Efficacy and safety of anlotinib combined with S-1 as a third- or later-line treatment for advanced non-small cell lung cancer in China: A systematic review and meta-analysis

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Abstract. Anlotinib is presently used as a third-line treatment for non-small cell lung cancer. However, it is not yet reported whether combining anlotinib with S-1 as a third- or later-line treatment offers superior outcomes compared with anlotinib alone. The present meta-analysis aimed to address this question by systematically searching the PubMed, Embase, Web of Science, Cochrane Library, CMB and China National Knowledge Infrastructure databases for eligible studies published from the establishment of the database to January 10, 2024. Primary outcomes of interest included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR) and the incidence of adverse effects, which were presented as hazard ratios and 95% CIs. The present analysis included 5 retrospective studies with a total of 317 patients and compared the outcomes of patients treated with a combination of anlotinib and S-1 (experimental group) compared with anlotinib alone (control group). The combination treatment significantly improved PFS, OS, ORR and DCR in the experimental group compared with the control group. Bone marrow suppression and fatigue were significantly higher in the experimental group compared with the control group. However, incidences of hypertension, proteinuria, gastrointestinal adverse reactions, hepatic and renal insufficiency and functional hand-foot syndrome were higher in the control group compared with the experimental group, but there was no statistical significance. In summary, combining anlotinib with S-1 may be more effective compared with anlotinib alone for treating advanced non-small cell lung cancer. Despite the higher incidence of adverse reactions with the combination therapy, these reactions could be considered manageable and controllable.

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Abbreviations: CSCO, Chinese Society of Clinical Oncology; DCR, disease control rate; mOS, median overall survival; PFS, progression-free survival; mPFS, median PFS; NSCLC, non-small cell lung cancer; ORR, objective response rate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial

Key words: anlotinib, non-small cell lung cancer, S-1, meta-analysis, progression-free survival

Introduction

Lung cancer is one of the most prevalent types of malignant tumors worldwide and is characterized by a high degree of malignancy and poor prognosis. Despite the advancements in understanding risk factors, development mechanisms and treatment modalities, lung cancer remains a leading cause of cancer-related mortality worldwide (1). The prognosis for lung cancer is relatively good as the 5-year survival rate for early-stage lung cancer (stage IA) is up to 90%, whereas for advanced-stage lung cancer (stage IVB) the 5-year survival rate is <10% (2). A total of ~83% of lung cancer cases are classed as non-small cell lung cancer (NSCLC) (3). The early symptoms of NSCLC are not easily detectable, which contributes to its high mortality rate (the mortality in China was 37 per 100,000 population in 2014) (4,5). Systemic therapy, including chemotherapy, targeted therapy or immunotherapy combined with local radiotherapy, is the primary treatment for patients with inoperable advanced NSCLC. However, patients with advanced NSCLC who develop drug resistance after targeted therapy or experience disease progression following chemotherapy show poor response rates to subsequent chemotherapy regimens, with a median survival time of no longer than 10 months (6). Consequently, further research is essential to develop effective treatment

strategies for advanced NSCLC. Currently, targeted therapy is the first-line treatment for advanced NSCLC with positive driver genes. Second-line treatments include pemetrexed, docetaxel and programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. However, options for third-line and beyond are limited, particularly for patients with squamous cell carcinoma who do not respond to PD-1/PD-L1 inhibitors (2). In recent years, antiangiogenic drugs have emerged as an viable treatment option. VEGF and VEGFR are crucial factors in angiogenesis, which makes them effective targets for anticancer therapies (7,8). Anlotinib, an innovative oral multitarget receptor tyrosine kinase inhibitor, strongly inhibits multiple targets, such as VEGFR, platelet-derived growth factor receptors, fibroblast growth factor receptors and c-Kit. This inhibition can suppress tumor angiogenesis, cell proliferation, migration and invasion in various types of tumor cells, including lung tumor cells. (9-11). Anlotinib effectively suppresses tumor angiogenesis and proliferation signaling pathways, exhibiting broad-spectrum inhibitory effects on tumor angiogenesis and growth (12-14). The ALTER-0303 trial, a randomized, double-blind multicenter phase 3 clinical trial, reported that anlotinib was superior to placebo in the third-line treatment of patients with advanced NSCLC, while also highlighting its manageable toxicities and side effects (7). Based on these findings, the China Food and Drug Administration approved anlotinib as a third-line treatment for refractory advanced NSCLC on May 8, 2018 (15). According to the 2022 Chinese Society of Clinical Oncology (CSCO) guidelines, anlotinib has been accorded level I recommendations (class 1 evidence) as third-line therapy for stage IV NSCLC without driver genes (16).

