

# Efficacy and safety of apatinib plus chemotherapy vs. chemotherapy alone for the treatment of advanced-stage non-small cell lung cancer: A meta-analysis

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**Abstract.** Apatinib has been widely applied for the treatment of gastrointestinal cancer since its development; however, available conclusive data regarding its use in non-small cell lung cancer (NSCLC) are lacking. Thus, the present meta-analysis aimed to compare the efficacy and safety of the use of apatinib plus chemotherapy vs. chemotherapy alone for the treatment of patients with advanced-stage NSCLC. Published studies reporting the treatment response, progression-free survival (PFS), overall survival (OS) and adverse events in patients with advanced-stage NSCLC treated with apatinib plus chemotherapy or chemotherapy alone were searched using the PubMed, China National Knowledge Infrastructure, EMBASE, Chongqing VIP Information, Cochrane and Wanfang databases until February 2023. Finally, 18 studies involving 677 patients with NSCLC receiving apatinib plus chemotherapy and 672 patients with NSCLC receiving chemotherapy were included in the present analysis. Apatinib plus chemotherapy was found to increase the objective response rate [relative risk (RR), 1.60; 95% confidence interval (CI), 1.38-1.86] and disease control rate (RR, 1.29; 95% CI, 1.21-1.38) compared to chemotherapy alone. Of note, apatinib plus chemotherapy also prolonged PFS compared with chemotherapy alone (hazard ratio, 0.54; 95% CI, 0.35-0.73), while no OS data were retrievable from the included studies. With regard to safety, apatinib plus chemotherapy elevated the risk of developing hypertension (RR, 3.78; 95% CI, 1.81-7.93) and

hand-foot syndrome (RR, 6.51; 95% CI, 3.70-11.46) vs. chemotherapy alone; however, no difference was observed between the two regimens in terms of the incidence of other adverse events. Furthermore, the bias was low and the pooled findings were reliable/stable, as indicated by a sensitivity analysis. On the whole, the present study demonstrates that apatinib plus chemotherapy increases the treatment response and PFS vs. chemotherapy alone, while it also elevates the risk of developing hypertension and hand-foot syndrome in patients with advanced-stage NSCLC.

## Introduction

Non-small cell lung cancer (NSCLC) is one of the most common types of cancer worldwide (1,2). Over the past decades, according to cancer registration in China, the prevalence and mortality of lung cancer have exhibited an increasing trend, which has led to an immense social burden (3). Current treatments for NSCLC include surgical resection, chemotherapy, radiotherapy and immunotherapy (4). However, >30% of patients with NSCLC are diagnosed at an advanced stage; thus, the treatment choices for these patients are limited and the therapeutic efficacy is not favorable (5,6). Hence, the exploration of effective therapeutic strategies with which to promote the management of patients with advanced-stage NSCLC is urgently required.

Apatinib was the first oral vascular endothelial growth factor receptor 2 (VEGFR2) tyrosine kinase inhibitor (TKI) approved in China, which was originally used to treat gastrointestinal tumors (7-9). Over the past decades, apatinib has also brought hope for patients with advanced-stage NSCLC; its application provides a favorable treatment response and survival with tolerable adverse events (10-12). Of note, it has also been reported that apatinib plus chemotherapy is associated with favorable progression-free survival (PFS) with tolerable adverse events among patients with advanced-stage NSCLC (11,13-29). Even though a previous meta-analysis compared the treatment response and safety between apatinib plus chemotherapy and chemotherapy alone among patients with advanced-stage NSCLC, no PFS or overall survival (OS) data were analyzed in that study (30).

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**Key words:** non-small cell lung cancer, apatinib plus chemotherapy, treatment response, progression-free survival, adverse events

Thus, in order to provide more substantial evidence supporting the use of apatinib in patients with advanced-stage NSCLC, the present meta-analysis synthesized the data of 18 studies and aimed to compare the efficacy and safety between apatinib plus chemotherapy and chemotherapy among patients with advanced-stage NSCLC.

## Data and methods

**Study search.** A systematic literature search was carried out through the medical databases of PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), China National Knowledge Infrastructure (CNKI; <https://www.cnki.net/>), EMBASE (<https://www.embase.com/>), Chongqing VIP Information (CQVIP; <http://www.cqvip.com/>), Cochrane (<https://www.cochranelibrary.com/>) and Wanfang (<https://www.wanfangdata.com.cn/>) up to February 2023, to screen the studies that compared the efficacy and safety of apatinib plus chemotherapy with chemotherapy in patients with advanced-stage non-squamous NSCLC. The following medical subject headings and keywords were used for searching: 'non-small cell lung cancer', 'NSCLC', 'carcinoma of the lung', 'lung cancer', 'lung neoplasm', 'apatinib', 'YN968D1', 'apatinib mesylate', 'chemotherapy', 'chemo', 'docetaxel', 'pemetrexed', 'gemcitabine', 'paclitaxel', 'vinorelbine', 'cisplatin' and 'carboplatin'. The reference lists of the retrieved articles were also screened by (SQ, XH and ZL).

