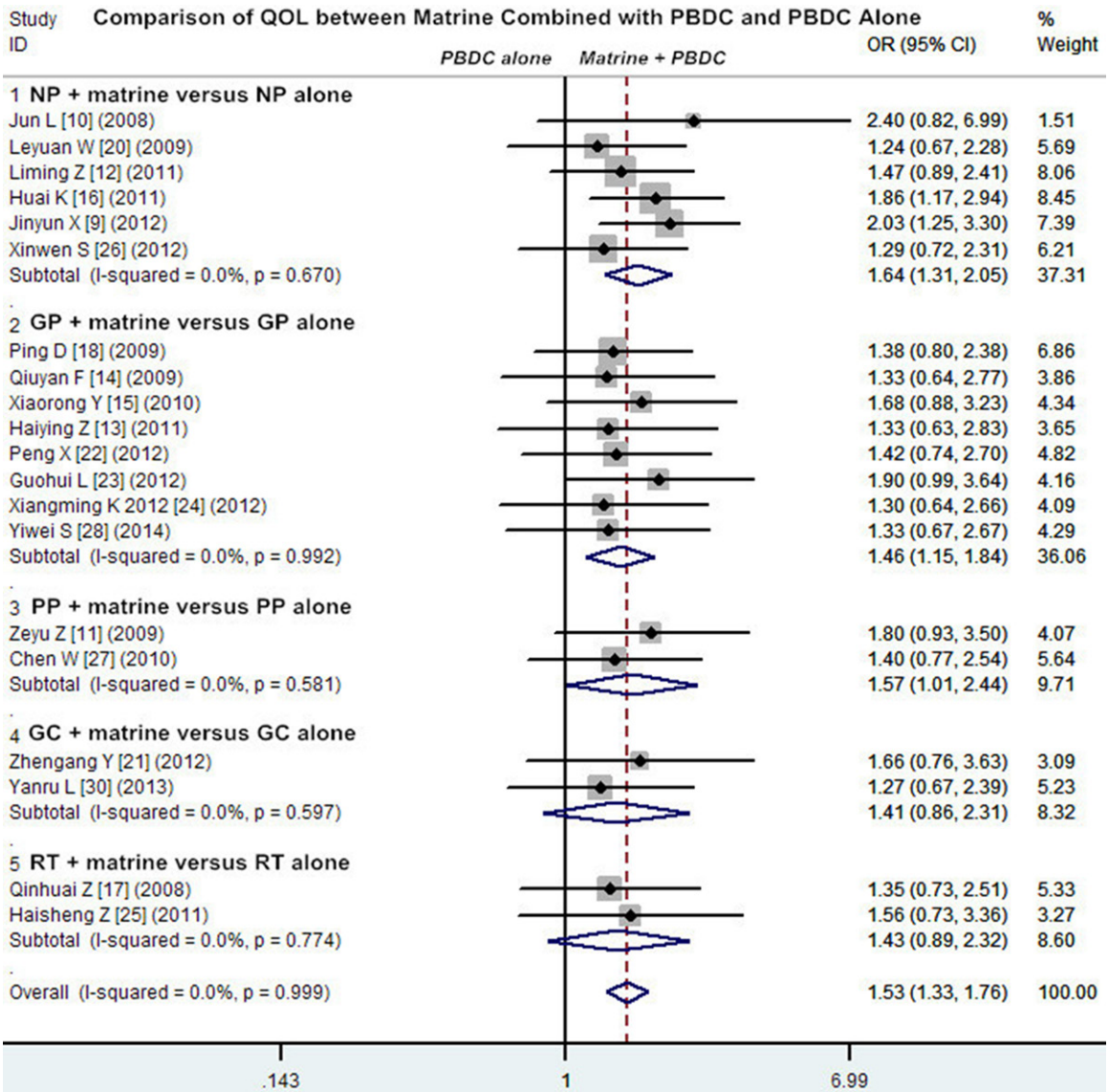

Figure 4. QOL improvement of matrine combined with PBDC versus PBDC alone for treating NSCLC. PBDC = platinum-based doublet chemotherapy; QOL = quality of life; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

removing any one trial (data not shown), with an OR pool oscillating between 0.99 and 2.56.

