


ORIGINAL ARTICLE

Efficacy and safety of apatinib alone or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced non-small cell lung cancer: A meta-analysis

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Abstract

Background: To investigate the efficacy and safety of apatinib alone or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced non-small cell lung cancer (NSCLC) through pooling of open published data.

Methods: The electronic databases of Medline (1960–2021.5), Cochrane central register of controlled trials (CENTRAL), EMBASE(1980–2021.5) and Wan fang (1986–2021.5) were systematically searched by two reviewers to identify the relevant clinical trials related to the above subject. The objective response rate (ORR), disease control rate (DCR) and drug relevant adverse reactions were pooled and demonstrated by risk ratio (RR) and 95% confidence interval (95% CI). The statistical heterogeneity across studies was assessed by I-square test. The publication bias was evaluated by Egger's line regression test and demonstrated by Begg's funnel plot.

Results: Eleven prospective studies were included in the meta-analysis. The pooled results indicated that the ORR (RR = 1.62, 95% CI: 1.32–2.00, $p < 0.05$) and DCR (RR = 1.29, 95% CI: 1.18–1.41, $p < 0.05$) of apatinib alone or apatinib plus paclitaxel/docetaxel was significantly higher than that of the paclitaxel/docetaxel group for advanced NSCLC, respectively. The drug-related adverse reaction was not statistically different between apatinib alone or apatinib plus paclitaxel/docetaxel with regard to the hand-foot syndrome, gastrointestinal reaction, thrombocytopenia, anemia and leukocytopenia ($p_{\text{all}} > 0.05$) except for hypertension (RR = 3.60, 95% CI: 1.26–10.31, $p < 0.05$). Subgroup analysis also indicated that the hypertension and hand-foot syndrome in apatinib + paclitaxel/docetaxel were higher than that of the paclitaxel/docetaxel group with a statistical difference ($p < 0.05$).

Conclusions: Apatinib alone or apatinib plus paclitaxel/docetaxel was superior to paclitaxel/docetaxel for ORR and DCR. However, combined treatment with apatinib appears to increase the risk of a patient developing an adverse reaction, especially hypertension and hand-foot syndrome.

KEYWORDS

apatinib, meta-analysis, non-small cell lung cancer, paclitaxel/docetaxel

INTRODUCTION

Cancer epidemiological studies have indicated that lung cancer, especially non-small cell lung cancer (NSCLC), which accounts for 80%–85% all lung carcinoma, is the leading cause of neoplasm-related death globally.¹ Due to the lack of

specific clinical symptoms, most of the cases are at advanced stages with a poor prognosis and low 5-year survival rate. Chemoradiation, target therapy and immunotherapy² are the main methods of treatment for advanced stage lung cancer. At present, the first-line treatment for advanced NSCLC patients with positive driver genes is targeted therapy, but the

recommended first-line treatment for advanced NSCLC patients with negative driver genes is platinum-based combination chemotherapy. However, many NSCLC patients cannot tolerate the toxicity of platinum-based combination chemotherapy or drug resistance after several cycles of chemotherapy. Therefore, for patients with advanced NSCLC who fail on first-line chemotherapy, the follow-up treatment appears to be complicated and difficult.

Apatinib is a tyrosine kinase inhibitor that selectively inhibits the vascular endothelial growth factor receptor-2 (VEGFR2).^{3,4} Apatinib is an orally bioavailable, small molecular agent which can inhibit angiogenesis in cancer cells, especially in VEGF-mediated endothelial cell migration and proliferation.^{5,6} As a VEGFR2 tyrosine kinase inhibitor, apatinib can inhibit the VEGF/VEGFR2 signal pathway and reduce the formation of MAPK, so as to inhibit the proliferation of vascular endothelial cells and achieve an antitumor effect. Currently, apatinib has been approved in China for the third-line treatment of advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma. It has also shown strong antitumor activity in *in vivo* and *in vitro* experiments of cholangiocarcinoma, hepatocellular carcinoma, colon cancer and non-small cell lung cancer, bringing new hope for NSCLC patients with negative driver genes. Over the past few years, studies have evaluated the efficacy and safety of apatinib alone or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC.^{7,8} However, the results were inconclusive due to the small sample sizes and other mixed factors that affect the treatment response.

METHODS

Studies identified in the electronic databases

The electronic databases of Medline (1960–2021.6), Cochrane central register of controlled trials (CENTRAL), EMBASE (1980–2021.5) and Wan fang (1986–2021.5) were systematically searched by two reviewers to identify the relevant clinical trials related to the efficacy and safety of apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC. The studies screening procedure was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement flow chart. The studies were electronically searched using the free terms of “non-small cell lung cancer,” “NSCLC,” “lung cancer,” “lung neoplasm,” “carcinoma of the lung” AND “Apatinib,” “YN968D1,” “Rivoceranib.” Searching of the studies was restricted to human trials, with a language restriction of English and Chinese. All references of the included clinical trials were also reviewed to further identify additional suitable publications.

Inclusion and exclusion criteria

The studies initially identified in the databases were further screened by two reviewers independently for evaluation as

to whether they fulfilled the inclusion criteria. The study was evaluated in the aspects of study design, comparing patient characteristics, type of intervention, control and outcome (PICO). The study design was limited to prospective clinical studies. Patients: advanced non-small cell lung cancer with pathology or PE-CT confirmation. Intervention: apatinib alone or apatinib plus paclitaxel/docetaxel. Control: paclitaxel/docetaxel. Outcome: response included ORR, DCR and drug relevant adverse reaction. The language was restricted to English and Chinese.