**Study selection.** A total of two independent investigators (SQ and XH) screened all of the relevant studies and any disagreements were resolved via discussion between them or consultation with a third investigator (ZL). The inclusion criteria for study screening were as follows: i) Patients with advanced-stage NSCLC; ii) studies comparing the efficacy and safety of apatinib plus chemotherapy and chemotherapy; iii) studies covering at least one outcome of this analysis, which involved the objective response rate (ORR), disease control rate (DCR), PFS, OS and adverse events. PFS was defined as the duration from treatment initiation to the occurrence of progressive disease, intolerable adverse reactions or all cause-death. The exclusion criteria were as follows: i) Systematic reviews, meta-analyses, case studies or animal studies; ii) duplicated studies; iii) the language of studies was not English or Chinese.

**Data extraction and quality evaluation.** The data of all studies were separately extracted by two researchers (SQ and XH). In the case of any disagreement, discussion between the readers or consultation with a third reader was conducted. The information extracted in this analysis was as follows: The first author's name, year of publication, study type, sample size, the age of the patients, treatment regimen, treatment line and outcomes. Patients who were treated with apatinib plus chemotherapy were assigned to the 'apatinib plus chemo' group, while those who were treated with chemotherapy alone were placed in the 'chemo' group. The quality of the included randomized controlled trials (RCTs) was assessed through a modified version of the Cochrane Collaboration tool (31), while the quality of non-RCTs was evaluated using the Newcastle-Ottawa scale criteria (32).

**Statistical analysis.** Statistical analyses were carried out using Stata (v.14.0; StataCorp). The relative risk (RR) with 95% confidence intervals (CI) were used to evaluate outcomes. For the assessment of heterogeneity,  $I^2 \leq 50.0\%$  and  $P \geq 0.05$  indicated that the heterogeneity was insignificant, and the fixed-effects model was applied; otherwise, the random-effects model was utilized. Begg's and Egger's tests were used for analyzing publication bias and a value of  $P < 0.05$  was considered to indicate a statistically significant difference. Sensitivity analysis (studies were excluded one by one) was used to assess the robustness and reliability of the results.

## Results

**Study selection process.** A total of 820 records were identified through the databases (281 from PubMed, 181 from CNKI, 121 from EMBASE, 90 from CQVIP, 64 from Cochrane and 83 from Wanfang), among which 517 duplicates were excluded. Subsequently, 303 records were screened based on title and abstract and 272 of these were excluded (including 179 irrelevant studies, 34 reviews or guidelines, 26 animal studies, 18 meta-analyses and 15 case reports). Subsequently, 31 records were assessed through full-text reading, of which 13 records were excluded (including 9 that administered targeted drugs other than apatinib and 4 without an eligible population). Finally, 18 studies involving 1,349 patients were included in the meta-analysis (Fig. 1).

**Features of the included studies.** A total of 18 studies comprising 677 patients with advanced-stage NSCLC receiving apatinib plus chemotherapy and 672 patients with advanced-stage NSCLC receiving chemotherapy alone were included in the meta-analysis. The ORR, DCR, PFS and adverse events were regarded as study outcomes to evaluate the efficacy and safety of apatinib plus chemotherapy and chemotherapy alone. Further detailed information is presented in Table I. The two groups showed no significant difference in age. Gender distributions of the pooled cohorts were 412 males vs. 265 females in the apatinib plus chemo group; and 397 males vs. 275 females in the chemo group. There was no significant difference in gender distribution between the two groups either. Additional features of the included studies (including sample size and EGFR mutation) were presented in Table SI.

**ORR and DCR.** In total, 17 studies compared the ORR between the apatinib plus chemo group and chemo group. There was no heterogeneity among these studies ( $I^2 = 0.0\%$ ,  $P = 0.982$ ). After the fixed-effects model was applied, it was found that the ORR was increased in the apatinib plus chemo group compared to the chemo group (RR, 1.60; 95% CI, 1.38-1.86;  $P < 0.001$ ; Fig. 2A). Furthermore, these 17 studies also compared the DCR between the apatinib plus chemo group and chemo group, and no heterogeneity existed between them ( $I^2 = 28.3\%$ ,  $P = 0.133$ ). Application of the fixed-effects model then revealed that the ORR was elevated in the apatinib plus chemo group compared to the chemo group (RR, 1.29; 95% CI, 1.21-1.38;  $P < 0.001$ ; Fig. 2B).