Comparison of QOL between matrine combined with PBDC and PBDC alone

Twenty trials compared the QOL between matrine combined with PBDC and PBDC alone for treating advanced NSCLC. The results of the fixed effects model showed that OR = 1.53 (95% CI 1.33 to 1.76; test for heterogeneity = 5.69; I^2 = 0%), test for overall effect: Z = 5.99, P < 0.0001. The QOL of matrine combined with PBDC for treating NSCLC was significantly higher than that of PBDC alone. The subgroup analyses showed that QOL favored the following five matrine combinations with the overall effect Z-value and p-values as follows: NP + matrine versus NP alone (Z = 4.32, P = 0.0001), GP + matrine versus GP alone (Z = 3.15, P = 0.002), PP + matrine versus PP alone (Z = 1.99, P = 0.047), GC + matrine versus GC alone (Z = 1.38, P = 0.168), and radiotherapy + matrine versus radiotherapy alone (Z =1.46, P = 0.143) (**Figure 4**). In the analysis of sensitivity, the exclusion of studies individually did not substantially modify the estimators, with an OR pool oscillating between 1.24 and 2.40.

Table 3. Time to progression of matrine combined with chemotherapy versus chemotherapy alone for treating NSCLC

	Matrine combined with PBDC (MST, months)	PBDC alone (MST, months)	T-value	95% CI	*p*-value
Jun L [10] 2008	7.00	4.90	T = 2.49 df = 12	1.32 to 3.28	0.0284
Liming Z [12] 2011	15.98	11.06			
Huai K [16] 2011	10.00	7.00			
Jinyun X [9] 2012	12.60	8.60			
Xinwen S [26] 2012	11.60	8.70			
Haiying Z [13] 2011	13.00	10.00			
Peng X [22] 2012	13.00	9.90			
Mean ± SD	11.9±1.06	8.5±0.78			

MST = mean survival time; 95% CI = 95% confidence interval; SD = standard deviation.

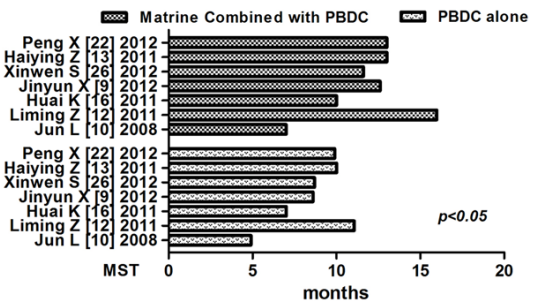

Figure 5. MST of matrine combined with PBDC versus PBDC alone for treating NSCLC. MST = mean survival time.

Comparison of MST between Matrine Combined with PBDC versus PBDC alone

Seven studies reported prolonged MST for randomized controlled trials of matrine combined with PBDC versus PBDC alone for treating advanced NSCLC. The results showed that the MST (mean ± SD) of matrine combined with PBDC versus PBDC alone was 11.9 ± 1.1 and 8.5 ± 0.71 months, respectively. The t-value was 2.491; the degrees of freedom was 12, P = 0.0284 (**Table 3**). The MST of matrine combined with PBDC for treating NSCLC was significantly longer than that of PBDC alone (**Figure 5**).

Comparison of immunologic function between matrine combined with PBDC and PBDC alone

Three trials [12, 15, 18] conducted a statistical analysis of the change of the immunologic function between matrine combined with PBDC and PBDC alone. Three trials indicated that the CD8 was significantly decreased by treating of matrine combined with PBDC than that of PBDC alone. Meanwhile, CD4 was significantly upregulated, as well as CD4/CD8, which indicates that matrine combined with PBDC may improve the immunologic function of NSCLC patients (P < 0.05) (**Table 4**).

