Systematic Review and Meta-Analysis

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Clinical efficacy and safety of Huachansu injection combination with platinum-based chemotherapy for advanced non-small cell lung cancer

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Huachansu injection (HCS) is a widely used traditional Chinese medicine for advanced non-small cell lung cancer (NSCLC) to alleviate the adverse drug reactions (ADRs) and enhance the clinical efficacy of chemotherapy.

Objective: To evaluate the efficacy and safety of HCS as an adjunctive treatment to platinum-based chemotherapy (PBC) for advanced NSCLC.

Methods: A systematic review and meta-analysis were conducted according to PRISMA guidelines. A total of nine databases were searched to select randomized controlled trials (RCTs) of HCS plus PBC to treat NSCLC from inception to October 10, 2020. RCTs on HCS plus PBC vs PBC alone for advanced NSCLC were included. Dichotomous data were pooled as risk ratio (RR) with 95% confidence intervals. RCTs compared to HCS plus PBC vs PBC alone were included. Primary outcomes were objective response rate (ORR) and disease control rate (DCR), and secondary outcomes were survival rate, quality of life (QOL), and adverse drug reactions (ADRs). GRADE software was used to access the quality of evidence.

Results: A total of 32 RCTs, including 2753 patients, were included. Compared to PBC alone, HCS plus PBC improved the ORR, DCR, 1- and 2-year survival rates, and QOL and alleviated neutropenia, thrombocytopenia, nausea, vomiting, anemia, liver injury, renal injury, and alopecia.

Conclusions: Compared to PBC alone, HCS plus PBC improved the clinical efficacy and alleviated the ADRs in advanced NSCLC patients. Considering the limitations of the included RCTs, high-quality trials with longer follow-ups are needed to further confirm the results.

Abbreviations: ADRs = adverse drug reactions, AP = pemetrexed plus cisplatin, CBM = China Biological Medicine Database, CI = confidence interval, CNKI = China National Knowledge Infrastructure, DC = docetaxel plus carboplatin, DCR = disease control rate, DP = docetaxel plus cisplatin, EP = etoposide plus cisplatin, GP = gemcitabine plus cisplatin, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HCS = Huachansu injection, NP = vinorelbine plus cisplatin, NSCLC = non-small cell lung cancer, ORR = objective response rate, PFS = progression-free survival, PRISMA guidelines = Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, QOL = quality of life, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria in Solid Tumors, RevMan5.4 = Review Manager 5.4, Taxol = paclitaxel, TBC = paclitaxel-based chemotherapy, TC = paclitaxel and carboplatin, TO = paclitaxel and oxaliplatin, TP = paclitaxel and cisplatin, VIP = Chinese Scientific Journals Full-Text Database, WHO = World Health Organization.

Keywords: huachansu injection, meta-analysis, non-small cell lung cancer, platinum-based chemotherapy, systematic review

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XMT, XYL and JXX contributed equally to this work.

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The datasets generated during and/or analyzed during the present study are publicly available.

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1. Introduction

Lung cancer accounts for 11.6% of all diagnosed cancers and is the leading cause of 18.4% of overall cancer-related mortalities, with 5% as the 5-year survival rate.[1] Lung cancer is of two major types: non-small cell lung cancer (NSCLC) that accounts for approximately 85%, and small cell lung cancer (SCLC) that accounts for 15% of all lung cancers.[2] Therefore, advanced progression and metastasis NSCLC patients are not suitable for surgery and have to receive chemotherapy, radiotherapy, or chemoradiotherapy that significantly improves the clinical efficacy.[3–6] However, patients receiving chemoradiotherapy often suffer from multiple toxic effects and adverse drug reactions (ADRs), such as neutropenia, neurotoxicity, hepatorenal dysfunction, and other toxicities.[7–9] All these ADRs lead to poor survival and affect the quality of life (QOL) in patients.[10,11] Hence, the development of novel treatment strategies to improve tumor responses and reduce the risk of ADRs is a salient issue.

Platinum-based chemotherapy (PBC) is the standard first-line therapy for advanced NSCLC,[12] which consists of several types of platinum regimens, such as cisplatin, carboplatin, or oxaliplatin and several types of chemotherapy regimens, such as paclitaxel, docetaxel, vinorelbine, or gemcitabine.[13–15] PBC doublet chemotherapy prolongs the median survival by approximately 1.5–2 months compared to single-agent PBC or other monotherapy in patients with NSCLC.[16–18]

Traditional Chinese medicine (TCM) combined with PBC has been widely used in China to treat advanced NSCLC. Previous meta-analyses[19–21] published in Chinese, have assessed the efficacy and safety, but no definitive conclusions were reached. Also, the dosage and optimal concentration for combination with PBC to achieve the best efficacy and safety of the treatment are yet to be determined. Huachansu injection (HCS) is a traditional Chinese medicine extract, which has a long-term adjuvant effect on chemotherapy in patients with NSCLC.[19–21] HCS is an injectable form of the sterilized hot-water extract of the skin glands of *B. gargarizans*,[19] and the vital bioactive compounds of *B. gargarizan* include cinobufagin, resibufogenin, bufotenine, cinobufotenine, and serotonin.[21] HCS was injected intravenously with 10–20 ml once a day. The treatment time per cycle was 7–28 days and treatment cycles were one to four cycles. Some clinical trials that evaluated the efficacy and safety of HCS combined with PBC for advanced NSCLC have been published. Therefore, the efficacy and safety of HCS plus PBC for patients with advanced NSCLC are yet to be clarified. Herein, we performed this systematic review and meta-analysis to provide evidence for the efficacy and safety of HCS plus PBC for the treatment of advanced NSCLC.

2. Materials and methods

We implemented this systematic review and meta-analysis following the Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) guidelines.[22] The protocol was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42020212821. The study was approved by the ethics institutional review board of the People's Hospital of Guangxi Zhuang Autonomous Region.

2.1. Search strategy

PubMed, Medline (via OVID SP), Embase (via OVID SP), Cochrane Central Register of Controlled Trials (CENTRAL), Nursing and Allied Health Literature (CINAHL), China National Knowledge Infrastructure (CNKI), China Biological Medicine Database (CBM), Chinese Scientific Journals Full-Text Database (VIP), and Wanfang databases were searched systematically from their inception until October 10, 2020. The specific search strategies of Pubmed database are shown in Item S1 Supplemental Digital Content (see Item S1, http://links.lww.com/MD2/A401, which illustrates the specific search strategies of Pubmed database). No language restrictions were imposed.

2.2. Inclusion criteria

Participants, interventions, control/comparisons, outcomes, and study (PICOS) strategy was used to guide the researchers on the selection of randomized controlled trials (RCTs) for this meta-analysis. All studies were required to fulfill the following inclusion criteria:

1. participants: Patients with advanced NSCLC and age ≥ 18 years. Patients should meet all of the following criteria: cytological or pathological examination diagnosis of NSCLC; at least one bidimensional measurable lesion; stage III/IV; Karnofsky performance status (KPS) scale ≥ 60;[23] life expectancy ≥ 3 months; not received chemotherapy, radiotherapy, or surgery recently.
2. interventions and comparisons: HCS combined with PBC; intervention in the control group: PBC alone and different types of PBC regimens are eligible.
3. outcome: the primary outcomes were objective response rate (ORR) and disease control rate (DCR), while the secondary outcomes were survival rate, QOL, and ADRs;
4. study design: RCTs.

2.3. Exclusion criteria

The studies that the following criteria were excluded from this meta-analysis:

1. non-RCTs, reviews, meta-analysis, non-clinical studies, case reports, meeting abstracts, and observations studies;
2. duplicated studies;
3. incomplete, incorrect, or unavailable data, or the study did not provide any primary or secondary outcomes;
4. treatment combined with any other herbs;
5. inappropriate outcome reports.

2.4. Selection of studies

Two researchers (Liang and Xi) independently searched the databases comprehensively. Then, the duplicate records were deleted separately, and the eligible articles were screened and selected by reading the titles, abstracts, and necessary assessment of the full-text of the studies. The references of previous reviews and retrieved articles were comprehensively checked to identify additional eligible studies. Discrepancies were resolved by consensus.

2.5. Data collection and quality assessment

Two reviewers (Liang and Xi) independently extracted the data and the study information, such as age, gender, KPS, and sample size; intervention protocol of HCS, such as dosage, frequency,

and course; concurrent PBC regimens; primary and secondary outcomes. The third reviewer examined the consistency of the extracted data. The methodological quality of the included studies was assessed by Xi and Liang using the Cochrane risk-of-bias tool.[24]

2.6. Statistical analysis

The statistical analysis of data was performed in Review Manager 5.4.0. (Cochrane Collaboration Software).[24] Dichotomous outcomes were shown as risk ratios (RR) with 95% confidence intervals (CI). Considering the potential heterogeneity between the trials, I^2 was used to quantitate the heterogeneity. $I^2 \geq 50\%$ or $P \leq .05$ indicated a high statistical heterogeneity among trials. If no heterogeneity was observed ($I^2 < 50\%$ or $P > .05$), the fixed-effects model was used, otherwise the data were evaluated using random-effects model. Subgroup analyses were performed based on the usage of HCS, different types of PBC regimens, and evaluation criteria of primary outcomes. Sensitivity analysis was performed by a leave-one-out analysis[25] to observe the magnitude of influence of each study on the pooled RR. The significance level for this meta-analysis model was P value less than 0.05.