Methodological quality assessment

The methodological quality of the included studies was evaluated by two reviewers, respectively according to the Cochrane Reviews Handbook 5.0. Particular attention was paid to the adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting and free of other bias, which mainly demonstrate the methodological quality of the RCT.⁹

Statistical analysis

STATA10.0 and RevMan 5.0 statistical software were applied to perform the statistical analysis. The response difference between two groups was expressed by risk ratio (RR) with a 95% confidence interval (CI). Statistical heterogeneity across the included studies was evaluated by I-square (I^2) test. The data was combined by random or fixed effect model according to statistical heterogeneity ($I^2 > 50%$, random effect model otherwise fixed effect model). The Egger's line regression test and Begg's funnel plot were applied to evaluate possible publication bias.¹⁰

RESULTS

Main characteristics of the studies included

Eleven prospective studies relevant to the efficacy and safety of apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC were identified and included in the meta-analysis (Figure 1). Four studies compared the efficacy and safety between apatinib alone versus paclitaxel/docetaxel and seven studies compared apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel for the treatment of NSCLC. The general characteristics of the included 11 studies are shown in Table 1.

Methodological quality of the included studies

The methodological quality of the included studies is shown in the Figure 2. The general methodological quality was

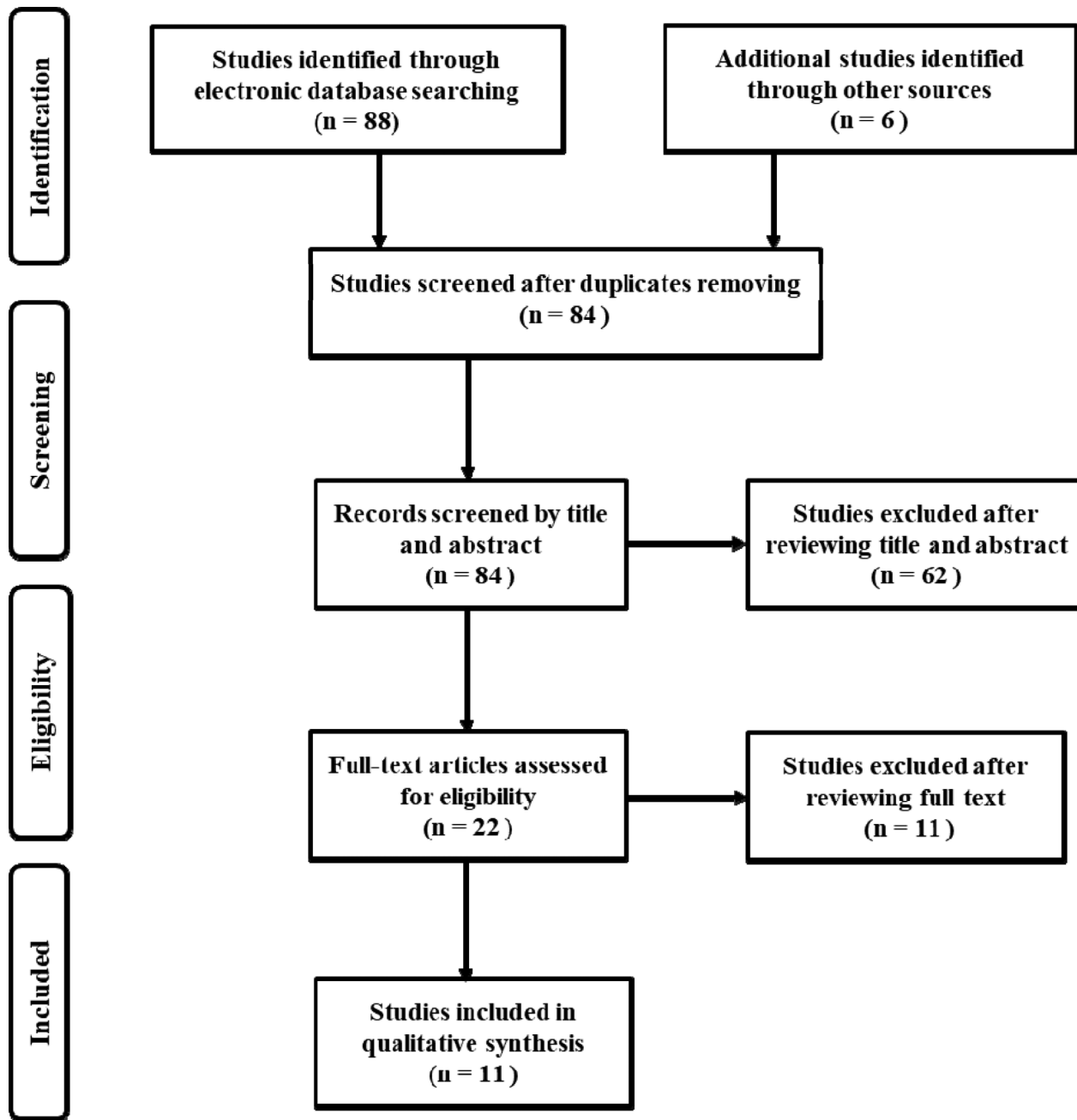


FIGURE 1 The studies included and exclusion flow chart

moderate with most studies having a relative moderate and high risk of quality bias.

Objective response rate

All the 11 clinical trials included in the study evaluated the ORR between apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment NSCLC. There was no statistical heterogeneity across the 11 studies ($I^2 = 0.0\%$, $p = 0.931$). Therefore, the ORR was pooled in a fixed effect model with

$RR = 1.62$ (95% CI: 1.32–2.00, $p < 0.05$), which demonstrated that ORR in advanced NSCLC patients who received apatinib alone, or apatinib plus paclitaxel/docetaxel, was superior to those who received paclitaxel/docetaxel (Figure 3).