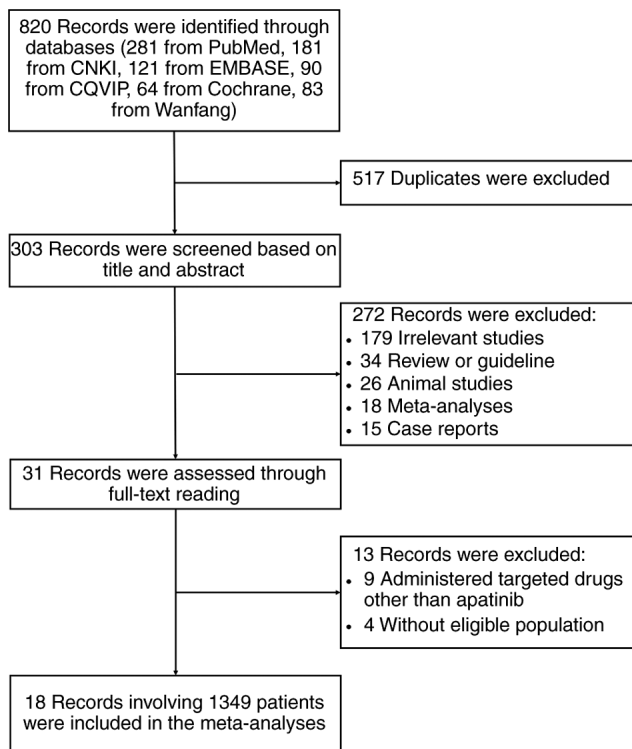


Figure 1. Flow chart of the study selection process. CNKI, China National Knowledge Infrastructure; CQVIP, Chongqing VIP.

**PFS.** A total of five studies compared PFS between the apatinib plus chemo group and chemo group. No heterogeneity was found among these five studies ( $I^2=0.0\%$ ,  $P=0.818$ ). The fixed-effects model then revealed that the PFS was prolonged in the apatinib plus chemo group compared to the chemo group (hazard ratio, 0.54; 95% CI, 0.35-0.73;  $P=0.001$ ; Fig. 3). However, no OS data were reported in the analyzed studies.

**Adverse events.** The incidence of hypertension between the two groups was compared in 11 studies, and heterogeneity was found among these ( $I^2=55.9\%$ ,  $P=0.012$ ). The random-effects model revealed that the incidence of hypertension was increased in the apatinib plus chemo group compared to the chemo group (RR, 3.78; 95% CI, 1.81-7.93;  $P<0.001$ ; Fig. 4A).

A total of nine studies compared the incidence of hand-foot syndrome between the two groups; the pooled analysis of these studies revealed that the incidence of hand-foot syndrome was increased in the apatinib plus chemo group in comparison to the chemo group (RR, 6.51; 95% CI, 3.70-11.46;  $P<0.001$ ) and heterogeneity existed among these studies ( $I^2=52.3\%$ ,  $P=0.032$ ; Fig. 4B).

However, no differences in the incidence of liver dysfunction (Fig. 4C), proteinuria (Fig. 4D), bone marrow depression (Fig. 4E), thrombocytopenia (Fig. 4F), leukopenia (Fig. 4G), fatigue (Fig. 4H), gastrointestinal reactions (Fig. 4I) or nausea/vomiting (Fig. 4J) were found between the two groups (all  $P>0.05$ ).

**Publication bias.** Both Begg's and Egger's tests revealed that no publication bias existed regarding the ORR, DCR, PFS, hypertension, hand-foot syndrome, liver dysfunction, proteinuria,

bone marrow depression, thrombocytopenia, leukocytopenia, fatigue and nausea/vomiting (all  $P>0.050$ ). However, publication bias was found for gastrointestinal reactions based on Begg's test ( $P=0.048$ ), but not Egger's test ( $P=0.183$ ) (Table II).

**Assessment of risk of bias and sensitivity analysis.** Application of the Cochrane Collaboration's tool revealed that the overall risk of bias in the included RCTs was relatively low. Specifically, all included RCTs were evaluated as low risk for sequence generation, completeness of outcome data and being free of selective reporting. However, concealment of allocation and blinded adjudication were unclear among all RCTs. Regarding the risk of other biases, four studies were rated as high risk and nine studies as unclear (Table III). Furthermore, the risk of bias of the five non-RCTs was assessed using the Newcastle-Ottawa Scale criteria, which indicated that the total score of these studies ranged from 7 to 8, suggesting a relatively low risk of bias (Table IV).

Furthermore, sensitivity analysis was conducted for all outcomes by omitting each study, one at a time. The results indicated that no single study substantially altered the RR of most outcomes. However, the RR of proteinuria, thrombocytopenia and fatigue were affected by omitting the studies by Liu and Zheng (15), Guo and Jing (13) and Song *et al* (27), respectively (Table SII).