To objectively measure the presence of publication bias, a Harbord test was performed.[26] Duval and Tweedie trim-and-fill methods[27] were used to evaluate the publication/reporting biases visually. In order to assess the confidence of the evidence and determine whether additional studies are required for sufficient conclusion, we conducted the trial sequential analysis (TSA) to guarantee against false positive (type I) or false negative (type II) errors. Two reviewers (Liang and Xi) independently evaluated the reliability of the evidence related to each outcome using the Grades of Recommendation Assessment, Development, and Evaluation (GRADE).[28] The quality of the evidence was graded at the four following levels: high, moderate, low, and very low.

3. Results

3.1. Study identification and selection

A total of 461 studies were retrieved by literature search, and 302 duplicate articles were excluded. Then, 159 studies remained for further analysis. After evaluation of the titles and abstracts, 93 irrelevant articles were excluded. After

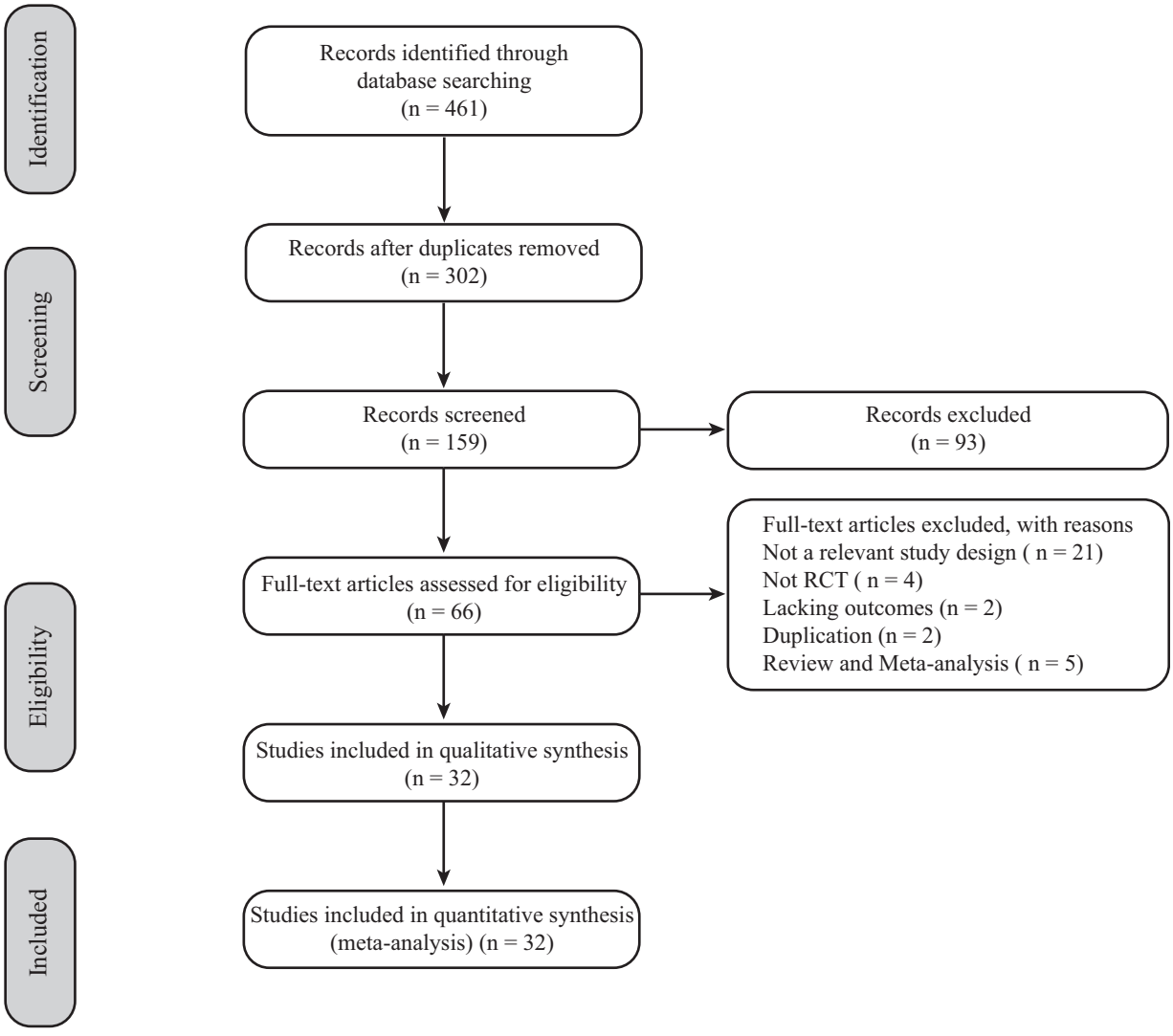

Figure 1. Flow diagram of study selection.

reading the remaining 66 full-text papers, 34 studies were excluded for the following reasons: studies with an irrelevant study design (n=21), non-RCTs (n=4), lacking outcomes (n=2), duplication of published articles (n=2), and review and meta-analysis (n=4). Finally, 32 studies were included in the current meta-analysis. Figure 1 showed the PRISMA schematic.

3.2. Characteristics of included studies

The main characteristics of the included studies are described in Table 1. Overall, 32 trials encompassing 2753 patients were included in the present meta-analysis. Patients received PBC as the pemetrexed plus cisplatin (AP, 1 trial), docetaxel plus carboplatin (DC, 1 trial), docetaxel plus cisplatin (DP, 4 trials), etoposide plus cisplatin (EP, 1 trial), gemcitabine plus cisplatin (GP, 6 trials), vinorelbine plus cisplatin (NP, 10 trials), paclitaxel plus carboplatin (TC, 1 trial), and paclitaxel plus cisplatin (TP, 8 trials). A total of 17 trials assessed the tumor responses based on the World Health Organization (WHO) guidelines,[29] and 11 trials evaluated the same according to the response evaluation criteria in solid tumors (RECIST).[30] Next, 8 trials assessed the ADRs based on WHO criteria, and 2 trials evaluated them based on Common Toxicity Criteria for Adverse Events.

3.3. Risk of methodological bias

The risk of bias of all included trials was evaluated and is summarized in Figure 2. The random sequence generation of 11 studies used the random number table, and 4 trials used hospital or clinic record numbers. The allocation concealment and blinding method were not clear in most of the included trials, except in one that used a sealed envelope. All trials had complete follow-up. Selective reporting existed in 2 trials[31,32] without completely report the DCR and another 1 trial[33] did not have a complete report on ADRs.

3.4. Outcome measures

The findings of this meta-analysis are summarized in Table 2. The subgroup analysis results are summarized in Table 3. GRADE assessments are described in Table 4.

Table 1

Characteristics of the included trials.