Disease control rate

All 11 studies investigated the disease control rate (DCR). Due to the lack of statistical heterogeneity across the included studies, the DCR was pooled in a fixed effect

TABLE 1 General characteristics of the included studies

Author	Year	Age	Treatment line	Apatinib		Control		Outcomes
				No.	Regiment	No.	Regiment	
Ren et al. ¹¹	2017	55–56	NA	25	Apatinib 500 mg/day, orally for 28 days	25	Docetaxel 75 mg/m ² intravenously, every 21 days	ORR, DCR
Bi et al. ¹²	2017	18–70	Second-line, recurrence disease	35	Apatinib 500 mg/day, orally for 28 days	30	Docetaxel 75 mg/m ² intravenously, every 21 days	ORR, DCR, hypertension, hand-foot syndrome, thrombocytopenia, leukocytopenia
Tang et al. ¹³	2019	50–58	Second-line	30	Apatinib 500 mg/day, orally for 21 days	30	Docetaxel 250 mg intravenously, every 21 days	ORR, DCR, hypertension, hand-foot syndrome, gastrointestinal reaction,
Chen et al. ¹⁴	2017	41–79	NA	42	Apatinib 850 mg/day, orally for 30 days + Paclitaxel 135–145 mg/m ²	42	Paclitaxel 135–145 mg/m ² , every 21 days	ORR, DCR, gastrointestinal reaction, thrombocytopenia, leukocytopenia
Guo and Jing ¹⁵	2017	33–75	Second-line, progressed disease	19	Apatinib 850 mg/day, orally for 21 days + docetaxel 60 mg/m ² intravenously, every 21 days	21	Docetaxel 60 mg/m ² intravenously, every 21 days	ORR, DCR, hypertension, hand-foot syndrome, thrombocytopenia, anemia, leukocytopenia
Zhao et al. ⁷	2019	40–70	NA	32	Apatinib 850 mg/day, orally	32	Docetaxel 75 mg/m ² intravenously, once every 3 weeks	ORR, DCR, gastrointestinal reaction, thrombocytopenia, anemia
Hu et al. ⁸	2020	47–75	Second-line, recurrent disease	19	Apatinib 500 mg/day, orally + docetaxel 60 mg/m ² intravenously	20	Docetaxel 60 mg/m ² intravenously, once every 3 weeks	ORR, DCR, hypertension, hand-foot syndrome, gastrointestinal reaction, thrombocytopenia, anemia, leukocytopenia
Yu et al. ¹⁶	2020	62(41–74)	Second-line		Apatinib 500 mg/day, orally + docetaxel 75 mg/m ² intravenously		Docetaxel 75 mg/m ² intravenously, once every 3 weeks	ORR, DCR, hypertension, hand-foot syndrome, gastrointestinal reaction,
Pan ¹⁷	2020	44–79	NA	27	Apatinib 500 mg/day, orally + docetaxel 75 mg/m ² intravenously	27	Docetaxel 75 mg/m ² intravenously, once every 3 weeks	ORR, DCR
Xie et al. ¹⁸	2020	35–75	NA	38	Apatinib 500 mg/day, orally + paclitaxel 75 mg/m ² intravenously	38	Paclitaxel 75 mg/m ² intravenously, every 21 days	ORR, DCR, hypertension, gastrointestinal reaction, thrombocytopenia, leukocytopenia
Li ¹⁹	2020	NA	Second-line	60	Apatinib 500 mg/day, orally + paclitaxel 75 mg/m ² intravenously	60	Paclitaxel 75 mg/m ² intravenously, every 21 days	ORR, DCR

Abbreviations: NA, not available.