S-1 is a combination of tegafur, gimeracil and oxo (17) that generates fluorouracil in both plasma and tumor tissues, exerting antitumor effects. Previous studies have reported the efficacy and tolerability of S-1 in advanced NSCLC, which led to its approval for NSCLC treatment in 2004 in Japan (18,19). Additionally, combining antiangiogenic drugs with chemotherapy has shown promise for lung cancer treatment (20). Clinical trials have reported that adding anti-angiogenic agents to conventional chemotherapy significantly improves progression-free survival (PFS) and overall survival (OS) rates in patients with advanced NSCLC (21-23).

A number of clinical trials have reported that adding anti-angiogenic drugs to conventional chemotherapy can significantly improve the PFS and OS of patients with advanced NSCLC (21-23). Novel antiangiogenic agents combined with chemotherapy are expected to further enhance survival outcomes for these patients. Both anlotinib and S-1 have demonstrated good responses in advanced NSCLC, with previous studies indicating favorable efficacy and safety outcomes when they are combined for the treatment of advanced NSCLC. However, systematic reviews of this combination therapy are lacking. Therefore, the present study aimed to systematically evaluate whether third-line or later-line treatment with anlotinib combined with S-1 for advanced NSCLC is more effective than anlotinib monotherapy. The findings of the present study could provide valuable insights into the clinical application of this combined regimen for the future treatment of NSCLC.

Materials and methods

Literature retrieval. A systematic evaluation and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and the PRISMA extension statement for network meta-analysis (24) (Fig. 1).

As of January 10, 2024, two investigators independently conducted comprehensive literature searches using the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/),Embase (https://www.embase.com/landing?status=grey), Web of Science (https://www.webofscience.com/wos/woscc/basic-search), Cochrane Library (https://www.wiley.com/en-cn/professionals), CMB (https://www.sinomed.ac.cn/index.jsp) and China National Knowledge Infrastructure (https://www.cnki.net/). The search items included 'lung cancer', 'anlotinib' and 'S-1'. Additionally, original references, reviews and internal medicine clinical trial data were searched. Relevant studies were included regardless of publication status, language or publication year.

Inclusion and exclusion criteria. The following inclusion criteria were used for the present study: i) Patients clinically diagnosed with advanced NSCLC; ii) randomized controlled clinical studies evaluating the combination of anlotinib and S-1 in the treatment of advanced NSCLC; and iii) treatment regimen is third-line or later-line. The following exclusion criteria were used for the present study: i) Studies with missing efficacy and adverse reaction data; ii) studies based on duplicate patient samples; iii) case studies, reviews, abstracts and conference reports; and iv) non-clinical randomized controlled trials.

Data extraction and quality assessment. A total of two researchers independently screened the literature, extracted data based on the inclusion and exclusion criteria and cross-checked the information. In cases of disagreement, a third researcher made the final judgment. The main content of the extracted information included: i) Title of the included study, author, source of literature and publication date; ii) number and age of patients, intervention measures and methods and treatment duration in the experimental and control groups; iii) study types and factors related to the risk of bias assessment; and iv) outcome indicators such as objective response rate (ORR), disease control rate (DCR), PFS, OS and adverse reactions.

The Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) was used to evaluate the included studies. It includes the following contents: i) Random sequence production; ii) allocation hiding; iii) blinding the subjects and investigators; iv) blinding outcome assessors; v) incomplete data; vi) selective result reporting; and vii) other biases (25,26).