## Discussion

The high morbidity and mortality associated with advanced-stage NSCLC have brought an immense burden globally, particularly in China (2,5,6). Over the past decade, anti-angiogenetic treatments have seen notable progress in the treatment of advanced-stage NSCLC, which enhances the treatment response and prolongs patient survival with tolerable adverse events (33). Previously, bevacizumab was the main angiogenesis inhibitor for patients with advanced NSCLC (34). Apatinib is a representative novel anti-angiogenetic drug approved in China, whose application in NSCLC has been reported in previous studies (9,11,30). In order to provide more sufficient evidence supporting the application of apatinib in advanced-stage NSCLC, the present meta-analysis reviewed 18 studies (including 13 RCTs and 5 observational studies) and found that apatinib plus chemotherapy enhanced the ORR and DCR compared to chemotherapy alone among patients with advanced-stage NSCLC. The potential explanation for this may be as follows: i) Apatinib, as a VEGFR2 TKI, was able to suppress VEGF/VEGFR2 and MAPK pathways, which consequently inhibited tumor activity (35). ii) The synergistic antitumor effects of apatinib and chemotherapy may increase the treatment efficacy among patients with advanced-stage NSCLC (36). iii) Apatinib has been found to enhance the sensitivity of chemotherapeutic drugs through the AKT/ $\beta$ -catenin pathway (37). Therefore, apatinib plus chemotherapy can enhance the treatment response compared to chemotherapy alone among patients with advanced-stage NSCLC.

According to the guidelines from the National Comprehensive Cancer Network, platinum-based chemotherapy is recommended as a first-line treatment for patients with advanced-stage NSCLC (1). However, according to previous studies, the survival of patients with advanced-stage

Table I. Features of included studies.

Author, year	Study type	Sample size		Age, years		Treatment regimen			Treatment line	Outcomes	(Refs.)
		Apatinib plus chemo	Chemo	Apatinib plus chemo	Chemo	Apatinib plus chemo	Chemo				
Guo, 2017	RCT	19	20	61.0 (33.0-72.0) <sup>a</sup>	58.0 (36.0-75.0) <sup>a</sup>	Apatinib 500 mg/d; docetaxel 60 mg/m <sup>2</sup>	Docetaxel 60 mg/m <sup>2</sup>		II	ORR, DCR, PFS, adverse events	(13)
Chen, 2017	RCT	42	42	61.3±2.6 <sup>b</sup>	61.2±2.5 <sup>b</sup>	Apatinib 850 mg/d; paclitaxel 135-145 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup>	Paclitaxel 135-145 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup>		NA	ORR, DCR, adverse events	(14)
Liu, 2018	RCT	40	40	50.5±7.1 <sup>b</sup>	52.7±7.1 <sup>b</sup>	Apatinib 500 mg/d; docetaxel 60 mg/m <sup>2</sup>	Docetaxel 60 mg/m <sup>2</sup>		II	ORR, DCR, adverse events	(15)
Shang, 2019	RCT	31	31	56.1±6.2 <sup>b</sup>	54.3±6.0 <sup>b</sup>	Apatinib 250-500 mg/d; docetaxel 75 mg/m <sup>2</sup>	Docetaxel 75 mg/m <sup>2</sup>		II	ORR, DCR, adverse events	(16)
Luo, 2019	Observational study	32	36	56.2±5.7 <sup>b</sup>	55.6±5.8 <sup>b</sup>	Apatinib 500 mg/d; docetaxel; pemetrexed; gemcitabine; paclitaxel	Docetaxel; pemetrexed; gemcitabine; paclitaxel		II, III	ORR, DCR, PFS, adverse events	(17)
Hu, 2020	Observational study	19	20	47.0-75.0 <sup>c</sup>	48.0-75.0 <sup>c</sup>	Apatinib 500 mg/d; docetaxel 60 mg/m <sup>2</sup>	Docetaxel 60 mg/m <sup>2</sup>		NA	ORR, DCR, adverse events	(11)
Yu, 2020	RCT	22	11	58.5 (31.0-73.0) <sup>a</sup>	NA	Apatinib 500 mg/d; docetaxel 75 mg/m <sup>2</sup> ; pemetrexed 500 mg/m <sup>2</sup>	Docetaxel 75 mg/m <sup>2</sup> ; pemetrexed 500 mg/m <sup>2</sup>		II	ORR, DCR, PFS, adverse events	(18)
Guo, 2020	RCT	50	50	61.6±7.2 <sup>b</sup>	62.9±6.5 <sup>b</sup>	Apatinib 500 mg/d; pemetrexed; gemcitabine; docetaxel; paclitaxel	Pemetrexed; gemcitabine; docetaxel; paclitaxel		I	Adverse events	(19)
Xie, 2020	RCT	38	38	52.3±7.3 <sup>b</sup>	53.4±7.3 <sup>b</sup>	Apatinib 850 mg/d; cisplatin 25 mg/m <sup>2</sup> ; paclitaxel 175 mg/m <sup>2</sup>	Cisplatin 25 mg/m <sup>2</sup> ; paclitaxel 175 mg/m <sup>2</sup>		NA	ORR, DCR, adverse events	(20)
Li, 2020	RCT	60	60	50.9±6.0 <sup>a</sup>	51.3±5.8 <sup>a</sup>	Apatinib 850 mg/d; paclitaxel 175 mg/m <sup>2</sup>	Paclitaxel 175 mg/m <sup>2</sup>		NA	ORR, DCR	(21)
Cui, 2021	RCT	40	40	43.0-75.0 <sup>c</sup>	41.0-74.0 <sup>c</sup>	Apatinib 500 mg/d; paclitaxel 75-145 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup>	Paclitaxel 75-145 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup>		NA	ORR, DCR, adverse events	(22)
Chen, 2021	RCT	48	50	NA	NA	Apatinib 500 mg/d; docetaxel 75 mg/m <sup>2</sup>	Docetaxel 75 mg/m <sup>2</sup>		II	ORR, DCR, PFS, adverse events	(23)