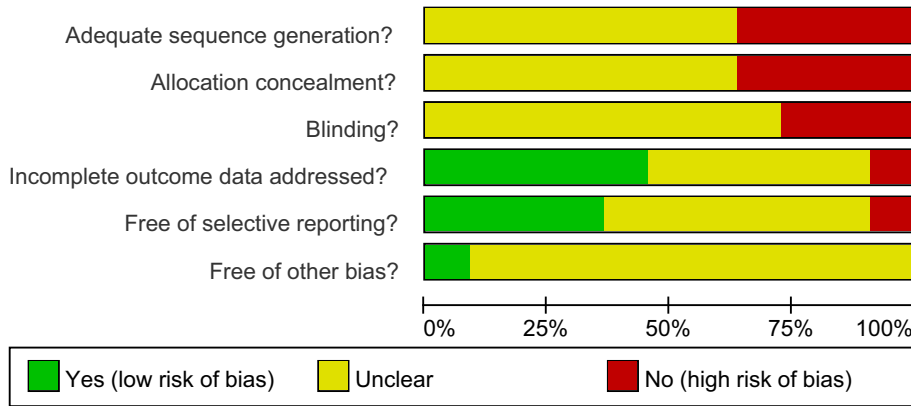


FIGURE 2 Methodological quality of the included studies

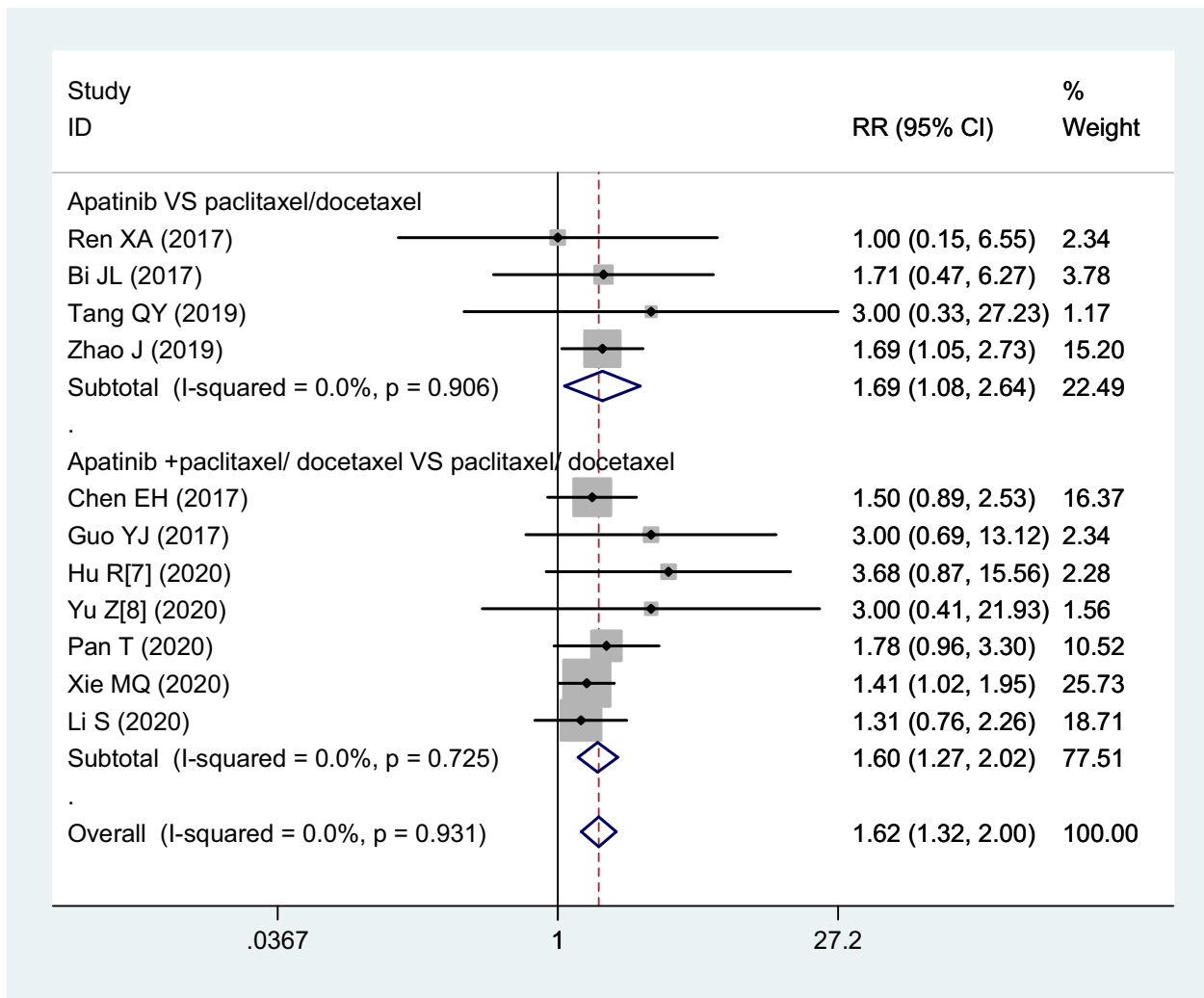


FIGURE 3 The forest plot of ORR for apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC

model. Pooled results indicated that the DCR in apatinib alone or apatinib plus paclitaxel/docetaxel was significantly higher than that of paclitaxel/docetaxel groups for advanced NSCLC (RR = 1.29, 95% CI: 1.18–1.41, $p < 0.05$) (Figure 4).

Adverse reactions

Due to statistical heterogeneity, the drug-related adverse reactions such as hypertension, hand-foot syndrome, gastrointestinal reaction, thrombocytopenia, anemia and