Statistical analysis. The meta-analysis was conducted using RevMan (version 5.3) software (Cochrane Collaboration). Odds ratios (OR) and 95% confidence intervals (Cis) were used for binary categorical variables. For continuous outcome measures, mean differences (MD) or standardized MD (SMD) and 95% CI were calculated. The χ^2 test was used to determine heterogeneity among the included studies. Due to the clinical

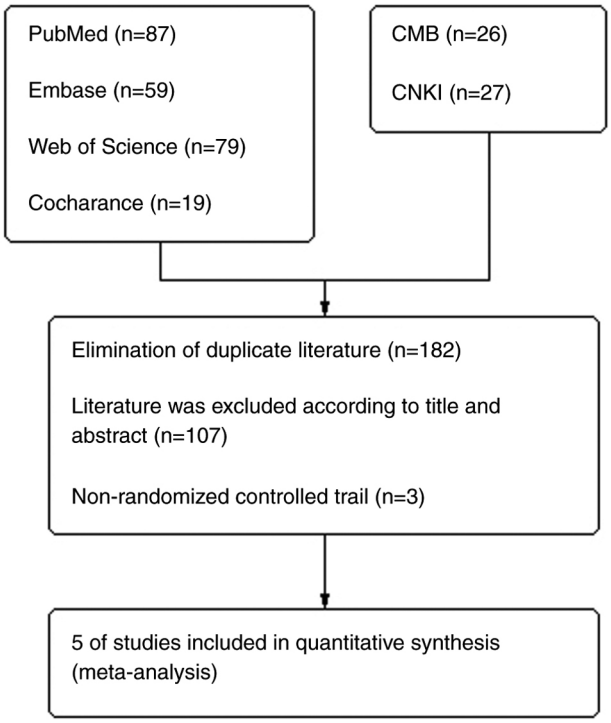

Figure 1. Literature retrieval and screening process of the present study. CMB, China Biology Medicine; CKNI, China National Knowledge Infrastructure.

heterogeneity of the studies, a random-effects model was used for the meta-analysis. The I^2 statistic assessment was used to estimate the curative effect of heterogeneity in the results of the meta-analysis. According to the statistical standards, each ending heterogeneity could be divided into the following categories: i) Not important (I^2, 0-40%); ii) medium (I^2, 30-60%); iii) significant (I^2, 50-90%); or iv) equivalent (I^2, 75-100%). If there were overlapping values, it was necessary to observe the I^2 values: i) the magnitude and direction of the effect; and ii) the strength of evidence of heterogeneity (e.g., P-values obtained from χ^2 tests, or CIs for I^2) (27). If heterogeneity was too large to be resolved, descriptive analyses were performed. Further, publication bias was estimated using funnel plots, Begg's test and Egger's test (28).

Results

Literature search results and basic features of included studies. A total of five randomized controlled trials were included. The basic characteristics of the included studies were presented in Table I (29-33).

Literature quality evaluation. In two articles, the investigators did not describe whether random methods were used in the sequence generation process, so whether there was a selection bias caused by inappropriate methods of generating random sequences was unknown (Fig. 2). Therefore, the text selection bias was not clear in these two cases (29,31). In addition, five articles did not clarify whether researchers understood the distribution, which could lead to selective bias (29-33). The subjects of the five articles may have received different medications within their groups, therefore, there was a risk of implementation bias across all studies (29-33). Furthermore, two studies did not report the expected long-term results, namely OS and PFS, therefore, reporting bias was suspected (32,33).

Meta-analysis results

Drug efficacy. Long-term evaluations of drug efficacy included OS and PFS, whereas short-term evaluations focused on ORR and DCR (Fig. 3).

Median PFS (mPFS). mPFS was reported in three studies included (29-31), which encompassed a total of 202 patients (n=106 anlotinib plus S-1 group). There was considerable heterogeneity among the studies (P<0.00001; I^2=97%). The results indicated that PFS in the anlotinib combined with the S-1 group was significantly longer compared with that of the control group Weighted Mean Difference (WMD)=1.27; 95% CI 0.75, 1.79; P<0.00001). The mPFS of the anlotinib combined with S-1 group was 3.87-6.34 months, which was 1.27 months longer compared with that of anlotinib alone group. (Fig. 3A). After excluding the study published by Xie *et al* (29), which contributed to the heterogeneity (WMD=1.50; 95% CI 1.44, 1.56; P<0.00001; I^2=0%), the heterogeneity of PFS decreased.

mOS. The mOS was reported in three of the included studies (29-31), which comprised a total of 202 patients, with 106 patients in the anlotinib plus S-1 group. There was significant heterogeneity among these studies (P<0.00001; I^2=91%). These results demonstrated that PFS in the anlotinib combined with the S-1 group was significantly longer than that in the control group (WMD=1.77; 95% CI 1.30, 2.25; P<0.00001). The mOS of anlotinib combined with S-1 group was 8.07-10.59 months, which was 1.77 months longer compared with that of the anlotinib alone group (Fig. 3B). After excluding the Kong study (31), which contributed to the heterogeneity (WMD=1.96; 95% CI 1.66, 2.26; P<0.00001; I^2=12%), the heterogeneity of OS decreased.