Adverse reactions analysis of matrine combined with PBDC versus PBDC alone

Included trials assessed 11 serious AEs, the most common being gastrointestinal, skin related, and hematologic diseases. Twelve-one studies compared the grade 3 or 4 leucopenia between matrine combined with PBDC and PBDC alone. The matrine combination arms had a lower incidence of grade 3 or 4 leucopenia relative to the PBDC arms (OR = 0.52, 95% CI 0. 43 to 0.64, *P* < 0.0001) (**Figure 6**). Eighteen studies compared the thrombocytopenia between matrine combined with PBDC and PBDC alone. The results indicated that matrine combined with PBDC had a lower incidence of thrombocytopenia than PBDC alone (OR = 0.61, 95% CI 0. 51 to 0.73, *P* < 0.0001) (**Figure 7**). Twelve studies compared nausea/vomiting between matrine combined with PBDC and PBDC alone. The incidence of nausea/vomiting of matrine combination arms was significantly lower than that of PBDC alone (OR = 0.55, 95% CI 0. 48 to 0.63, *P* < 0.0001) (**Figure 8**). No difference in hepatorenal functions was found between matrine combined with PBDC and PBDC alone (P = 0.305). Other common AEs including skin rash, dysfunction of liver, dysfunction of kidney, alopecia, nerve toxicity, and mucositis occurred with similar incidence in the two groups (P > 0.05).

Analysis of publication bias

In the present study, the shape of the funnel plot appeared to be approximately symmetrical and suggested that publication biases may not

Table 4. Comparison of immunologic function between Matrine Combined with PBDC and PBDC alone

Item	Liming Z [12]			Ping D 2009 [18]			Xiaorong Y [15]		
	Group 1	Group 2	*p*-value	Group 1	Group 2	*p*-value	Group 1	Group 2	*p*-value
CD3									
Before	61.72±9.04	21.37±8.62	> 0.05	56.48±7.75	53.47±7.09	> 0.05	55.46±7.25	52.56±7.11	> 0.05
After	24.86±6.38	19.06±5.93		57.23±7.94	52.13±7.43		56.98±7.64	51.97±7.21	
CD4									
Before	38.72±8.04	40.23±8.64	< 0.05	34.94±5.54	35.74±6.93	> 0.05	33.99±5.26	36.11±6.88	< 0.05
After	49.39±9.82	34.69±8.32		38.52±5.98	33.96±6.27		38.22±5.88	33.46±6.11	
CD8									
Before	30.38±6.39	29.78±7.48	< 0.05	26.71±5.41	33.16±4.36	< 0.05	25.21±4.28	32.11±4.16	< 0.05
After	32.56±9.03	32.13±8.77		17.80±4.29	35.84±5.22		16.51±3.92	34.98±4.92	
CD4/CD8									
Before	1.27±0.26	1.35±0.16	< 0.05	2.04±0.13	1.13±0.12	< 0.05	1.56±0.21	1.08±0.12	< 0.05
After	1.52±0.09	1.08±0.05		1.58±0.24	1.11±0.21		2.01±0.11	1.09±0.98	

Group 1 = matrine combined with PBDC; Group 2 = PBDC alone; Before = before the treatment; After = after the treatment.