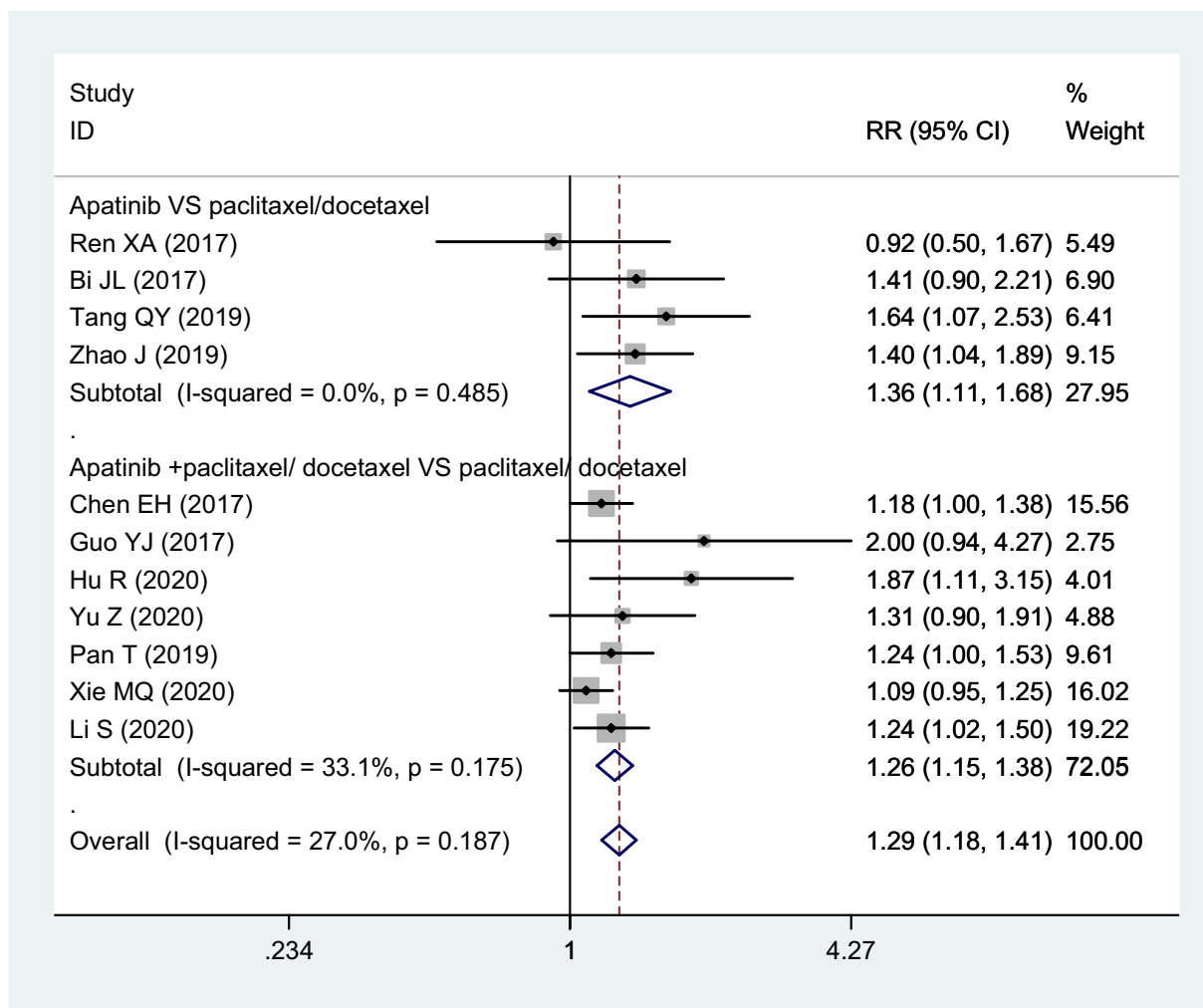


FIGURE 4 The forest plot of DCR for apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC

leukocytopenia were combined in a random effect model. The pooled results indicated the drug-related adverse reaction was not statistically different between apatinib alone, or apatinib plus paclitaxel/docetaxel in, hand-foot syndrome, gastrointestinal reaction, thrombocytopenia, anemia and leukocytopenia ($p_{\text{all}} > 0.05$). However, the hypertension risk in the apatinib group was significantly higher than that of the control group (RR = 3.60, 95% CI: 1.26–10.31, $p < 0.05$) (Figure 5).

Subgroup analysis

The ORR, DCR and drug-related adverse reaction was further analyzed in subgroup analysis according to treatment regimen (apatinib vs. paclitaxel/docetaxel or apatinib + paclitaxel/docetaxel vs. paclitaxel/docetaxel). The pooled results indicated the ORR and DCR were higher in apatinib alone, or the apatinib + paclitaxel/docetaxel group compared to the corresponding control groups ($p < 0.05$) (Table 2). However, the drug-related adverse reaction of hypertension and

hand-foot syndrome in apatinib + paclitaxel/docetaxel was higher than that of the paclitaxel/docetaxel group with a statistically significant difference ($p < 0.05$) (Figures 6 and 7).

Publication bias

The funnel plot was generally left and right asymmetric for ORR (Figure 8(a)) and DCR (Figure 8(b)). The Egger's line regression test also indicated obvious publication bias for effect size of ORR ($t = 2.91$, $p = 0.017$) and DCR ($t = 3.372$, $p = 0.008$).

DISCUSSION

Eleven prospective clinical studies relevant to the efficacy and safety of apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC, were included in the meta-analysis by pooling of open published data. Of the included 11 trials,