ORR. ORR was reported in five of the included studies (29-33), which encompassed a total of 317 patients, with 163 patients in the anlotinib plus S-1 group. Homogeneity among the studies was not statistically significant. (P=0.83; I^2=0%). These results indicated that the ORR of the anlotinib combined with the S-1 group was significantly higher compared with that in the control group (RR=3.00; 95% CI 1.64, 5.49; P=0.004) (Fig. 3C).

DCR. Further, five studies reported the DCR (29-33), which totaled 317 patients, with 163 in the anlotinib plus S-1 group. Homogeneity was not statistically significant among the studies (P=0.87; I^2=0%). These results indicated that the DCR of the anlotinib combined with the S-1 group was significantly higher compared with that in the control group (RR=2.13; 95% CI 1.27, 3.57; P=0.004) (Fig. 3D).

Adverse reactions. Adverse drug reactions were evaluated across various categories, which included gastrointestinal adverse reactions, bone marrow suppression, hypertension, fatigue, proteinuria, hepatic and renal insufficiency and functional hand-foot syndrome (Fig. 4).

i) *Gastrointestinal adverse reactions*. All five studies reported gastrointestinal adverse reactions (29-33), with a total of 317 patients which included 163 in the anlotinib plus S-1 group. Analysis of the studies demonstrated that there was not significant homogeneity among the studies (P=0.27; I^2=23%). These results indicated that the anlotinib combined with S-1

Table I. Basic characteristics of the included studies.

First author, year	Patient group	Number of cases, n	Mean age, years	Male/ female, n	Adeno-carcinoma/ squamous cell carcinoma, n	Treatment options	Median overall survival, months	Median progression-free survival, months	Outcomes measured	(Refs.)
Xie *et al*, 2020	Experimental	40	63.1	36/4	0/40	Anlotinib 12 mg/d qd D1-14 + S-1 25 mg bid D1-14	8.07	3.87	PFS, OS,OOR, DCR, gastrointestinal reactions, hypertension and fatigue	(29)
	Control	30	61.7	24/6	0/30	Anlotinib 12 mg/d qd D1-14	6.17	3.00		
Liu, 2021	Experimental	36	55.32	22/14	13/23	Anlotinib 10 mg/d qd D1-14 + S-1 40 mg bid D1-14	10.59	6.34	PFS, OS, OOR, DCR, gastrointestinal reactions, hypertension, fatigue, bone marrow suppressison, hand-foot dysfunction syndrome and proteinuria	(30)
	Control	36	55.21	21/15	24/12	Anlotinib 10 mg/d qd D1-14	8.23	4.83		
Kong, 2021	Experimental	30	59	18/12	24/6	Anlotinib 12 mg/d qd D1-14 + S-1 40-60 mg qd D1-14	8.1	5.2	PFS, OS ORR, DCR, gastrointestinal reactions, hypertension, fatigue, bone marrow suppression, abnormal liver and kidney function, hand-foot dysfunction syndrome and proteinuria	(31)
	Control	30	63	14/16	23/7	Anlotinib 12 mg/d qd D1-14	3.7	6.7		
Zhan *et al*, 2021	Experimental	22	61.71	15/7	22/10	Anlotinib 12 mg/d qd D1-14 + S-1 40-60 mg qd D1-14	N/A	N/A	ORR, DCR, gastrointestinal reactions, hypertension, fatigue, bone marrow suppression, abnormal liver and kidney function, hand-foot dysfunction syndrome and proteinuria	(32)
	Control	23	61.71	16/7	12/11	Anlotinib 12 mg/d qd D1-14	N/A	N/A		

Table I. Continued.