Table I. Continued.

Author, year	Study type	Sample size		Age, years		Treatment regimen			Treatment line	Outcomes	(Refs.)
		Apatinib plus chemo	Chemo	Apatinib plus chemo	Chemo	Apatinib plus chemo	Chemo				
Huang, 2021	RCT	40	40	67.1±3.2 <sup>b</sup>	67.1±3.2 <sup>b</sup>	Apatinib 250 mg/d; cisplatin 25 mg/m <sup>2</sup> ; paclitaxel 135 mg/m <sup>2</sup>	Cisplatin 25 mg/m <sup>2</sup> ; paclitaxel 135 mg/m <sup>2</sup>	NA	NA	ORR, DCR, adverse events	(24)
Liu, 2021	Observational study	43	43	NA	NA	Apatinib 500 mg/d; paclitaxel 175 mg/m <sup>2</sup>	Paclitaxel 175 mg/m <sup>2</sup>	III	III	ORR, DCR, adverse events	(25)
Guo, 2021	Observational study	30	30	62.5±8.3 <sup>b</sup>	62.3±8.2 <sup>b</sup>	Apatinib 850 mg/d; cisplatin 20 mg/m <sup>2</sup> ; paclitaxel 150 mg/m <sup>2</sup>	Cisplatin 20 mg/m <sup>2</sup> ; paclitaxel 150 mg/m <sup>2</sup>	NA	NA	ORR, DCR, adverse events	(26)
Song, 2021	RCT	34	34	63.0±5.1 <sup>b</sup>	63.0±5.0 <sup>b</sup>	Apatinib 500 mg/d; vinorelbine 25 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup> ; gemcitabine 250 mg/m <sup>2</sup>	Vinorelbine 25 mg/m <sup>2</sup> ; cisplatin 25 mg/m <sup>2</sup> ; gemcitabine 250 mg/m	NA	NA	ORR, DCR, PFS, adverse events	(27)
Chen, 2022	RCT	47	45	51.5±8.3 <sup>b</sup>	53.9±7.2 <sup>b</sup>	Apatinib 250 mg/d; paclitaxel 135 mg/m <sup>2</sup> ; cisplatin 20 mg/m <sup>2</sup>	Paclitaxel 135 mg/m <sup>2</sup> ; cisplatin 20 mg/m <sup>2</sup>	NA	NA	ORR, DCR, adverse events	(28)
Lu, 2022	Observational study	42	42	63.9±6.4 <sup>b</sup>	63.9±6.4 <sup>b</sup>	Apatinib 850 mg/d; paclitaxel 175 mg/m <sup>2</sup>	Paclitaxel 175 mg/m <sup>2</sup>	NA	NA	ORR, DCR, adverse events	(29)

<sup>a</sup> Age was described as median (interquartile range); <sup>b</sup> age was described as mean ± standard deviation; <sup>c</sup> age was described as minimum-maximum. Chemo, chemotherapy; RCT, random control trial; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; NA, not available.

<sup>a</sup>Age was described as median (interquartile range); <sup>b</sup>age was described as mean ± standard deviation; <sup>c</sup>age was described as minimum-maximum. Chemo, chemotherapy; RCT, random control trial; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; NA, not available.