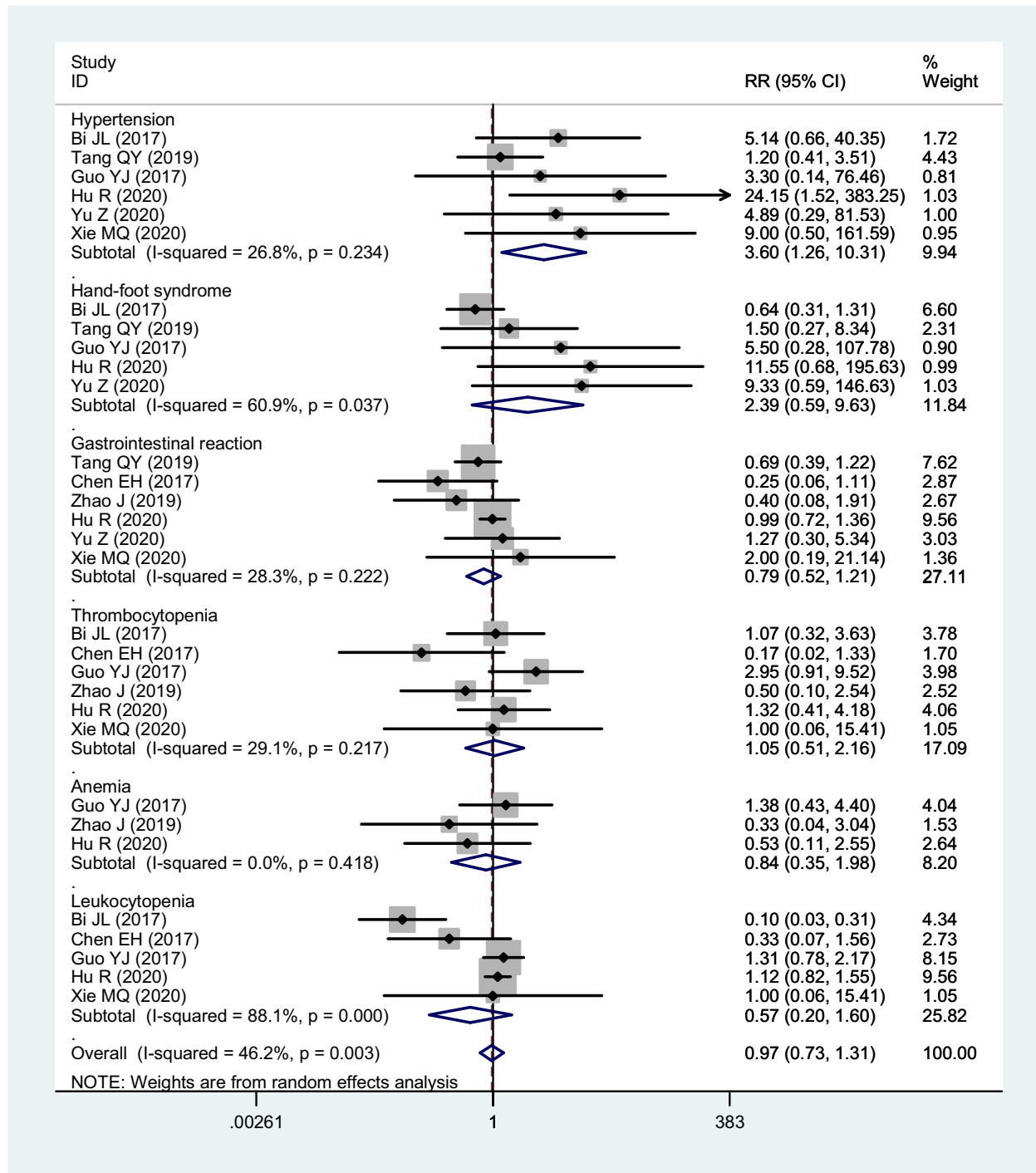


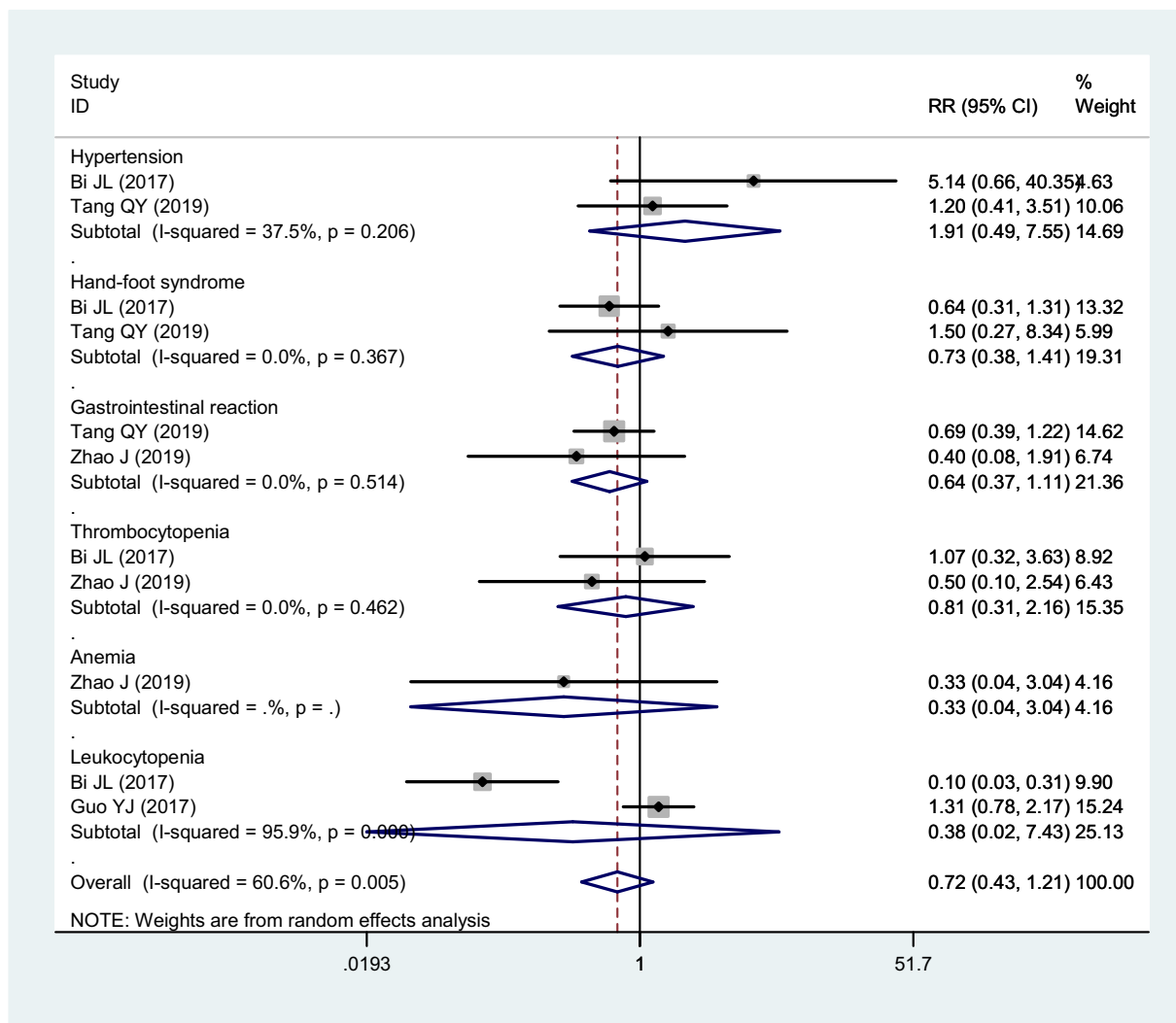
FIGURE 5 The forest plot of adverse reactions for apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC

four studies compared the efficacy and safety between apatinib alone versus paclitaxel/docetaxel and seven studies compared the apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of NSCLC. The combined results showed the ORR and DCR of apatinib alone, or apatinib plus paclitaxel/docetaxel were significantly higher than that of the paclitaxel/docetaxel groups for advanced NSCLC, respectively. The drug-related adverse reaction was

not statistically different between apatinib alone, or apatinib plus paclitaxel/docetaxel with regard to the hand-foot syndrome, gastrointestinal reaction, thrombocytopenia, anemia and leukocytopenia except for hypertension. These findings indicated apatinib alone, or plus paclitaxel/docetaxel was superior to paclitaxel/docetaxel chemotherapy in treatment response but increased the adverse reaction of hypertension. The subgroup analysis also indicated that the hypertension

TABLE 2 Subgroup analysis for efficacy and safety of apatinib alone or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced non-small cell lung cancer