First author, year	Patient group	Number of cases, n	Mean age, years	Male/ female, n	Adeno-carcinoma/ squamous cell carcinoma, n	Treatment options	Median overall survival, months	Median progression-free survival, months	Outcomes measured	(Refs.)
Wang *et al*, 2022	Experimental	35	60.41	18/17	18/17	Anlotinib 8-12 mg/ d qd D1-14 + S-1 40-60 mg qd D1-14	N/A	11.8	ORR, DCR, gastrointestinal reactions, hypertension, fatigue, bone marrow suppression, abnormal liver and kidney function, hand-foot dysfunction syndrome and proteinuria	(33)
	Control	35	59.82	22/13	23/12	Anlotinib 8-12 mg/ d qd D1-14	N/A	10.2		

OOR, overall response rate; DCR, disease control rate; N/A, not applicable; qd, quaque die; bid, bis in die; D1-14, from day 1 of treatment to day 14 of treatment; mg/d, mg/day.

group had significantly more gastrointestinal adverse reactions compared with the control group (RR=1.72; 95% CI 0.95, 3.13; P=0.07) (Fig. 4A).

ii) *Bone marrow suppression*. Myelosuppression was reported in four studies (30-33), encompassing a total of 247 patients, with 123 in the anlotinib plus S-1 group. Homogeneity among the studies was not statistically significant (P=0.40; I^2=0%). Myelosuppression was significantly higher in the anlotinib combined with the S-1 group compared with the control group (RR=2.62; 95% CI 1.35, 5.10; P=0.005) (Fig. 4B).

iii) *Hypertension*. Hypertension was reported in 5 studies (29-33), which involved 317 patients, with 163 patients in the anlotinib plus S-1 group. Homogeneity among the studies was not statistically significant (P=0.75; I^2=0%). These results demonstrated a higher incidence of hypertension in the anlotinib plus S-1 group compared with the control group (RR=1.30; 95% CI 0.81, 2.08; P=0.28), although this difference was not statistically significant (Fig. 4C).

iv) *Fatigue*. Fatigue was reported in 5 included studies (29-33), in a total of 317 patients, including 163 patients in the anlotinib plus S-1 group. Homogeneity among the studies was not statistically significant (P=0.79; I^2=0%). These results indicated that the incidence of fatigue in the anlotinib combined with S-1 group was significantly higher compared with the control group (RR=1.66; 95% CI 1.04, 2.66; P=0.03) (Fig 4D).

v) *Proteinuria*. Proteinuria was reported in 4 of the included studies (30-33), which involved 247 patients, with 123 patients in the anlotinib plus S-1 group. Homogeneity was not statistically significant among the studies (P=0.74; I^2=0%). These results indicated that the incidence of proteinuria in the anlotinib plus S-1 group was higher compared with that in the control group (RR=1.16; 95% CI 0.63, 2.13; P=0.63); however, this difference was not statistically significant (Fig. 4E).

vi) *Hepatic and renal insufficiency*. Hepatic and renal dysfunctions were reported in 3 of the included studies (29-33), which involved 175 patients, including 87 in the anlotinib plus S-1 group. Homogeneity was not statistically significant among the studies (P=0.65; I^2=0%). These results indicated that the incidence of hepatic and renal insufficiency in the anlotinib plus S-1 group was higher compared with that in the control group (RR=1.26; 95% CI 0.59, 2.67; P=0.55); however, this difference was not statistically significant (Fig. 4F).

vii) F*unctional hand-foot syndrome*. Functional hand-foot syndrome was reported in four of the included studies (30-33), which involved 247 cases, with 123 in the anlotinib plus S-1 group. Homogeneity among the studies was not statistically significant (P=0.99; I^2=0%). These results demonstrated that the incidence of functional hand-foot syndrome in the anlotinib plus S-1 group was higher compared with that in the control group (RR=1.43; 95% CI 0.78, 2.63; P=0.25); however, the difference was not statistically significant (Fig. 4G).

Discussion

Lung cancer is a significant public health concern due to its high morbidity, mortality and recurrence rates (34). Despite advancements in treatment options over the past four decades, treatment strategies for advanced NSCLC, such as third-line