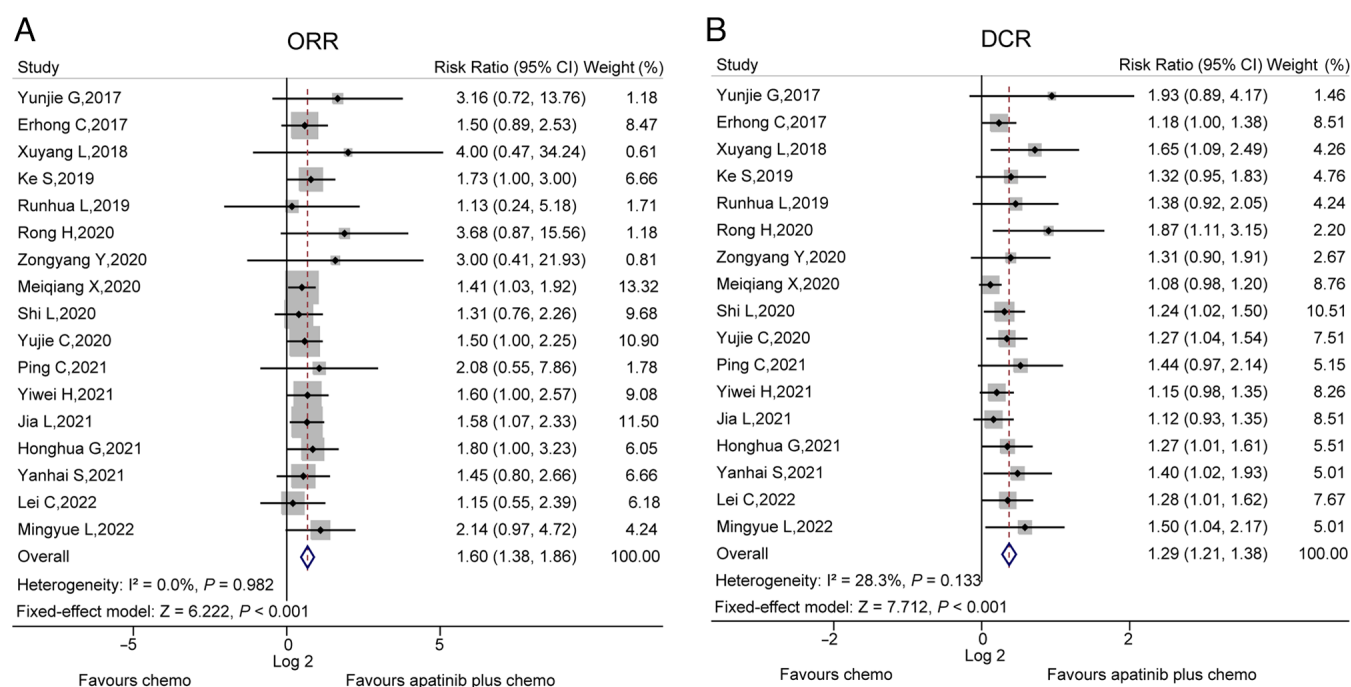


Figure 2. Forest plot of the treatment response between the apatinib plus chemotherapy group and the chemotherapy alone group. Pooled analysis of the (A) ORR and (B) DCR. ORR, objective response rate; DCR, disease control rate; chemo, chemotherapy.

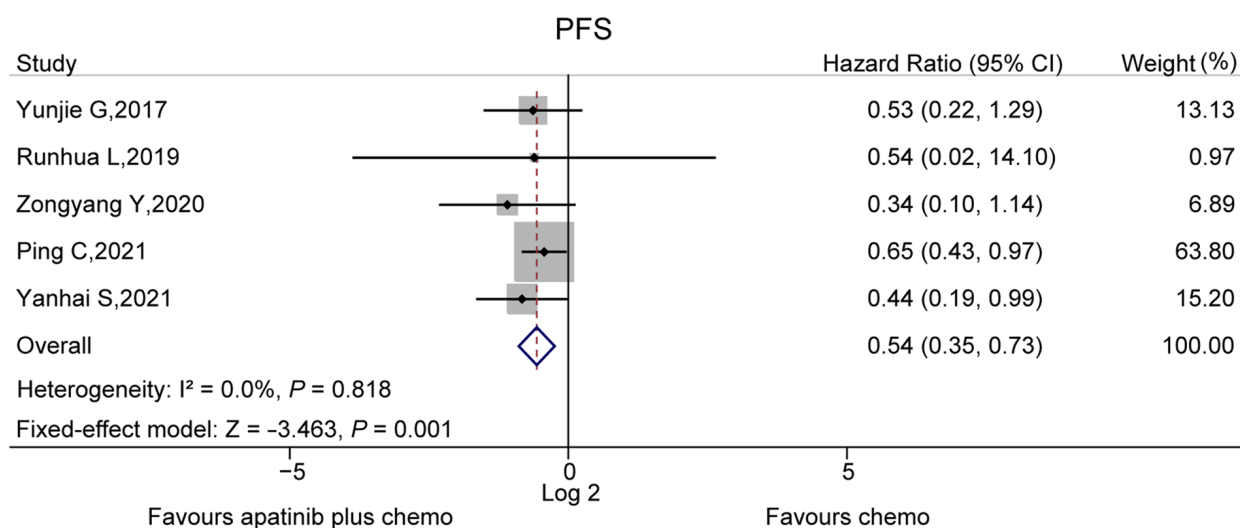


Figure 3. Forest plot of PFS between the apatinib plus chemotherapy group and the chemotherapy alone group. PFS, progression-free survival; chemo, chemotherapy.