	NSCLC(III-IV)			Intervention and control protocol			
First author, year	Sample size (M/F)	E/C	Age	Experimental	Control	Dose/Days/Cycles	Outcomes (evaluation criteria)
Bian et al 2015	63 (33/30)	32/31	25–56	HCS + GP	GP	20 ml × 21d × 2	ORR (RECIST), DCR (RECIST), QOL, ADRs (NR)
Bao et al 2011	93	45/48	54 (34–76)	HCS + GP	GP	20 ml × 15d × 2	ORR (WHO), DCR (WHO), QOL, ADRs (WHO)
Cao 2009	50 (28/22)	25/25	58 (40–75)	HCS + NP	NP	20 ml × 21d × 3	ORR (WHO), DCR (WHO), Survival rate
Cao et al 2016	80 (49/31)	40/40	57.41 ± 9.04	HCS + DP	DP	10–20 ml × 28d × 1	ORR (RECIST), DCR (RECIST), Survival rate, ADRs (NR)
Chen 2016	90 (50/40)	45/45	59.75 (39–76)	HCS + GP	GP	20 ml × 28d × 2	ORR (RECIST), DCR (RECIST), Survival rate, ADRs (WHO)
Chi et al 2019	98 (54/44)	49/49	54.5 ± 10	HCS + DP	DP	10–20 ml × 28d × 3	ORR (RECIST), DCR (RECIST), QOL, ADRs (CTCAE v4.0)
Deng 2018	68 (43/25)	34/34	53.23 ± 7.05	HCS + TC	TC	20 ml × 21d × 2	ORR (NR), DCR (NR)
Dong 2013	86 (47/39)	46 /40	46-69	HCS + AP	AP	30 ml × 21d × 4	ORR (RECIST), DCR (RECIST), QOL
Hao et al 2016	92 (64/28)	42/50	58.13 ± 9.05	HCS + TP	TP	20 ml × 5d × 3	ORR (WHO), ADRs (NR)
Hu 2012	74 (43/31)	36/38	NR	HCS + TP	TP	20 ml × 14d × 4–6	ORR (RECIST), DCR (RECIST), Survival rate, QOL, ADRs (WHO)
Huang 2009	62 (35/27)	32/30	61.5 (49–74)	HCS + GP	GP	20 ml × 21d × 2	ORR (WHO), DCR (WHO)
Ji et al 2017	98 (45/53)	49/49	54.2 (25–75)	HCS + DC	DC	20 ml × 14d × 4	ORR (RECIST), DCR (RECIST), QOL, ADRs (CTCAE v4.0)
Jin 2007	60 (42/18)	32/28	65 (52–77)	HCS + NP	NP	20 ml × 28d × 2	ORR (WHO), DCR (WHO), QOL, ADRs (NR)
Lan 2017	96 (51/45)	48/48	43-73	HCS + TP	TP	20 ml × 28d × 2	ORR (NR), DCR (NR), ADRs (NR)
Li 2015	60 (29/31)	30/30	36-55	HCS + TP	TP	20 ml × 21d × 2	ORR (WHO), DCR (WHO)
Li et al 2009	62	30/32	34-76	HCS + NP	NP	20 ml × 10–15d × 2	ORR (WHO), DCR (WHO), QOL, ADRs (WHO)
Liu et al 2007	62 (42/20)	32/30	49.7 (33–68)	HCS + NP	NP	20 ml × 21–28d × 2	ORR (WHO), DCR (WHO), ADRs (NR)
Lu and Lu 2015	62 (37/25)	31/31	57 (41–71)	HCS + NP	NP	20 ml × 10d × 2	ORR (RECIST), DCR (RECIST)
Ma and Lu 2011	217 (114/103)	109/108	45.8 (40–73)	HCS + GP	GP	20 ml × 28d × 3	ORR (RECIST), DCR (RECIST), Survival rate, ADRs (NR)
Miao et al 2007	87 (50/37)	43/44	53.5 (34–74)	HCS + NP	NP	20 ml × 5d × 3–6	ORR (WHO), DCR (WHO), QOL, ADRs (WHO)
Qiao et al 2006	120 (87/33)	60/60	69.5 (60–76)	HCS + NP	NP	20 ml × 28d × 1	ORR (RECIST), DCR (RECIST), Survival rate, QOL, ADRs (NR)
Wang 2006	60 (42/18)	30/30	59.5 (38–72)	HCS + TP	TP	20 ml × 28d × 2	ORR (WHO), ADRs (WHO)
Wang and Shu 2009	120 (67/53)	60/60	58.5 (37–77)	HCS + TP	TP	20 ml × 21d × 2	ORR (WHO), DCR (WHO), QOL
Wang et al 2018	77 (43/34)	38/39	68	HCS + TP	TP	20 ml × 28d × 2	Survival rate, QOL, ADRs (WHO),
Xiong and Li 2005	62 (42/20)	32/30	49.7 (33–68)	HCS + NP	NP	20 ml × 21–28d × 2	ORR (WHO), DCR (WHO), ADRs (WHO)
Yang and Sun 2016	44	32/12	67.98 (61–81)	HCS + GP	GP	20 ml × 8d × 4	ORR (WHO), DCR (WHO)
Yang and Xi 2006	60 (38/22)	30/30	52 (35–69)	HCS + NP	NP	15 ml × 21d × 2	ORR (WHO), DCR (WHO), QOL, ADRs (NR)
Yao et al 2018	200 (121/79)	100/100	34-75	HCS + DP	DP	20 ml × 5d × 3	ORR (NR), DCR (NR), Survival rate
Ying and Hong 2018	120 (83/37)	60/60	63 (45–75)	HCS + EP	EP	20 ml × 28d × 3	ORR (RECIST), DCR (RECIST)
Yu et al 2012	64 (39/25)	32/32	62 (49–71)	HCS + DP	DP	20 ml × 28d × 2	ORR (WHO), DCR (WHO), QOL, ADRs (NR)
Zhang et al 2001	72 (49/23)	37/35	50 (20–74)	HCS + NP	NP	20–30 ml × 28d × 3	ORR (WHO), DCR (WHO), QOL, Survival rate
Zhou 2014	94 (49/45)	47/47	59-82	HCS + TP	TP	20 ml × 14d × 3	ORR (WHO), DCR (WHO)

ADRs = adverse drug reactions, AP = pemetrexed plus cisplatin, CTCAE = Common terminology criteria for adverse events version, DC = docetaxel plus carboplatin, DCR = disease control rate, DP = docetaxel plus cisplatin, E/C = experimental group (Huachansu injection plus paclitaxel-based chemotherapy)/control group (paclitaxel-based chemotherapy), EP = etoposide plus cisplatin, GP = gemcitabine plus cisplatin, HCS = Huachansu injection, M/F = male/female, NP = vinorelbine plus cisplatin, NSCLC = non-small cell lung cancer, ORR = objective response rate, QOL = quality of life, RECIST = Response Evaluation Criteria in Solid Tumors, TC = paclitaxel plus carboplatin, TP = paclitaxel plus cisplatin, WHO = World Health Organization guidelines for solid tumor responses.

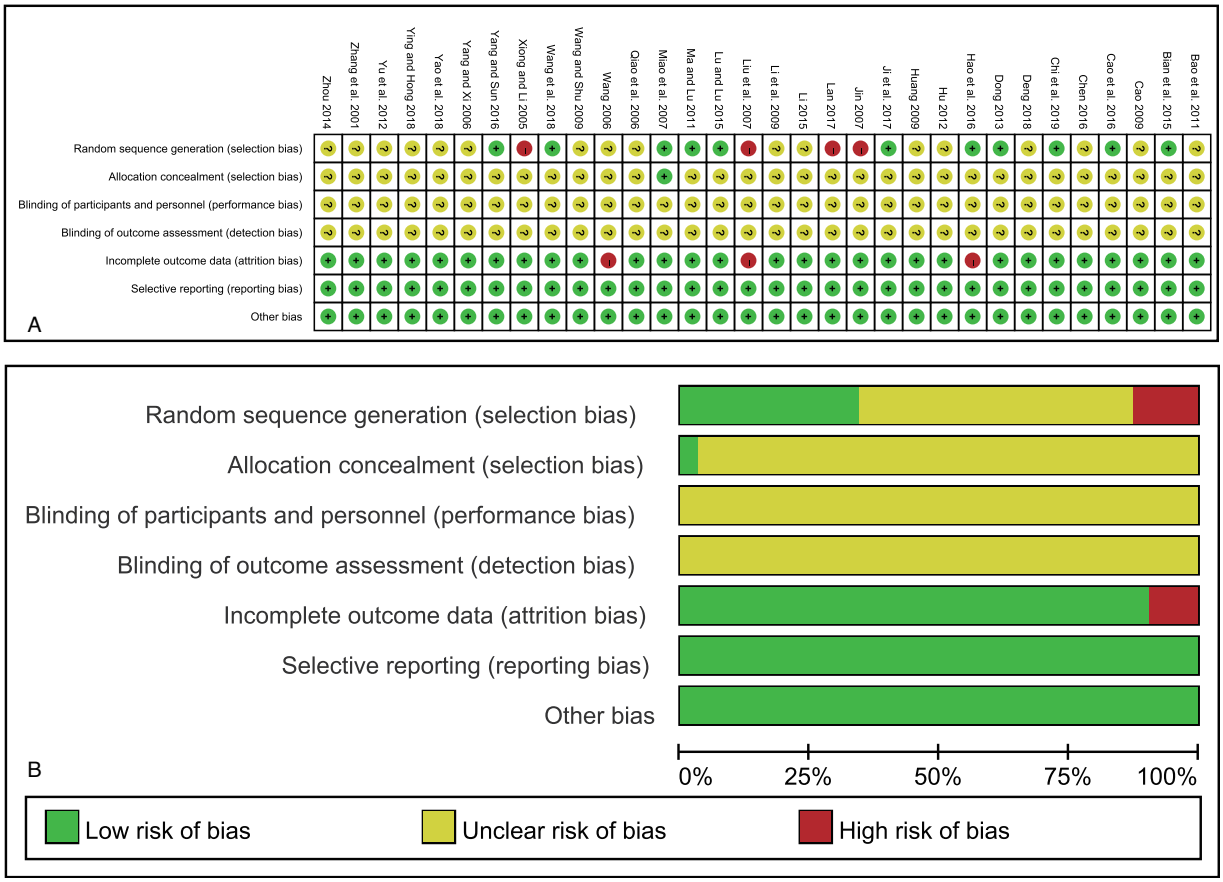

Figure 2. Risk of bias of included studies. (A) Risk of bias summary: judgments about each bias item for each study; (B) Risk of bias summary graph.

3.5. Objective response rate (ORR)

A total of 31 trials, including 2676 participants, reported the ORR (Fig. 3). No statistical heterogeneity was detected among the trials ($I^2 = 15\%$). Therefore, we applied the fixed-effects model for the analysis. Compared to PBC alone, HCS plus PBC significantly increased the ORR (RR = 1.43, 95% CI: 1.31–1.56, $P < .00001$; Fig. 3).

3.6. Disease control rate (DCR)

A total of 29 trials with 2524 participants reported the DCR. Acceptable statistical heterogeneity was observed among the trials ($I^2 = 41\%$); hence, a fixed-effects model was used to evaluate the data. The results showed that HCS plus PBC significantly increased the DCR (RR = 1.18, 95% CI: 1.13–1.23, $P < .00001$; Fig. 4) compared with PBC alone.

Table 2

Summary of the meta-analysis.