Response/toxicity	Apatinib vs. paclitaxel/docetaxel	<i>p</i> -value	Apatinib +paclitaxel/docetaxel vs. paclitaxel/docetaxel	<i>p</i> -value
ORR	1.69 (1.08–2.64)	<0.05	1.60 (1.27–2.02)	<0.05
DCR	1.36 (1.11–1.68)	<0.05	1.26 (1.15–1.38)	<0.05
Hypertension	1.19 (0.49–7.55)	>0.05	9.85 (2.45–39.59)	<0.05
Hand-foot syndrome	0.73 (0.38–1.14)	>0.05	8.88 (1.69–46.62)	<0.05
Gastrointestinal reaction	0.64 (0.37–1.11)	>0.05	0.84 (0.57–1.23)	>0.05
Thrombocytopenia	0.81(0.31–2.16)	>0.05	1.13 (0.58–2.18)	>0.05
Anemia	0.33 (0.04–3.04)	>0.05	0.95 (0.38–2.36)	>0.05
Leukocytopenia	0.38 (0.02–7.43)	>0.05	1.03 (0.76–1.40)	>0.05

**FIGURE 6** The forest plot of toxicity for apatinib alone versus paclitaxel/docetaxel in the treatment of advanced NSCLC

and hand-foot syndrome in apatinib+paclitaxel/docetaxel were higher than that of paclitaxel/docetaxel group with statistical difference ($p < 0.05$), but not different between apatinib alone versus paclitaxel/docetaxel treatment cases. Therefore, apatinib alone, or apatinib plus paclitaxel/docetaxel were superior to paclitaxel/docetaxel for ORR and

DCR. However, combined treatment with apatinib appears to increase the risk of patients developing an adverse reaction, especially hypertension and hand-foot syndrome.

Lung cancer is the most common malignant tumor with the highest mortality rate in the world. In 2020, there were more than 2 206 771 new cases of lung cancer and

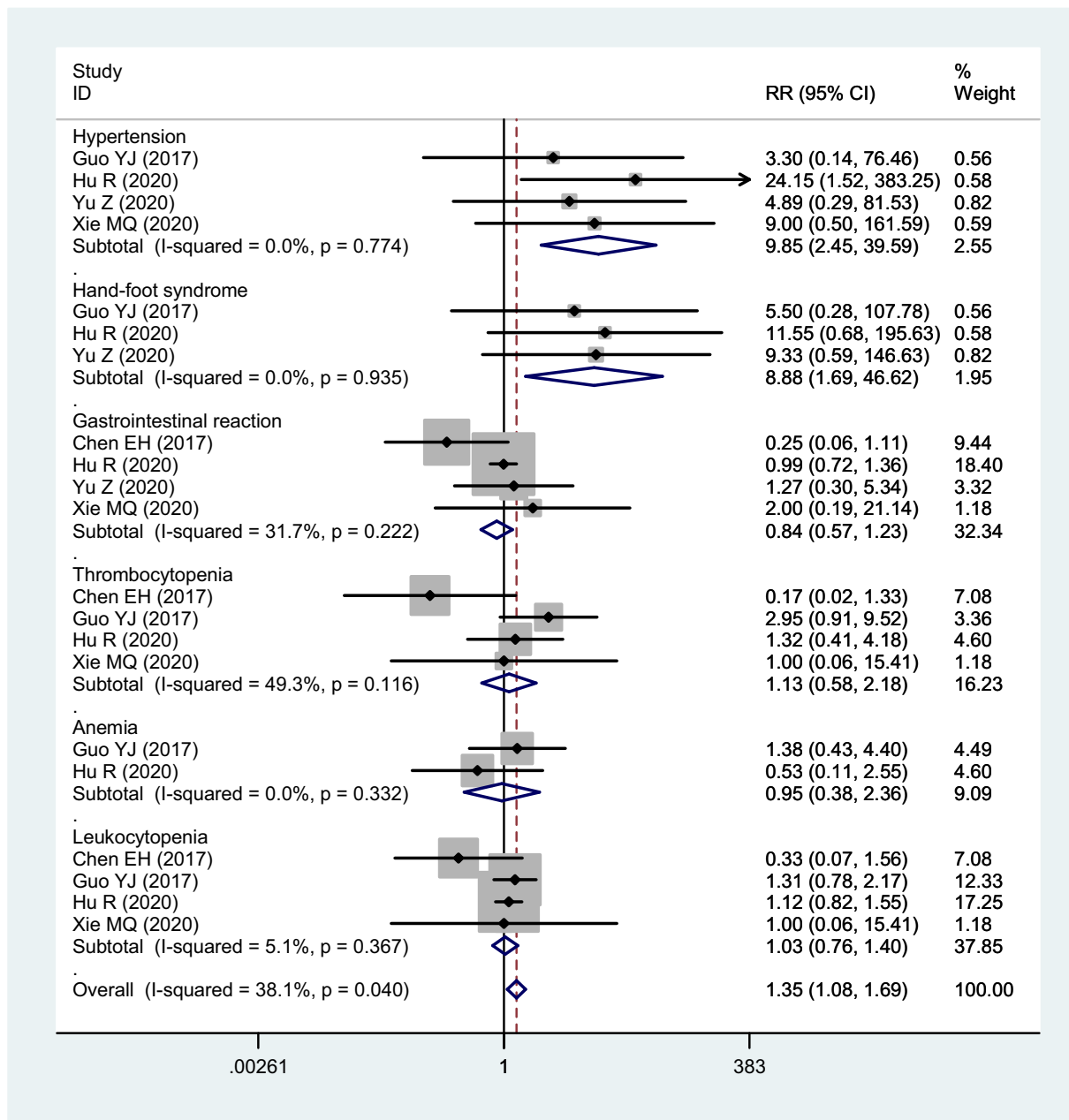


FIGURE 7 The forest plot of toxicity for apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC