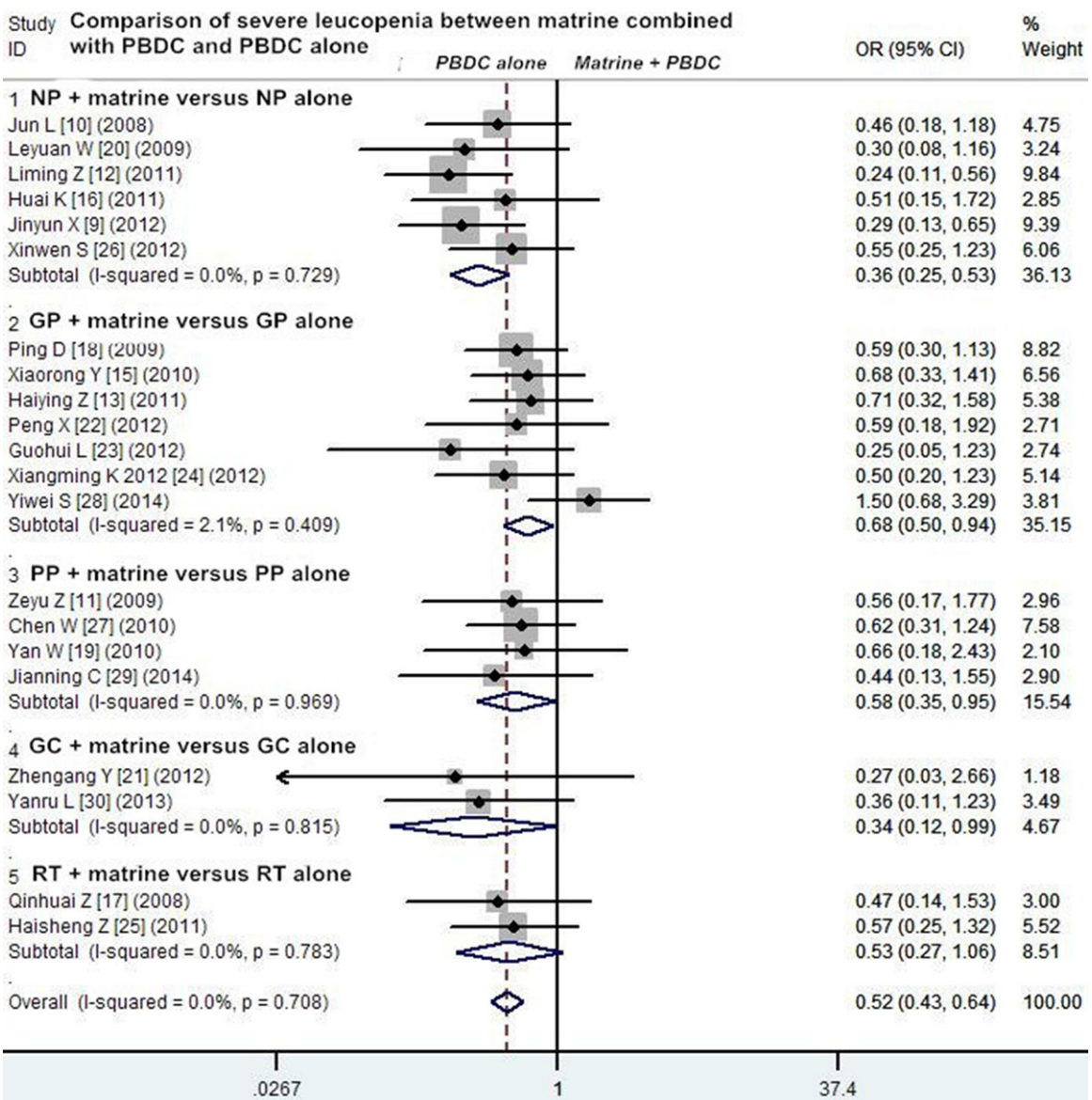

Figure 6. Comparison of severe leucopenia between matrine combined with PBDC and PBDC alone. PBDC = platinum-based doublet chemotherapy; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