Outcomes	Trials	HCS plus PBC (Evens/Total)	PBC (Evens/Total)	RR (95% CI)	I^2	*P*
ORR	31	706/1350	487/1326	1.43 (1.31, 1.56)	15%	<.0001*
DCR	29	1085/1278	899/1246	1.18 (1.13, 1.23)	41%	<.0001*
Survival rate						
1-year survival rate	8	368/465	327/465	1.12 (1.05, 1.20)	31%	.0007*
2-year survival rate	5	80/287	46/286	1.72 (1.26, 2.36)	0%	.0007*
QOL	15	331/619	202/615	1.62 (1.43, 1.85)	45%	<.0001*
ADRs						
Neutropenia	17	347/722	487/721	0.71 (0.65, 0.78)	36%	<.0001*
Thrombocytopenia	13	201/603	324/604	0.62 (0.54, 0.70)	24%	<.0001*
Nausea and vomit	17	300/713	470/722	0.65 (0.59, 0.71)	28%	<.0001*
Anemia	5	113/233	154/238	0.74 (0.64, 0.87)	0%	.0002*
Liver injury	9	120/437	177/447	0.68 (0.58, 0.81)	0%	<.0001*
Renal injury	7	65/346	113/424	0.63 (0.50, 0.78)	0%	<.0001*
Alopecia	6	216/331	258/333	0.84 (0.77, 0.92)	46%	.0002*

DCR = disease control rate, HCS = Huachansu injection, ORR = objective response rate, PBC = paclitaxel-based chemotherapy, QOL = quality of life, RR = relative ratio.
* Favours HCS plus PBC with statistical significance.

3.7. Survival rate

The summary estimates of 8 trials reported data on 1- and 2- year survival rates. The results revealed that compared to PBC alone, HCS plus PBC improved the 1-year survival rate (RR = 1.12, 95% CI: 1.05–1.20, $P = .0007$; Fig. 5A) and 2-year survival rate (RR = 1.72, 95% CI: 1.26–2.36, $P = .0007$; Fig. 5B), without significant heterogeneity ($I^2 = 31\%$ and 0%, respectively). The fixed effects model was applied.

3.8. Improvement of QOL

A total of 15 trials with 1234 participants reported data on QOL. These trials were pooled, and compared to PBC, HCS plus PBC was significantly improved the QOL (RR = 1.62, 95% CI: 1.43–1.85, $P < .00001$; Fig. 6), without significant heterogeneity ($I^2 = 45\%$). The fixed-effects model was applied.

3.9. ADRs

A total of 20 trials reported the ADRs with respect to neutropenia, thrombocytopenia, nausea and vomiting, anemia, liver injury, renal injury, and alopecia (see Figure S1–7 Supplemental Digital Contents, http://links.lww.com/MD2/A381, http://links.lww.com/MD2/A382, http://links.lww.com/MD2/A383, http://links.lww.com/MD2/A384, http://links.lww.com/MD2/A385, http://links.lww.com/MD2/A386, http://links.lww.com/MD2/A387, which illustrate the forest plots of different types of ADRs). This pooled analysis showed that HCS plus PBC was related to lower risk of neutropenia (RR = 0.71, 95% CI: 0.65–0.78, $P < .00001$), thrombocytopenia (RR = 0.62, 95% CI: 0.54–0.70, $P < .00001$), nausea and vomiting (RR = 0.65, 95% CI: 0.59–0.71, $P < .00001$), anemia (RR = 0.74, 95% CI: 0.64–0.87, $P = .0002$), liver injury (RR = 0.68, 95% CI: 0.58–0.81, $P < .0001$), renal injury (RR = 0.63, 95% CI: 0.50–0.78, $P < .0001$), and alopecia (RR = 0.84, 95% CI: 0.77–0.92, $P = .0002$) compared with PBC alone. No significant heterogeneity was detected ($I^2 = 36\%$, 24%, 28%, 0%, 0%, 0%, and 46%, respectively), and hence, the fixed effects model was applied.

3.10. Subgroup analysis of ORR and DCR

Subgroup analyses were conducted to explore and explain the sources of heterogeneity (Table 3). The doses were divided into <

Table 3

Subgroups analysis of primary outcomes.

	Objective response rate (ORR)						Disease control rate (DCR)					
		Study event rates						Study event rates				
Subgroups	Trials	HCS plus PBC (Evens/ Total)	PBC (Evens/ Total)	RR (95% CI)	I^2	*P*	Trials	HCS plus PBC (Evens/ Total)	PBC (Evens/ Total)	RR (95% CI)	I^2	*P*
Subgroups analysis via doses												
HCS (< 20 ml/times)	3	42/119	28/119	1.50 (1.00–2.25)	0%	.05	3	90/119	73/119	1.23 (1.04, 1.46)	0%	0.02*
HCS (20 ml/times)	26	617/1148	424/1132	1.44 (1.32–1.58)	26%	< .0001*	24	920/1076	766/1052	1.18 (1.13, 1.23)	31%	< 0.0001*
HCS (> 20 ml/times)	2	47/83	35/75	1.20 (0.89, 1.61)	0%	.23	2	75/83	60/75	1.12 (0.99, 1.28)	88%	0.08
Subgroups analysis via treatment time												
<14 days	6	164/278	108/269	1.52 (1.28, 1.82)	82%	< .0001*	5	207/236	170/219	1.14 (1.05, 1.25)	52%	0.003*
14 days	3	72/132	46/134	1.59 (1.22, 2.08)	0%	.0007*	3	107/132	78/134	1.39 (1.19, 1.63)	75%	< 0.0001*
15 days	1	24/45	21/48	1.22 (0.80, 1.86)	NA	.36	1	39/45	40/48	1.04 (0.88, 1.23)	NA	0.65
21 days	10	192/353	131/340	1.40 (1.19, 1.64)	0%	< .0001*	10	307/353	269/340	1.10 (1.03, 1.17)	0%	0.006*
28 days	11	254/542	181/535	1.38 (1.19, 1.59)	0%	< .0001*	10	425/512	342/505	1.22 (1.14, 1.31)	0%	< 0.0001*
Subgroups analysis via treatment cycles												
1	2	41/100	36/100	1.14 (0.80, 1.62)	0%	.47	2	79/100	67/100	1.18 (0.99, 1.40)	0%	0.058
2	16	310/575	227/569	1.35 (1.19, 1.53)	0%	< .0001*	15	475/545	420/539	1.12 (1.06, 1.18)	0%	< 0.001*
3	9	266/512	178/518	1.54 (1.34, 1.76)	62%	< .0001*	8	396/470	327/468	1.21 (1.12, 1.29)	37%	< 0.001*
4	4	89/163	46/139	1.65 (1.25, 2.17)	48%	.0003*	4	135/163	85/139	1.34 (1.16, 1.55)	92%	< 0.001*
Subgroups analysis via chemotherapy												
HCS plus AP vs AP	1	33/46	23/40	1.25 (0.90, 1.72)	NA	.18	1	43/46	38/40	0.98 (0.89, 1.09)	NA	0.76
HCS plus DC vs DC	1	17/49	8/49	2.13 (1.01, 4.46)	NA	.05	1	34/49	17/49	2.00 (1.31, 3.06)	NA	0.001*
HCS plus DP vs DP	4	103/221	55/221	1.87 (1.43, 2.45)	53%	< .0001*	4	180/221	142/221	1.27 (1.13, 1.42)	0%	< 0.0001*
HCS plus EP vs EP	1	15/60	9/60	1.67 (0.79, 3.51)	NA	.18	1	47/60	31/60	1.52 (1.15, 2.00)	NA	0.003*
HCS plus GP vs GP	6	164/295	101/274	1.53 (1.26, 1.85)	0%	< .0001*	6	253/295	205/274	1.16 (1.06, 1.26)	2%	0.0007*
HCS plus NP vs NP	10	177/352	141/345	1.22 (1.04, 1.44)	0%	.01	10	301/352	273/345	1.08 (1.01, 1.16)	0%	0.03*
HCS plus TC vs TC	1	11/34	10/34	1.10 (0.54, 2.24)	NA	.79	1	32/34	25/34	1.28 (1.03, 1.59)	NA	0.03*
HCS plus TP vs TP	7	186/293	140/303	1.39 (1.21, 1.60)	38%	< .0001*	5	195/221	168/223	1.17 (1.07, 1.28)	0%	0.0005*
Subgroups analysis via evaluation criteria												
WHO criteria	17	357/611	260/593	1.35 (1.21, 1.51)	0%	< .0001*	15	470/539	405/513	1.11 (1.05, 1.17)	0%	0.0003*
RECIST	11	262/557	185/551	1.39 (1.21, 1.61)	0%	< .0001*	11	453/557	362/551	1.23 (1.15, 1.32)	72%	< 0.0001*

AP = pemetrexed plus cisplatin, DC = docetaxel plus carboplatin, DCR = disease control rate, DP = docetaxel plus cisplatin, EP = etoposide plus cisplatin, GP = gemcitabine plus cisplatin, HCS = Huachansu injection, NP = vinorelbine plus cisplatin, ORR = objective response rate, RECIST = Response Evaluation Criteria in Solid Tumors, TC = paclitaxel plus carboplatin, TP = paclitaxel plus cisplatin, WHO = World Health Organization guidelines for solid tumor responses.

* Favours HCS plus PBC with statistical significance.

Table 4

GRADE evidence profile of clinical efficacy and safety.