NSCLC following chemotherapy remains unsatisfactory (38,39). Several clinical trials have indicated that, in comparison to chemotherapy alone, apatinib plus chemotherapy prolongs the survival of patients with advanced-stage NSCLC (13,17,21,23,27). However, to date, at least to the best of our knowledge, there is no study available that comprehensively compares the survival of patients with advanced-stage NSCLC receiving these treatment methods. In the present systematic meta-analysis, the pooled data of the five studies demonstrated that PFS of patients with advanced-stage NSCLC was longer in the group receiving apatinib plus chemotherapy compared to chemotherapy alone. The possible reason for this may be that the favorable treatment response of apatinib plus

chemotherapy contributed to satisfactory survival outcomes among patients with advanced-stage NSCLC.

Previous studies have demonstrated that common apatinib-related adverse events are mild hypertension, hand-foot syndrome and fatigue (40,41). In addition, the main toxic effects associated with chemotherapy are leukopenia, neutropenia, thrombocytopenia and anemia (42). Of note, previous studies have demonstrated that apatinib plus chemotherapy does not increase the numbers of severe adverse events compared to chemotherapy alone when used in the treatment of patients with advanced-stage NSCLC (11,13-29). However, a comprehensive analysis of the safety of apatinib plus chemotherapy in patients with advanced-stage NSCLC



Table II. Publication bias.

Outcome	Studies included, n	P-value (Begg's test)	P-value (Egger's test)
ORR	17	1.000	0.729
DCR	17	0.466	0.215
PFS	5	0.806	0.200
Hypertension	11	0.876	0.970
Hand-foot syndrome	9	0.602	0.713
Liver dysfunction	7	0.230	0.261
Proteinuria	13	0.951	0.139
Bone marrow depression	8	0.902	0.758
Thrombocytopenia	7	0.368	0.179
Leukocytopenia	5	1.000	0.812
Fatigue	5	0.221	0.299
Gastrointestinal reaction	9	0.048	0.183
Nausea/vomiting	6	0.707	0.277

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival.

Table III. Assessment of the risk of bias in randomized controlled trials by Cochrane Collaboration's tool.

Author, year	Sequence generation	Concealment of allocation	Blinded adjudication	Completeness of outcome data	Free of selective reporting	Free of other bias	(Refs.)
Guo, 2017	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(13)
Chen, 2017	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(14)
Liu, 2018	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(15)
Shang, 2019	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(16)
Yu, 2020	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(18)
Guo, 2020	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(19)
Xie, 2020	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(20)
Li, 2020	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	(21)
Cui, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(22)
Chen, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	(23)
Huang, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	(24)
Song, 2021	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	(27)
Chen, 2022	Low risk	Unclear	Unclear	Low risk	Low risk	Unclear	(28)

Table IV. Assessment of the risk of bias in non-randomized controlled trials by the Newcastle-Ottawa Scale criteria.

Author, year	Selection	Comparability	Outcome	Total score	(Refs.)
Luo, 2019	4	1	3	8	(17)
Hu, 2020	4	2	2	8	(11)
Liu, 2021	4	1	2	7	(25)
Guo, 2021	4	2	2	8	(26)
Lu, 2022	4	2	2	8	(29)

is still warranted. Herein, the pooled analysis revealed that apatinib plus chemotherapy only increased the risk of developing hypertension and hand-foot syndrome; however, no other adverse events in comparison to chemotherapy alone

were found among the patients with advanced-stage NSCLC; this finding was consistent with that of a previous related meta-analysis (30). The potential reasons for this may be the following: i) Apatinib inhibited the VEGFR-2-mediated