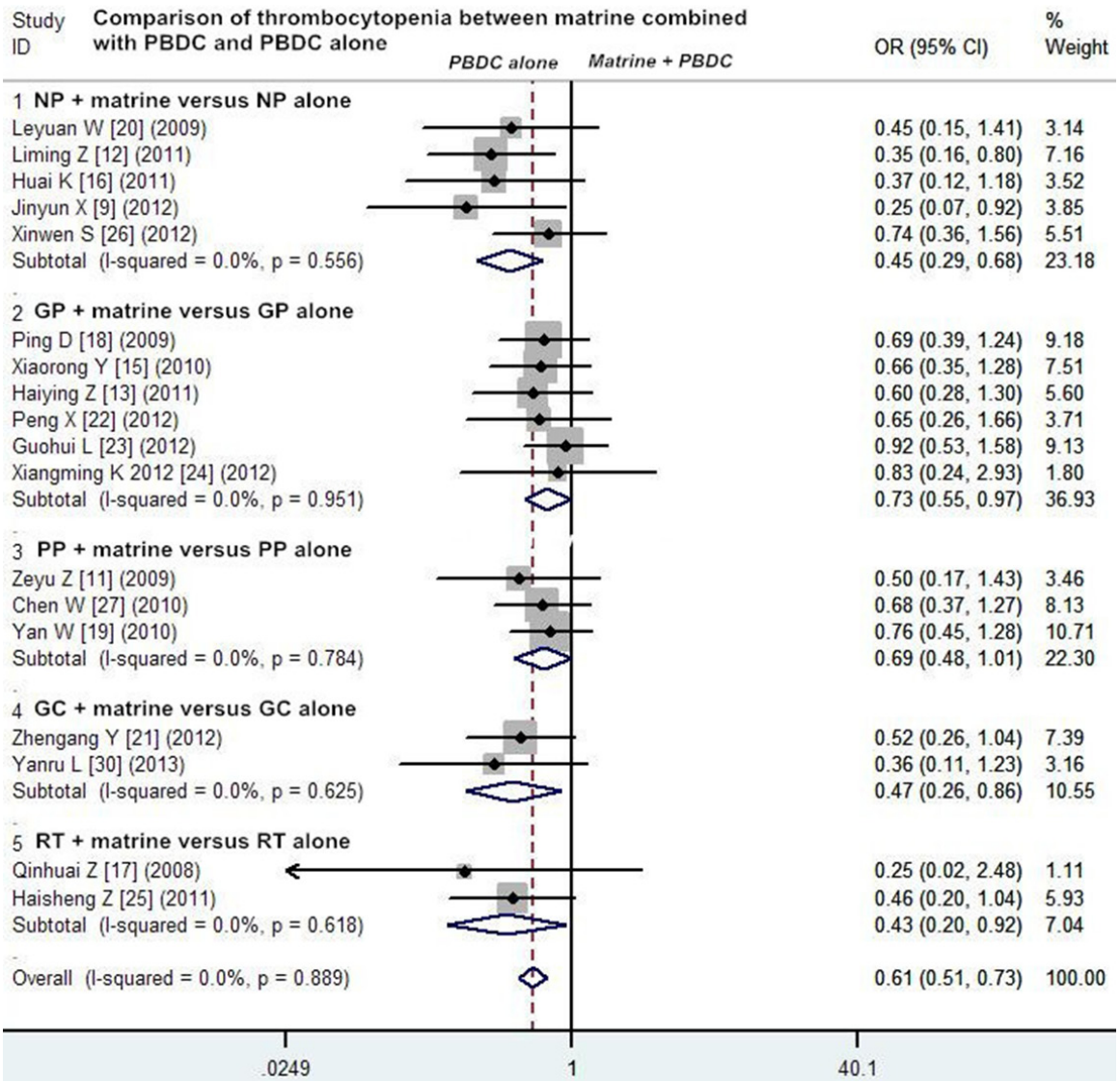

Figure 7. Comparison of thrombocytopenia between matrine combined with PBDC and PBDC alone. PBDC = platinum-based doublet chemotherapy; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

have a significant effect on the results. The result of the Egger's test was t = 1.22 (P = 0.237) (**Figure 9A**), whereas that of the Begg's test was Std. Dev. of Score = 35.46 (P = 0.185). Therefore, both tests suggested that publication biases may not have a significant effect on the results (**Figure 9B**).

Discussion

Matrine, a kind of alkaloid components found in the roots of Sophora species, are demonstrated to have anti-inflammatory, anti-virus, anti-fibrotic, and cardiovascular protective effects. They are recently proved to have anticancer potentials, such as inhibiting cancer cell proliferation, inducing cell cycle arrest, accelerating apoptosis, restraining angiogenesis, inducing cell differentiation, inhibiting cancer metastasis and invasion, reversing multidrug resistance, and preventing or reducing chemotherapy or radiotherapy induced toxicity when combined with other chemotherapeutic drugs [31]. Sophora root, which is a traditional herb