Out comes (trials)	Quality assessment				No of patients		Clinical efficacy and safety		Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	HCS plus PBC	PBC	Relative ratio (95% CI)	Absolute effects	
ORR (31)	serious*	no serious	no serious	no serious	none†	706/1350 (52.3%)	487/1326 (36.7%)	1.43 (1.31–1.56)	158 more per 1000 (from 114 more to 206 more)	⊕⊕⊕ moderate
DCR (29)	serious*	no serious‡	no serious	no serious	none§	1085/1278 (84.9%)	899/1246 (72.2%)	1.18 (1.13–1.23)	130 more per 1000 (from 94 more to 166 more)	⊕⊕⊕ moderate
1-year survival rate (8)	serious*	no serious	no serious	no serious	none	368/465 (79.1%)	327/465 (70.3%)	1.12 (1.05–1.2)	84 more per 1000 (from 35 more to 141 more)	⊕⊕⊕ moderate
2-year survival rate (5)	serious*	no serious	no serious	serious¶	none	80/287 (27.9%)	46/286 (16.1%)	1.72 (1.26–2.36)	116 more per 1000 (from 42 more to 219 more)	⊕⊕ low
QOL (15)	serious*	no serious	no serious	no serious	none†	331/619 (53.5%)	202/615 (32.8%)	1.62 (1.43–1.85)	204 more per 1000 (from 141 more to 279 more)	⊕⊕⊕ moderate
Neutropenia (17)	serious*	no serious	no serious	no serious	none	347/722 (48.1%)	487/721 (67.5%)	0.71 (0.65–0.78)	196 fewer per 1000 (from 149 fewer to 236 fewer)	⊕⊕⊕ moderate
Renal injury (7)	serious*	no serious	no serious	no serious	none	65/346 (18.8%)	113/424 (26.7%)	0.63 (0.5–0.78)	99 fewer per 1000 (from 59 fewer to 133 fewer)	⊕⊕⊕ moderate
Liver injury (9)	serious*	no serious	no serious	no serious	none	120/437 (27.5%)	177/447 (39.6%)	0.68 (0.58–0.81)	127 fewer per 1000 (from 75 fewer to 166 fewer)	⊕⊕⊕ moderate
Nausea and vomit (17)	serious*	no serious	no serious	no serious	none	300/713 (42.1%)	470/722 (65.1%)	0.65 (0.59–0.71)	228 fewer per 1000 (from 189 fewer to 267 fewer)	⊕⊕⊕ moderate
Thrombocytopenia (13)	serious*	no serious	no serious	no serious	none†	201/603 (33.3%)	324/604 (53.6%)	0.62 (0.54–0.70)	204 fewer per 1000 (from 161 fewer to 247 fewer)	⊕⊕⊕ moderate
Anemia (5)	serious*	no serious	no serious	serious¶	none	113/233 (48.5%)	154/238 (64.7%)	0.74 (0.64–0.87)	168 fewer per 1000 (from 84 fewer to 233 fewer)	⊕⊕ low
Alopecia (6)	serious*	no serious	no serious	serious¶	none	216/331 (65.3%)	258/333 (77.5%)	0.84 (0.77–0.92)	124 fewer per 1000 (from 62 fewer to 178 fewer)	⊕⊕ low

* Certainty in the evidence downgraded by one level due to most trials mentioned applying a randomization methodology, but few of included study specified the method and none of the trials specified the methods of allocation concealment and the blinding procedures.
† The publication bias was presented but the results had good robustness. Not rated down.
‡ Considerable heterogeneity and the results had good robustness. Not rated down.
§ There was publication bias. The result had good robustness calculated by trim-and-fill method, therefore, the evidence was not rated down.
¶ The total sample size did not reach the optimal information size, and the sample size for each indicator was less than 300 cases, and the evidence was rated down by one level.

20 mL/times, 20 mL/times, and >20 mL/times, respectively. The results of subgroup analysis revealed that patients who received <20 mL/times and 20 mL/times of HCS showed improved ORR and DCR, respectively (Table 3 and Figure S8-9 Supplemental Digital Contents, http://links.lww.com/MD2/A388, http://links.lww.com/MD2/A389, which illustrate the forest plots of subgroups analysis of ORR and DCR via different doses of HCS). The treatment time in one cycle was divided into <14 days, 14 days, 15 days, 21 days, and 28 days, respectively. These findings suggested that except for treatment with 15 days, all different treatment times of HCS in one cycle could improve the ORR and DCR (Table 3 and Figure S10-11 Supplemental Digital Contents, http://links.lww.com/MD2/A390, http://links.lww.com/MD2/A391, which illustrate the forest plots of subgroups analysis of ORR and DCR via different treatment time of HCS). The treatment cycles were divided into 1–4 cycles, respectively. The results showed that except for treatment with one cycle, all the different treatment cycles of HCS increased the ORR and DCR (Table 3 and Figure S12-13 Supplemental Digital Contents, http://links.lww.com/MD2/A392, http://links.lww.com/MD2/A393, which illustrate the forest plots of subgroups analysis of ORR and DCR via different treatment cycles of HCS). The included type of PBC regimens was divided into AP, DC, DP, EP, GP, NP, TC, and TP, respectively. The results showed that except for AP, the other types of PBC regimens plus HCS improved the ORR and DCR (Table 3 and Figure S14-15 Supplemental Digital Contents, http://links.lww.com/MD2/A394, http://links.lww.com/MD2/A395, which illustrate the forest plots of subgroups analysis of ORR and DCR via different types of chemotherapy regimens of HCS). Finally, tumor responses were assessed according to WHO or RECIST guidelines. The subgroup analysis based on the above criteria revealed that HCS plus PBC improved the ORR and DCR (Table 3 and Figure S16-17 Supplemental Digital Contents, http://links.lww.com/MD2/A396, http://links.lww.com/MD2/A397, which illustrate the forest plots of subgroups analysis of ORR and DCR via different evaluation criteria of HCS).

3.11. Publication bias

Three types of funnel plots of primary and secondary outcomes are shown in Figure 7 and Figure S18 Supplemental Digital Content (see Figure S18, http://links.lww.com/MD2/A398, which illustrates the funnel plots of secondary outcomes), respectively. Most of the funnel plots displayed asymmetry on visual inspection. ORR results from the Harbord test did not reveal any significant publication bias ($P = .115$, Figure 7 and Table S1 Supplemental digital Content, http://links.lww.com/MD2/A402, which illustrates the evaluation results of publication bias). However, a significant publication bias was detected in DCR ($P < .001$, Figure 7 and Table S1 Supplemental Digital Content Table S1, http://links.lww.com/MD2/A402, which illustrates the evaluation results of publication bias). A sensitivity analysis was implemented using the trim-and-fill method, which yielded a symmetrical funnel plot (Fig. 7, Figure S18 Supplemental Digital Content, http://links.lww.com/MD2/A398, which illustrates the funnel plots of secondary outcomes and Table S1 Supplemental Digital Content, http://links.lww.com/MD2/A402, which illustrates the evaluation results of publication bias). The results of the trim-and-fill method exhibited robust RRs (Table S1 Supplemental Digital Content, http://links.lww.com/MD2/A402, which illustrates the evaluation results of