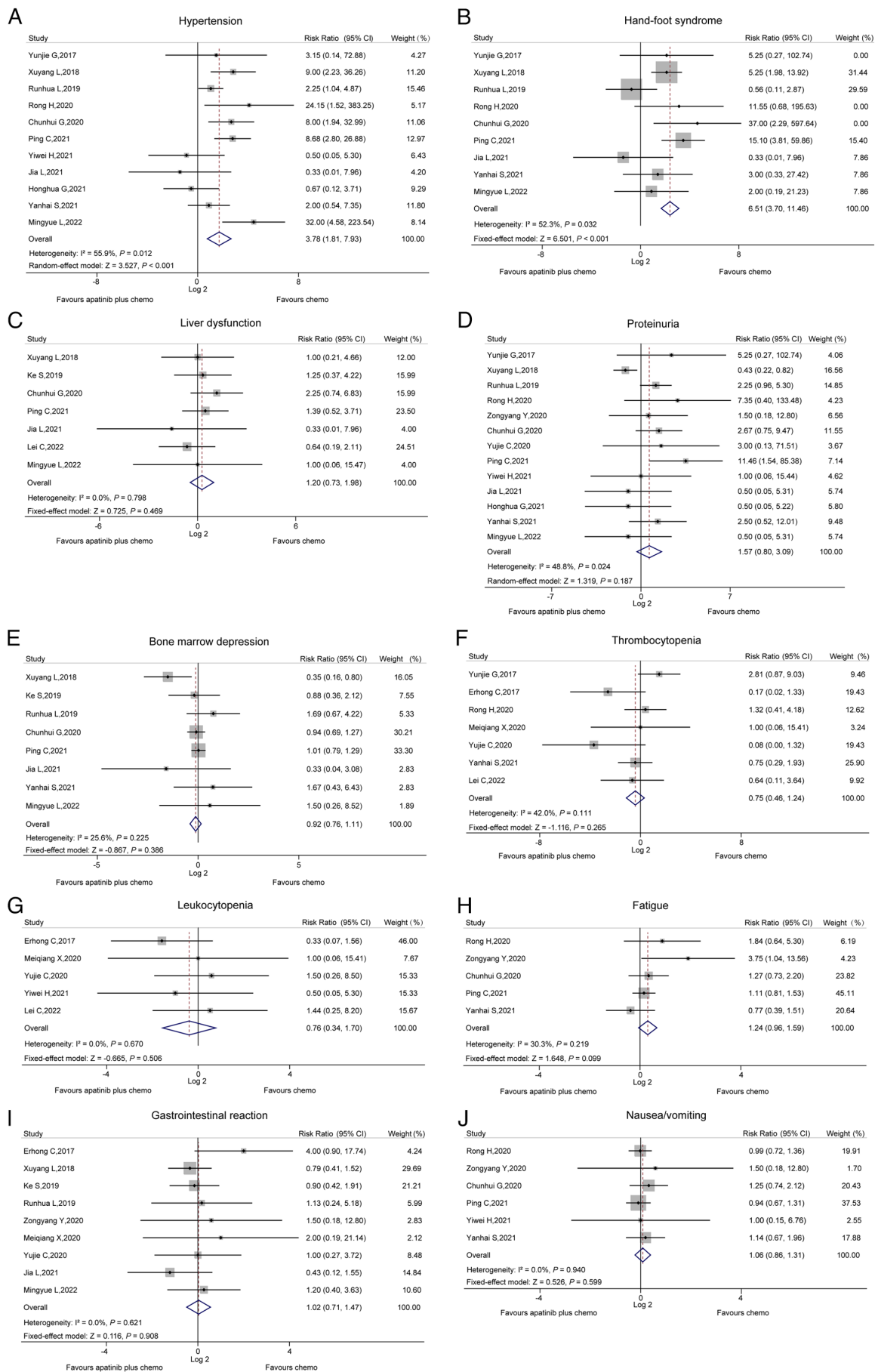


Figure 4. Forest plot of adverse events between the apatinib plus chemo group and chemo group. Pooled analysis of (A) hypertension, (B) hand-foot syndrome, (C) liver dysfunction, (D) proteinuria, (E) bone marrow depression, (F) thrombocytopenia, (G) leukocytopenia, (H) fatigue, (I) gastrointestinal reaction and (J) nausea/vomiting. Chemo, chemotherapy.



signaling pathway and the latter has an essential role in maintaining vascular tone and blood pressure regulation. As a result, apatinib may cause the incidence of hypertension (43). ii) The apatinib-induced keratinocyte apoptosis, the persistent existence of subclinical trauma and impaired vascular function may have resulted in the development of hand-foot syndrome (44).

The purpose of the current study was to compare the efficacy and safety of apatinib plus chemotherapy vs. chemotherapy alone for patients with advanced NSCLC, since the benefit of bevacizumab plus chemotherapy in these patients was already suggested in other meta-analyses (45,46). However, the present study has certain limitations, which should be mentioned: i) The present study was limited by the fact that OS data were not reported in the previous studies and a meta-analysis on this aspect was thus difficult to conduct. Further studies are required to focus on the OS benefit from the use of apatinib plus chemotherapy in patients with advanced-stage NSCLC. ii) Sensitivity analysis revealed that omitting the studies by Liu and Zheng (15), Guo and Jing (13) and Song *et al* (27) affected the pooled analysis finding of proteinuria, thrombocytopenia and fatigue, respectively; thus, more updated studies are required to validate this finding. iii) There were four studies with a high risk of other biases, which may have interfered with the results. iv) As the original studies provided limited relevant information, it was not possible to perform subgroup analyses; hence, it was difficult to demonstrate what type of patient group benefited from the combination therapy. v) Previous treatment may have influenced the outcome, while most studies did not present this information in detail; thus, it was difficult to analyze.

In conclusion, the present meta-analysis demonstrated that the use of apatinib plus chemotherapy enhanced the treatment response and PFS. However, it increased the risk of developing hypertension and hand-foot syndrome compared with chemotherapy alone among patients with advanced-stage NSCLC.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

SQ and XH designed the study. ZL supervised the study. SQ and XH conceived the study. SQ, XH and ZL participated in data collection. SQ and XH performed the data analysis and wrote the manuscript. SQ, XH and ZL contributed to the interpretation of the results and revised the manuscript. SQ and XH confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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