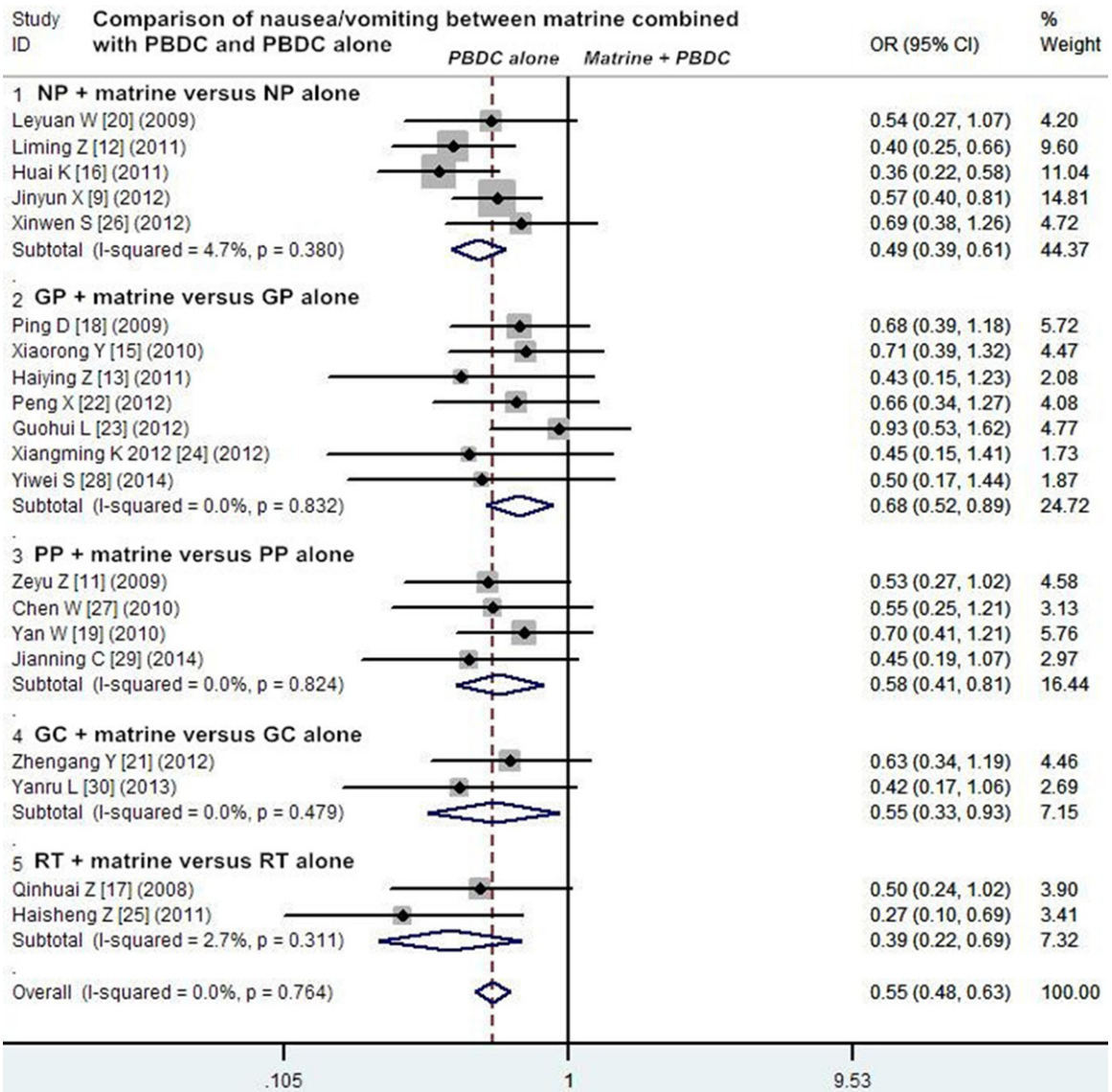

Figure 8. Comparison of nausea/vomiting between matrine combined with PBDC and PBDC alone. PBDC = platinum-based doublet chemotherapy; OR = odds ratio; NP = vinorelbine + cisplatin; GP = gemcitabine + cisplatin; PP = paclitaxel + cisplatin; GC = gemcitabine + carboplatin; RT = radiotherapy.

medicine found in China, Japan and some European countries, is the dried root of Sophora flavescens Aiton (Leguminosae) and includes matrine and oxymatrine, two major tetracycloquinolizindine alkaloids, as its primary components [31, 32]. Compound Kushen Injection (CKI), manufactured by Shanxi Zhendong Pharmaceuticals Company (Z14021231, China Pharmaceutical and Biological products, Xi'an, China), commonly known as Yanshu injection, is extracted from Kushen and Baituling (Rhizoma smilacis Glabrae), with the primary components being matrine and oxymatrine [31, 32].