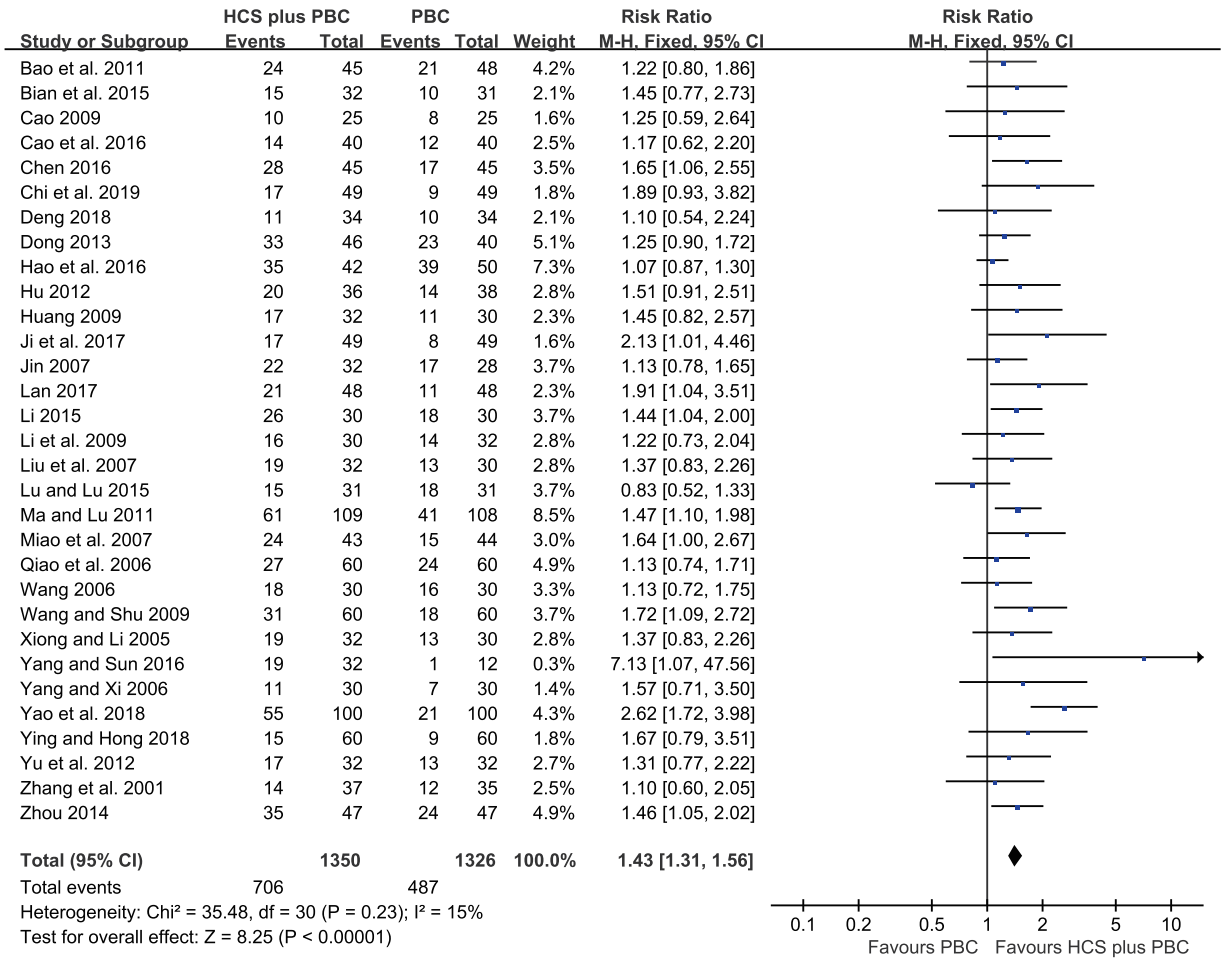

Figure 3. Forest plot of improved ORR with HCS plus PBC versus PBC alone.

publication bias), and the potential publication bias did not influence the significance of our results.

3.12. Sensitivity and meta-regression analysis

Sensitivity analyses were used to explore the potential sources of heterogeneity in primary outcomes and secondary outcomes, assess the influence of various exclusions on the pooled RRs, and evaluate the stability of the quantitative synthesis results. In the leave-one-out analysis by excluding each study sequentially, the overall pooled RRs did not change substantially (see Figure S19 Supplemental Digital Content, http://links.lww.com/MD2/A399, which illustrates the results of sensitivity analysis), indicating that the results were related to robustness.

The meta-regression analysis suggested that the ORR and DCR were not improved as the HCS dosage (from 10 mL to 30 mL) or treatment time (from 5 days to 28 days) or cycle number increased (from 1 to 4) (Fig. 8).

3.13. TSA

We used TSA boundaries to evaluate the robustness of the results and calculated the a priori information size (APIS) in the meta-analysis. As shown in Figure 9, the Z-score curve (blue line) crossed the statistical significance boundary (red polylines), the required information size (vertical red line), and the conventional statistical significance boundary corresponding to a two-sided *P*-value of .05 (dark green lines). The results indicated that HCS plus PBC increased the ORR and DCR in NSCLC patients.

Also, as shown in Figure S20 Supplemental Digital Content (see Figure S20, http://links.lww.com/MD2/A400 which illustrates the results of trial sequential analysis), the improvement in the 1-year survival rate and QOL and the reduction in neutropenia, thrombocytopenia, nausea and vomiting, anemia, and liver injury are definite and well-documented. The improvement in the 2-year survival rate and the decrease in the risk of renal injury need to be substantiated by additional studies (see Figure S20 Supplemental Digital Content, http://links.lww.com/MD2/A400, which illustrates the results of trial sequential analysis). However, although the graph results showed a significant difference between HCS plus PBC and PBC alone, the reduction in the risk of alopecia might be a false-positive result (see Figure S20 Supplemental Digital Content, http://links.lww.com/MD2/A400, which illustrates the results of trial sequential analysis).

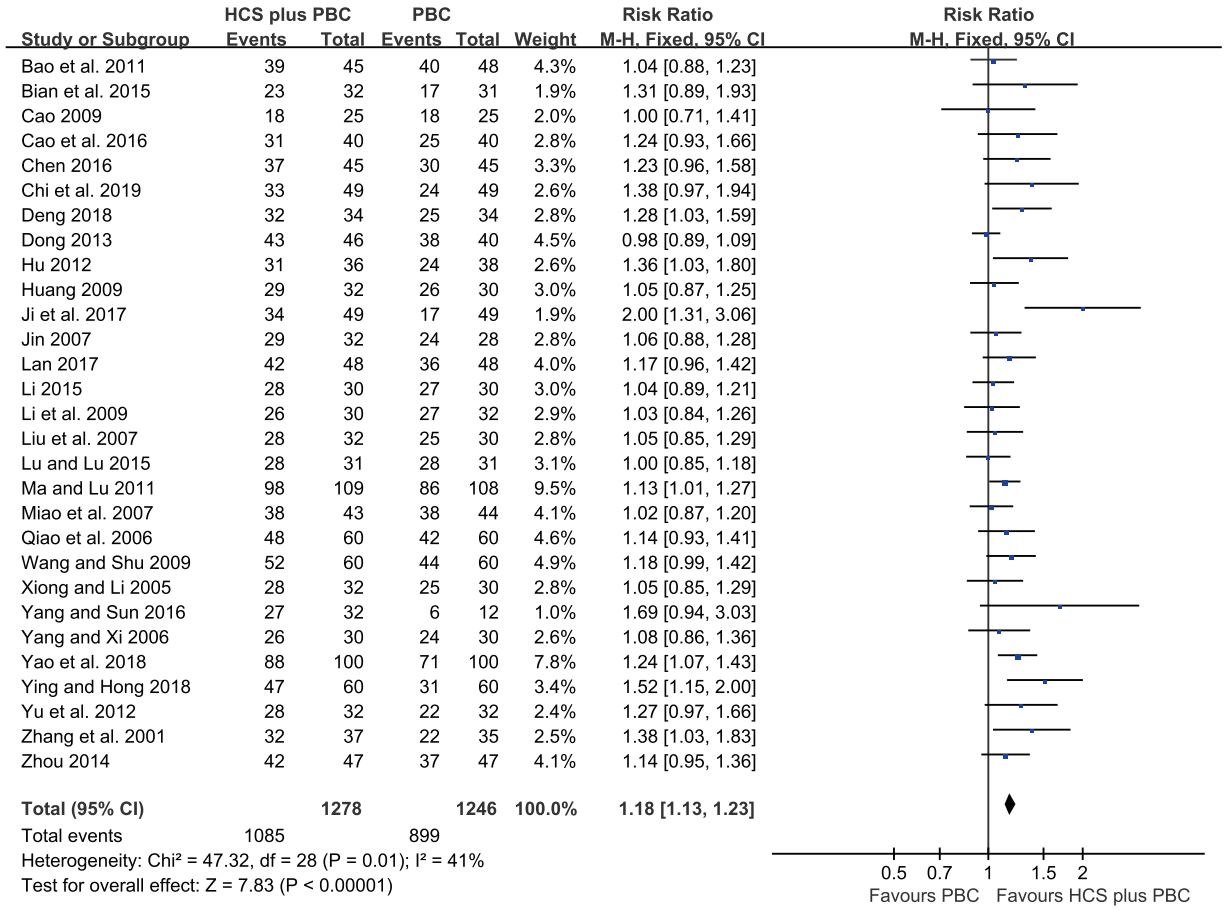

Figure 4. Forest plot of improved DCR with HCS plus PBC versus PBC alone.

3.14. Quality of evidence

We used GRADE to assess the quality of evidence with respect to the clinical efficacy and safety of HCS. Due to some uncertainty about the methodological risk of bias, and since the evidence was rated down by only one level, we were moderately confident in the outcomes of ORR, DCR, 1-year survival rate, QOL, neutropenia, renal injury, liver injury, nausea and vomiting, and thrombocytopenia. On the other hand, we had low confidence in the outcomes of 2-year survival rate, anemia, and alopecia, because except for the possible risk of bias, other factors need to be considered to assess the level of evidence, including insufficient sample size and few relevant studies (Table 4).

4. Discussion

This systematic review and meta-analysis encompassing 32 trials with 2753 patients demonstrated that PBC combination with HCS in the treatment of advanced NSCLC significantly improves the ORR, DCR, and QOL and decreases the risk of ADRs compared to PBC alone treatment. These findings are objective and completely unaffected by any focus groups, such as health professionals, users, policymakers, and providers.

PBC is one of the standards first-line chemotherapy regimens for NSCLC. Despite continual improvements in chemotherapy agents, the clinical efficacy is unsatisfactory, with limited benefits, and patients suffer from chemotherapy-induced toxicity. Furthermore, the prognosis of advanced NSCLC remains poor, and hence, novel therapeutic strategies are urgently required. Prior to our study, one meta-analysis[19] evaluated the effects of HCS plus first-line PBC, and two meta-analyses[20,21] evaluated the effects of HCS plus chemotherapy on lung cancer, but no definitive conclusions were drawn because of the lower methodological quality of the RCTs included. Moreover, the latest published meta-analysis by Xu et al.[19] did not determine the objective response, and insufficient data on ADRs, incomplete trials, and small sample size might weaken the statistical characteristics and reduce the credibility of the evidence. Therefore, we performed a comprehensive search and included several recently published RCTs to achieve clinical advancement and provide convincing evidence for the clinical application of a combination of HCS and PBC in the treatment of advanced NSCLC.