1 796 144 death caused by lung carcinoma.²⁰ According to the NCCN guideline for NSCLC, platinum-based double drug chemotherapy is generally applied as first-line treatment for advanced NSCLC. However, relevant studies have found that the 5-year survival rate of patients undergoing platinum-based double drug chemotherapy was unsatisfactory with low long-term survival rates and severe drug-related adverse reactions.²¹ Paclitaxel and docetaxel are both third generation antitumor drugs, and their antitumor mechanism promotes microtubule polymerization, inhibits depolymerization, and blocks cancer cell synthesis. Paclitaxel or docetaxel are generally recommended for the single

drug chemotherapy regimen in patients with advanced NSCLC as maintenance therapy with the response rate of 16%–27%.^{22,23} The mainstream view supports that traditional chemotherapy has reached a bottleneck with regard to tumor treatment response due to dosage restriction and drug-related toxicity. In recent years, with the development of new drugs, targeted therapy immunotherapy and anti-angiogenic treatment have made great progress in improving treatment response, long-term survival and decreasing treatment-related toxicity. Targeted treatment can significantly improve the prognosis of NSCLC patients with positive driver gene mutations, but for NSCLC cases with

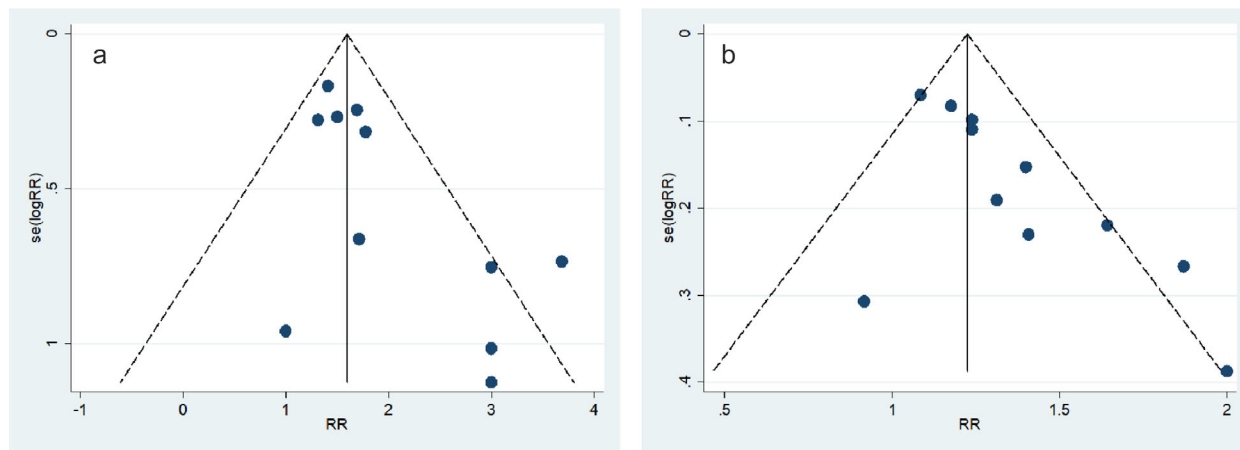


FIGURE 8 The funnel plot for apatinib alone, or apatinib plus paclitaxel/docetaxel versus paclitaxel/docetaxel in the treatment of advanced NSCLC ((a) Objective response rate; (b) disease control rate)

negative driver genes, the target treatment appears to be invalid.^{24,25} Since the 20th century, a series of clinical studies have confirmed that tumor angiogenesis plays an important part in tumor development.^{26–28} The vascular endothelial growth factor (VEGF) pathway plays an important role in the process of tumor angiogenesis. Among the VEGFR family, VEGFR-2 is an important protein, which is considered to be a key molecule related to tumor angiogenesis. VEGF-2 promotes the proliferation of vascular endothelial cells by activating the mitogen activated protein kinase (MAPK) signaling pathway.²⁹

Apatinib is an antiangiogenic drug of VEGFR2 tyrosine kinase inhibitor, which can inhibit the VEGF/VEGFR2 signaling pathway and reduce the formation of MAPK, thereby inhibiting the proliferation of vascular endothelial cells and achieving an antitumor effect.³⁰ At present, apatinib has been approved as third-line treatment for advanced gastric adenocarcinoma or gastroesophageal junction adenocarcinoma in China.³¹ It has also shown strong antitumor activity in vivo and in vitro in cholangiocarcinoma, hepatocellular carcinoma, colorectal cancer and non-small cell lung cancer, which brings new hope for advanced NSCLC patients with negative driver gene.³²

In 2019, Yu et al.³³ wrote a meta-analysis relevant to apatinib in the treatment of advanced NSCLC. In their study, the authors found that apatinib was a viable treatment alternative for advanced NSCLC, as it offered a clinically meaningful and statistically significant improvement in PFS, ORR, and DCR. Moreover, therapy with apatinib did not significantly increase toxicity. However, in the study by Yu et al., only five studies were included in the analysis with a small sample size. In our meta-analysis, we systematically searched the relevant electronic databases and finally included 11 prospective clinical studies. The pooled data of the 11 studies included indicated apatinib alone or apatinib plus paclitaxel/docetaxel were superior to paclitaxel/docetaxel for ORR and DCR. However, combined treatment with

apatinib appears to place patients more at risk of developing an adverse reaction especially hypertension and hand-foot syndrome. This finding was generally in accordance with the conclusions of Yu et al.

However, the limitation of the present study is obvious. First, although 11 studies were included in the analysis, the sample size was still relatively small with weak statistical power. Second, statistical heterogeneity existed in pooling the drug-related adverse reactions which indicated the results of the included studies were inconsistent with regard to adverse reactions. Third, publication bias was identified for the effect size of ORR and DCR, which may decrease the power of the conclusions. Fourth, the general methodological quality was moderate with most studies with a relatively moderate and high risk of quality bias.

In conclusion, based on the current evidence, apatinib alone, or apatinib plus paclitaxel/docetaxel was superior to paclitaxel/docetaxel for ORR and DCR. However, there appears to be more risk of patients developing adverse reactions, especially hypertension and hand-foot syndrome, in the combined treatment with apatinib. Furthermore, due to the above limitations, the conclusions should be validated by high quality multiple center prospective clinical trials. Regimens containing apatinib have been widely discussed and network meta-analysis are needed to compare the treatment response among different chemotherapy regimens.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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