In recent years, some studies have reported on the efficacy and safety of matrine in the treatment of advanced lung cancer. This systematic analysis was performed to quantify better the benefits and toxicities of matrine combined with PBDC versus PBDC alone for treating advanced NSCLC. In this work, 22 reports of randomized trials were identified by searching from the start of each database up to Jan 2015. A significant benefit of matrine plus PBDC in ORR was found (OR = 1.66, 95% CI 1.43 to 1.94), translating into a 15.1% absolute improvement. A meta-analysis of DCR was also

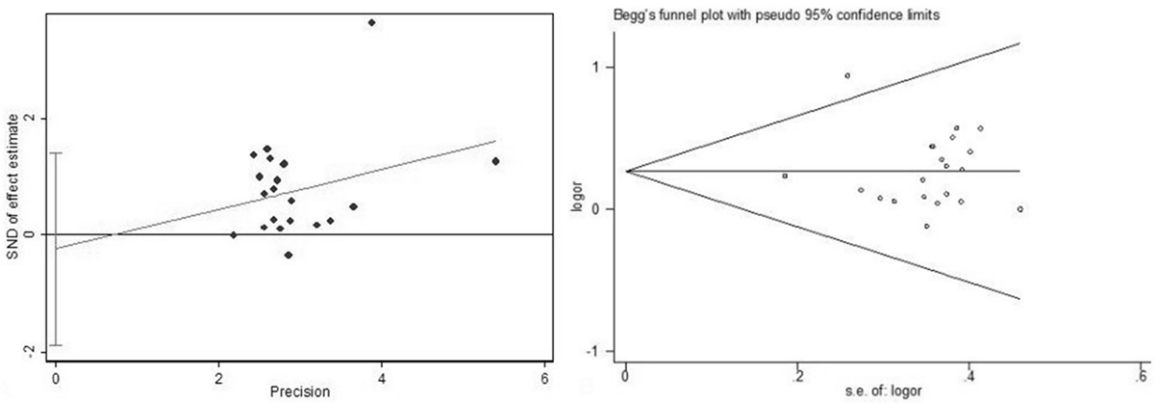

Figure 9. Assessment of publication bias. A. Egger's publication bias plot for the ORR of matrine combined with PBDC versus PBDC alone: B. Begg's publication bias plot for the ORR of matrine combined with PBDC versus PBDC alone.

conducted (OR = 1.41, 95% CI 1.25 to 1.59), and a 19.7% improvement of matrine plus PBDC was found compared with PBDC alone. NP plus matrine versus NP alone, GP plus matrine versus GP alone, PP plus matrine versus PP alone, GC plus matrine versus GC alone, and radiotherapy plus matrine versus radiotherapy alone showed improvements of 16.1%, 14.7%, 12.7%, and 16.5% in ORR, respectively, and 20.6%, 20.3%, 16.9%, and 18.2% in DCR, respectively. Seven reports analyzed that the MST of matrine combined with PBDC (11.9 ± 1.06 months) for treating NSCLC was significantly longer than that of PBDC alone (8.5 ± 0.78 months). However, only seven trials providing relative data were included, which were insufficient to reach a decisive conclusion. Therefore, more research is required to gain a clear understanding of the probability. One of the outstanding characteristics of the tumor cells is growing out of control and infinite multiplication. Matrine treatment has been shown to inhibit the proliferation of tumor cells in various cancers, including gastric cancer, breast cancer, hepatoma, colon cancer, melanoma, glioma, osteosarcoma, pancreatic cancer, and leukemia in a dose-dependent manner [31]. Resistance to apoptosis is a hallmark of cancer. Studies have reported that matrine exert anti-cancer effects by inducing apoptosis in different type of cancers. In non-small cell lung carcinoma (NSCLC), matrine increases the phosphorylation of p38 and generates reactive oxygen species (ROS) in a dose- and time-dependent manner, which indicated that matrine could activate p38 pathway and lead to a caspase-dependent apoptosis by inducing the generation of ROS [33].