Although most of the included trials had an unclear methodological risk of bias, the quality of the methods in the trials was consistent. TSA performed based on most of the outcomes revealed that the required information for a robust meta-analysis was collected, and the efficacy and safety of HCS plus PBC were significantly superior to those of PBC alone. The confidence of our study and the quality of the evidence were assessed by GRADE. The results of GRADE assessment suggested that the quality of evidence was moderate in most of the outcomes, including ORR, DCR, 1-year survival rate, QOL,

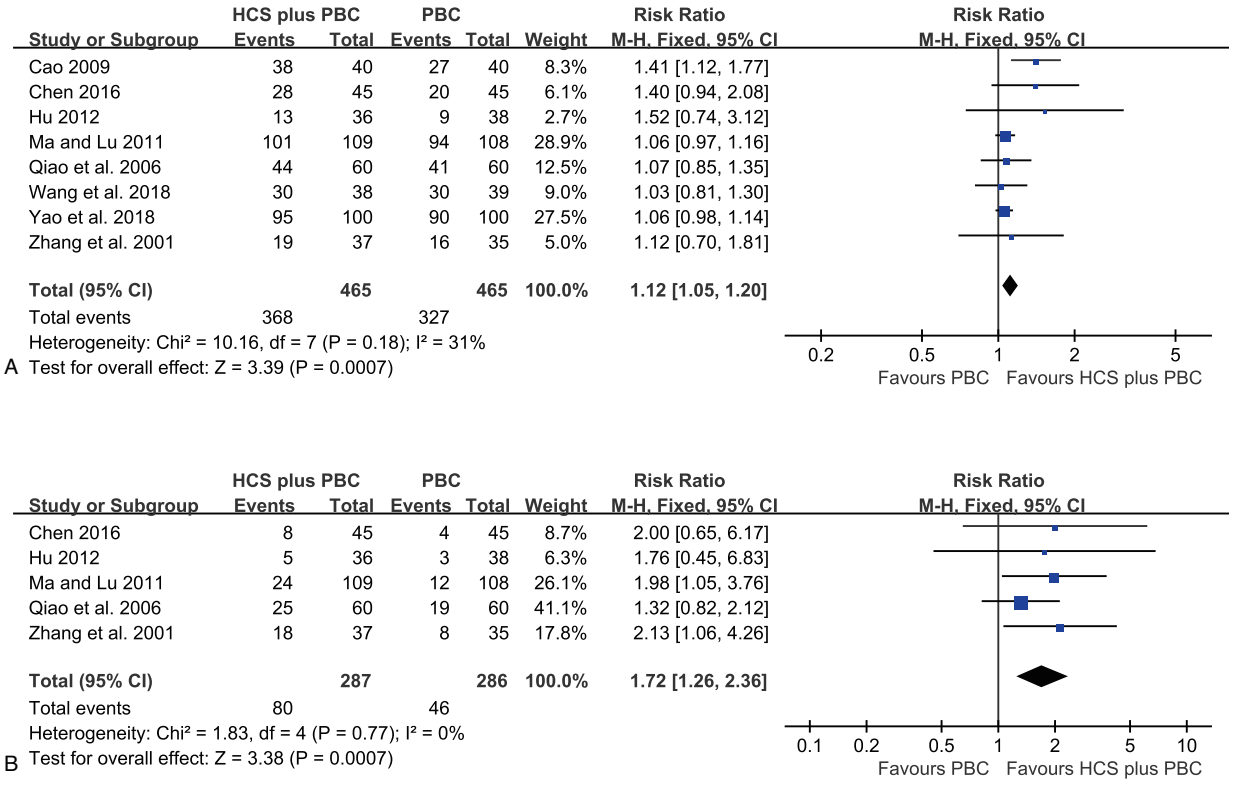

Figure 5. Forest plot of survival rate with HCS plus PBC versus PBC alone. (A) 1-year survival rate; (B) 2-year survival rate.

neutropenia, renal injury, liver injury, nausea, vomiting, and thrombocytopenia.

According to WHO and RECIST guidelines, the evaluation of the objective response and disease progression are crucial for the clinical assessment of cancer therapeutics.[34] Both DCR and ORR are valuable endpoints for the evaluation of the efficacy of cancer treatment. Especially, the definition of DCR, including complete response (CR), partial response (PR), and no change (NC, stable disease), has been suggested to be the best response outcome to predict the overall survival (OS) and progression-free

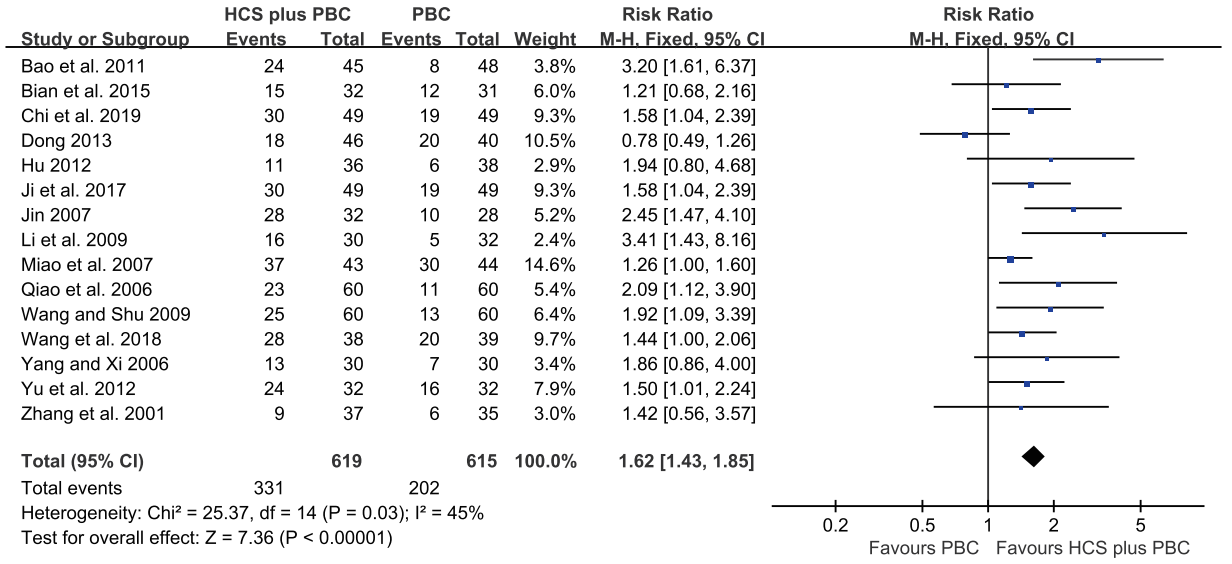

Figure 6. Forest plot of improved QOL with HCS plus PBC versus PBC alone.

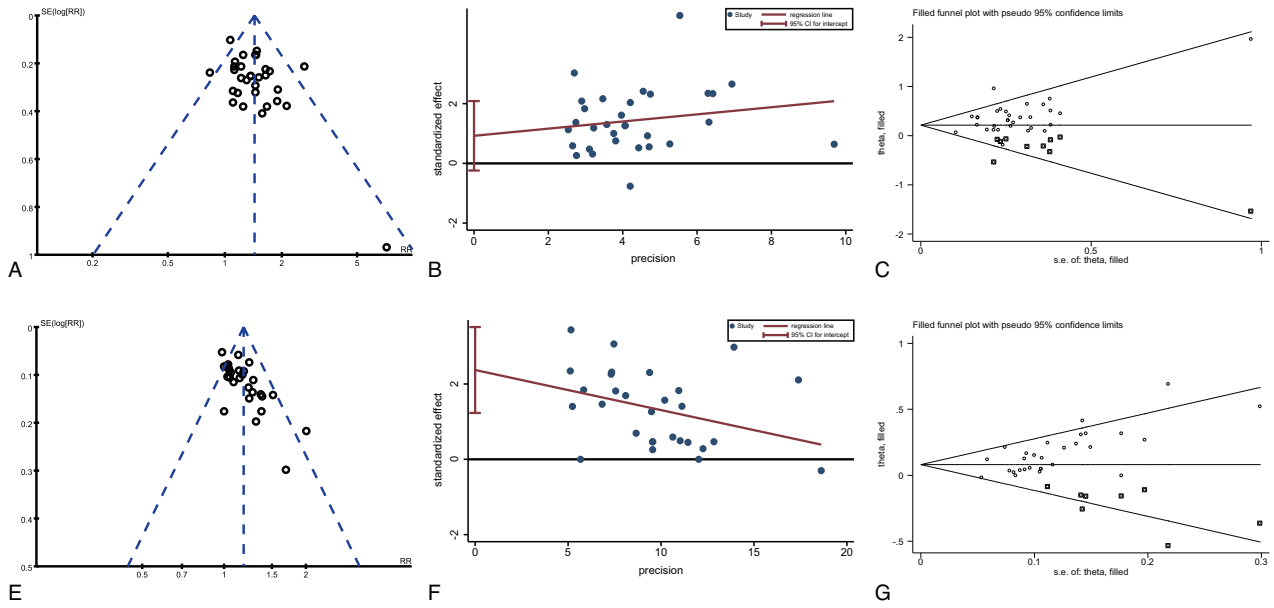

Figure 7. Funnel plots, Harbord test funnel plots to assess publication bias and trim-and-fill funnel plots of primary outcomes. (A) funnel plot of ORR; (B) Harbord test funnel plot of ORR; (C) trim-and-fill funnel plot of ORR; (D) funnel plot of DCR; (E) Harbord test funnel plot of DCR; (F) trim-and-fill funnel plot of DCR. Trim-and-filled funnel plot of RR from studies that investigated the association between insomnia and the risk of depression. The circles alone are real studies and the circles enclosed in boxes are 'filled' studies. The horizontal line represents the summary effect estimates, and the diagonal lines represent pseudo-95% CI limits.