As a solid tumor with low antigenicity and heterogenic phenotype lung cancer evades host immune defense. The cytotoxic anti-cancer effect is suppressed by a complex mechanism in tumor microenvironment. T cell has a central role in supporting and shaping immune responses and may have a key role in antitumor immunity. In the present study, three reports compared the changes of CD3, CD4 and CD8 between matrine combined with PBDC and PBDC alone for treating advanced NSCLC. The results indicated that matrine combined with PBDC significantly increased the CD4 and CD4/CD8 than that of PBDC alone after therapy. From this result, it is possible that the therapy of matrine combined with PBDC improve the antitumor immunity of body of NSCLC patients. Because QOL can be measured by various means, it is also quite easy to use it to measure and predict many variables during treatment. The benefit of chemotherapy in incurable cancers needs to be assessed directly through validated health-related QOL instruments, rather than inferred from RRs, survival benefits, and other traditional endpoints. In the present study, 20 trials were enrolled in the assessment of QOL. A significant benefit of matrine plus PBDC in the overall improvement rate of QOL (OR = 1.53, 95% CI 1.33 to 1.76) was found, translating into a 23.5% absolute improvement. Chemotherapy of PBDC in NSCLC given intravenously can cause not only local region side effects, but also general side effects. Form this study' result, matrine can be either used alone, or used together with PBDC to relieve general side effects and improve patients' QOL if it's not possible to cure NSCLC. The AEs found in the present analysis were

mainly hematological reactions, diarrhea, hepatic toxicity, and nausea/vomiting, most of which were grade 1 or 2 and were well tolerated. The matrine combination arms had a lower incidence of grade 3 or 4 leucopenia and thrombocytopenia relative to the PBDC arms. And the incidence of nausea/vomiting of matrine combination arms were also significantly lower than that of PBDC alone. The results supported that the matrine combination arms had a lower incidence of AEs compared with PBDC alone, which indicates that matrine does has a impact on improving safety of chemotherapy and relieving general side effects. Although no significant differences were found between the two groups, including skin rash, dysfunction of liver, dysfunction of kidney, alopecia, nerve toxicity, and mucositis. Whether matrine combination could relieve these AEs of chemotherapy should be followed up in future studies. Overall, these results indicate that the potential benefit of matrine may be widely applicable to a patient population closely resembling clinical reality in advanced NSCLC.

Addressing statistical heterogeneity is one of the most important aspects of systematic reviews. The interpretative problems are dependent on heterogeneity because it might affect the conclusions of the meta-analysis. Therefore, heterogeneity among the collection of studies must be quantified. In this review, the included studies were carefully assessed. A good clinical homogeneity was confirmed, and publication bias was not found according to the funnel plot analysis, the Egger's test, and the Begg's test. However, some deficiencies in the present work were found. First, the quality of subgroup analysis (age, sex, smoking, histology, and treatment status) according to the different agents (matrine plus PBDC compared with PBDC) was low because the subgroup data were only provided by a few trials. Second, some reports failed to report the method for concealment of allocation, blinding, and ITT. In addition, the partial reports comprise a small sample size, and some of the reports' experimental control is not very balanced. Most of the included studies were published in Chinese, with heterogeneous data and analysis methods (e.g., the different scored scales were used to assess the life quality). Although such studies were reported to be of low quality, they still contain credible evidence pointing toward such new drugs. Clinical trials are expensive and difficult. Hence, these findings can help choose the most promising agents for study. However, matrine, as a new strategy, has still many issues to be resolved in further studies. Confirmation of these conclusions in rigorously controlled randomized trials is required before firm conclusions about this therapy can be drawn.

Conclusion

The results showed that matrine combined with PBDC was associated with higher ORR, DCR, and MST as well as superior QOL profiles as compared with PBDC alone. Moreover, matrine combined with PBDC was shown to decrease AEs. Matrine combined with PBDC exhibited superior efficacy and safety compared with PBDC alone. However, matrine, as a new strategy, has still many issues to be resolved in further studies. The notable efficacy and activity of matrine in combination with PBDC suggest that this regimen may have a value in the treatment of previously untreated patients, including those who cannot tolerate more aggressive therapies. However, confirmation of these conclusions in rigorously controlled randomized trials is required before firm conclusions about this therapy can be drawn.

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Disclosure of conflict of interest

None.

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