survival (PFS). Therefore, DCR was considered the primary outcome in our study.[35,36] The current study revealed that HCS plus PBC significantly improves the 1- and 2-year survival rates in patients with advanced NSCLC compared to PBC alone. A previously published meta-analysis[19] suggested that HCS combined with PBC significantly improves the QOL of patients with advanced NSCLC. Our results also demonstrated a significant improvement in the QOL in HCS plus PBC compared to PBC alone. PBC is related to many toxic ADRs in patients with NSCLC, which can severely reduce the QOL and decrease clinical efficacy. Thus, methods to reduce the risk of ADRs of chemotherapy while maintaining clinical efficacy are currently

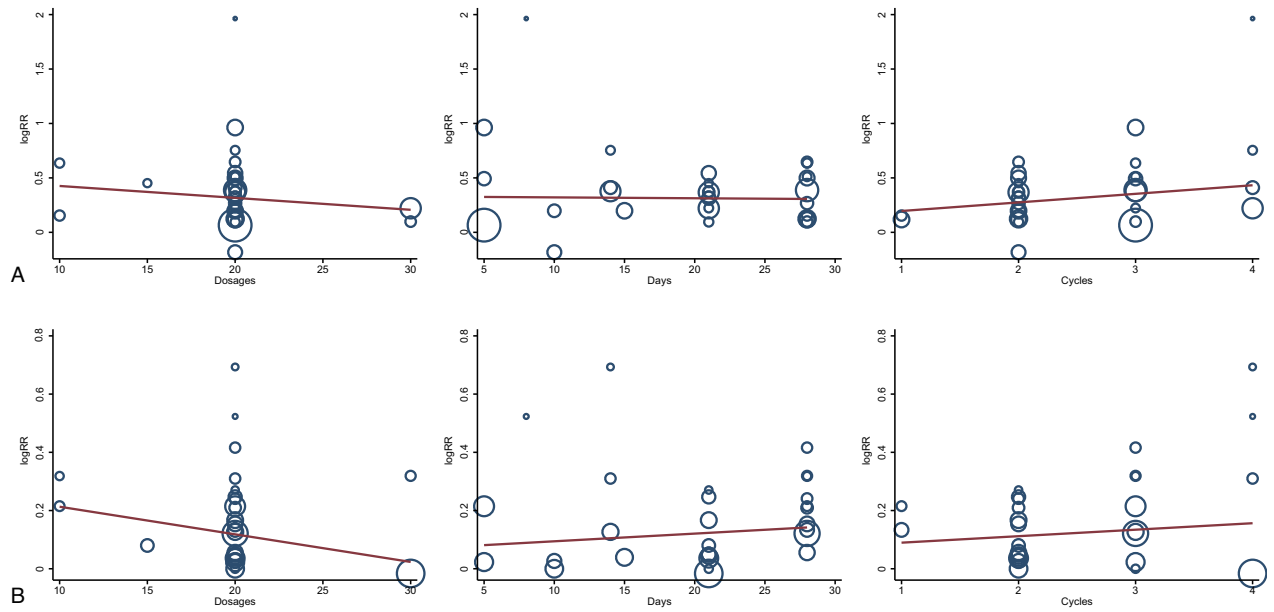

Figure 8. Meta-regression analysis showing that the ORR and DCR was not improved with increased dosages, treatment time, and cycle number of HCS.

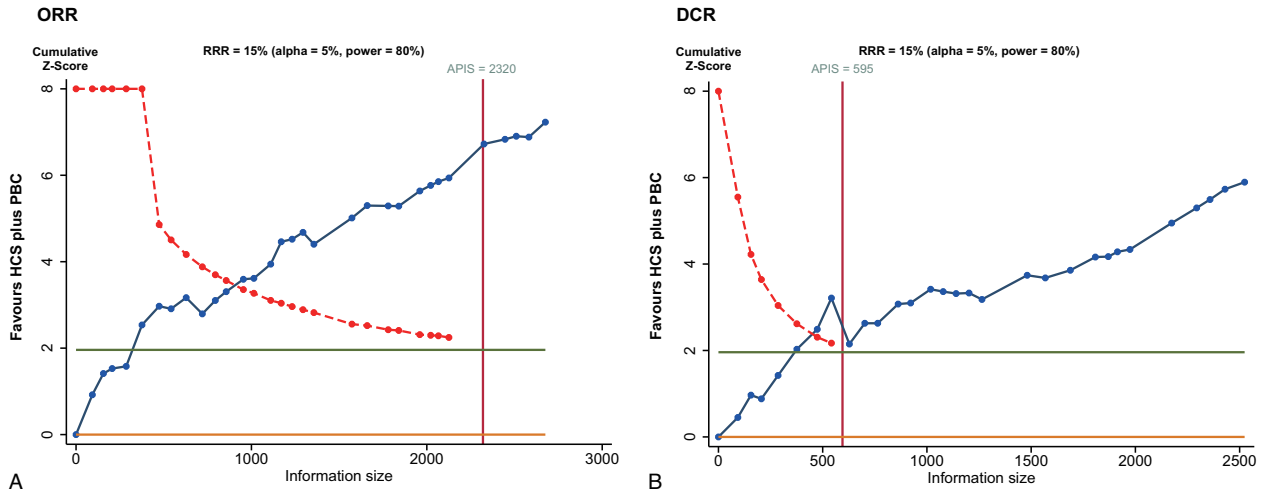

Figure 9. Trial sequential analysis. (A) ORR; (B) DCR.

a research hotspot. This study confirmed that compared to PBC alone, HCS plus PBC significantly reduced the ADRs in patients with advanced NSCLC.

B. gargarizans (*Bufonidae* family) is a small amphibian traditional medicinal animal for the pharmaceutical value of Chansu and Chanpi, and HCS (cinobufacini) is an injectable form of the sterilized hot-water extract of the skin glands of *B. gargarizans*.[19,37] According to the principles of TCM, HCS is commonly used to counteract toxicity, alleviate pain, and induce resuscitation.[38–40] More than 30 components have been discovered in the skin extract of *B. gargarizans*, and the vital bioactive compounds include cinobufagin, resibufogenin, bufotenine, cinobufotenine, and serotonin. Modern pharmacological published studies demonstrated that resibufogenin, cinobufagin, and bufalin inhibit tumor cells, and bufotenine, cinobufotenine, and serotonin regulate the nervous system.[41,42] However, to clarify the function of HCS as an adjunct to chemotherapy, the specific mechanisms need to be elucidated.

Although the present meta-analysis revealed favorable outcomes, several limitations cannot be ignored. First, the quality of the original studies was generally not high because most of the included studies reported inadequate detailed information of generating random sequences methods, allocation concealment methods, and blinding study design. Second, although we searched all the mainstream Chinese and English electronic databases, all the included trials were conducted in China, and thus, it is unclear whether the conclusions of this meta-analysis could be applied to advanced NSCLC patients worldwide, which reduces the universality of the conclusions. Third, GRADE revealed that the quality of 2-year survival rate, anemia, and alopecia was "low" due to the risk of bias and insufficient sample sizes. Despite the above limitations, the results of the current meta-analysis revealed a systematic evaluation of the efficacy and safety in multiple outcomes and provided clinical evidence of HCS plus PBC for the treatment of advanced NSCLC patients.

5. Conclusion

In summary, the moderate-quality evidence reveals that the combination of HCS with PBC is beneficial for the clinical efficacy and QOL and reduces the risk of chemotherapy-induced ADRs for patients with advanced NSCLC. HCS may be a valuable adjunctive treatment to PBC for the treatment of advanced NSCLC. However, eligible RCTs lack high methodological quality and potential risk of bias, and HCS needs to be further explored with respect to these outcomes. To further confirm the conclusion of the current study, high-quality, larger sample size, and well-designed RCTs are an urgent requisite.

Author contributions

Conceptualization: Xueyan Liang, Jiaxi Xi, Xinmei Tan.
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Formal analysis: Xueyan Liang, Xinmei Tan.
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Investigation: Xiaoyu Chen, Yan Li, Xinmei Tan.
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Software: Xueyan Liang, Jiaxi Xi, Xinmei Tan, Sitong Guo, Mingyu Meng, Xiaoyu Chen, Yan Li.
Validation: Jiaxi Xi, Sitong Guo, Yan Li.
Visualization: Xueyan Liang, Mingyu Meng, Xiaoyu Chen.
Writing – original draft: Xueyan Liang, Jiaxi Xi.
Writing – review & editing: Xiaoyu Chen, Yan Li, Xinmei Tan.

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