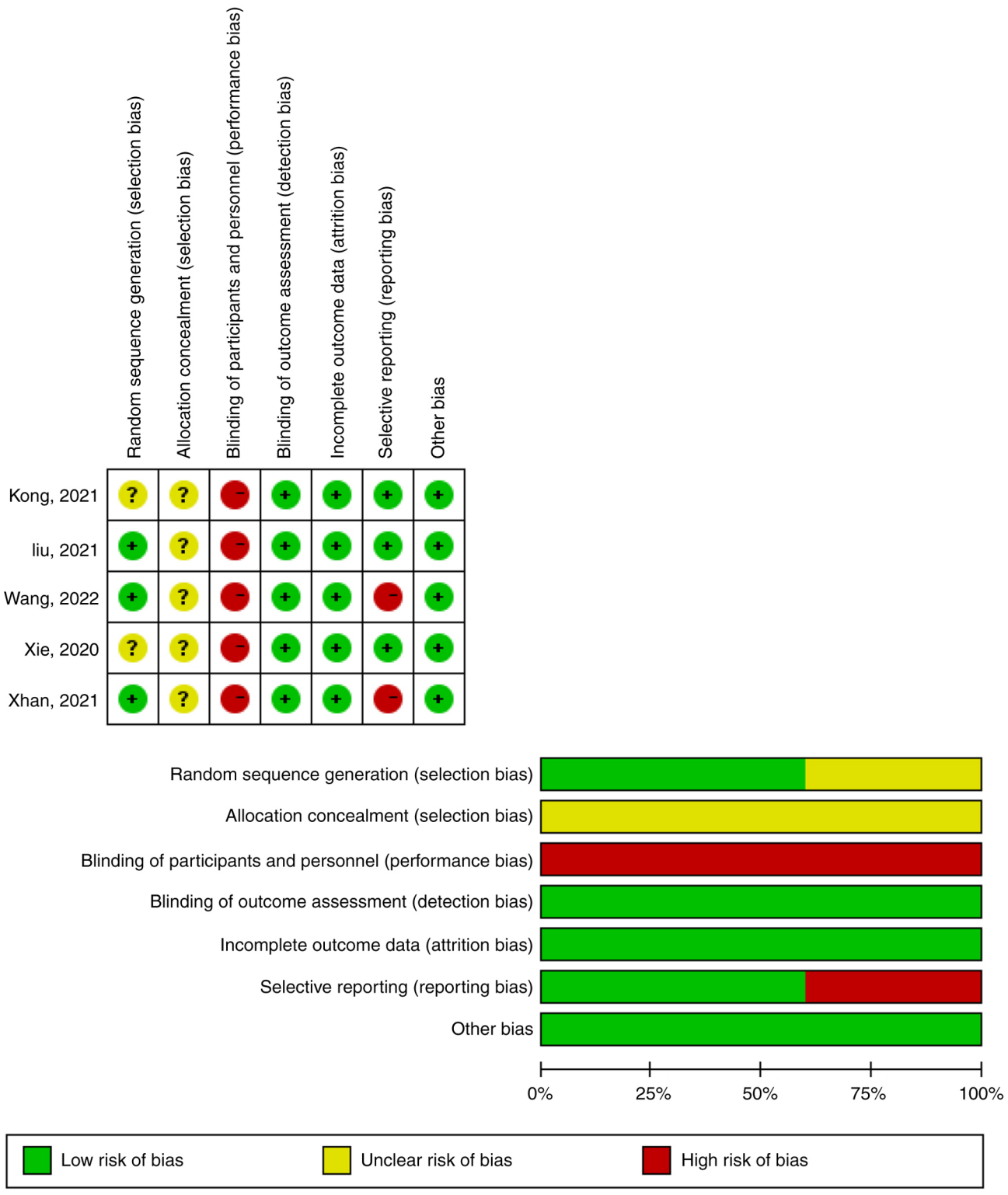

Figure 2. Detailed results of bias assessment.

treatments, have remained elusive. Currently, anlotinib and single-agent chemotherapy, such as platinum, pemetrexed, docetaxel and paclitaxel, are the standard recommendations for patients with NSCLC for whom third-line or later-line treatment was not successful in China. However, these patients often derive limited benefits from single-agent chemotherapy (2,3). For instance, the mPFS of the third-line treatment with platinum, pemetrexed, docetaxel and paclitaxel intravenous chemotherapy ranges from 0.7-1.4 months and mOS from 4.0-6.3 months. Moreover, after multiline treatment, patients are generally in poor condition and often cannot tolerate the toxic and side effects of the above intravenous chemotherapy drugs (35). Given these challenges, there is a pressing clinical need for novel and effective antitumor therapies. Anlotinib and S-1 represent promising oral antineoplastic drugs that are convenient for daily use. The present study conducted

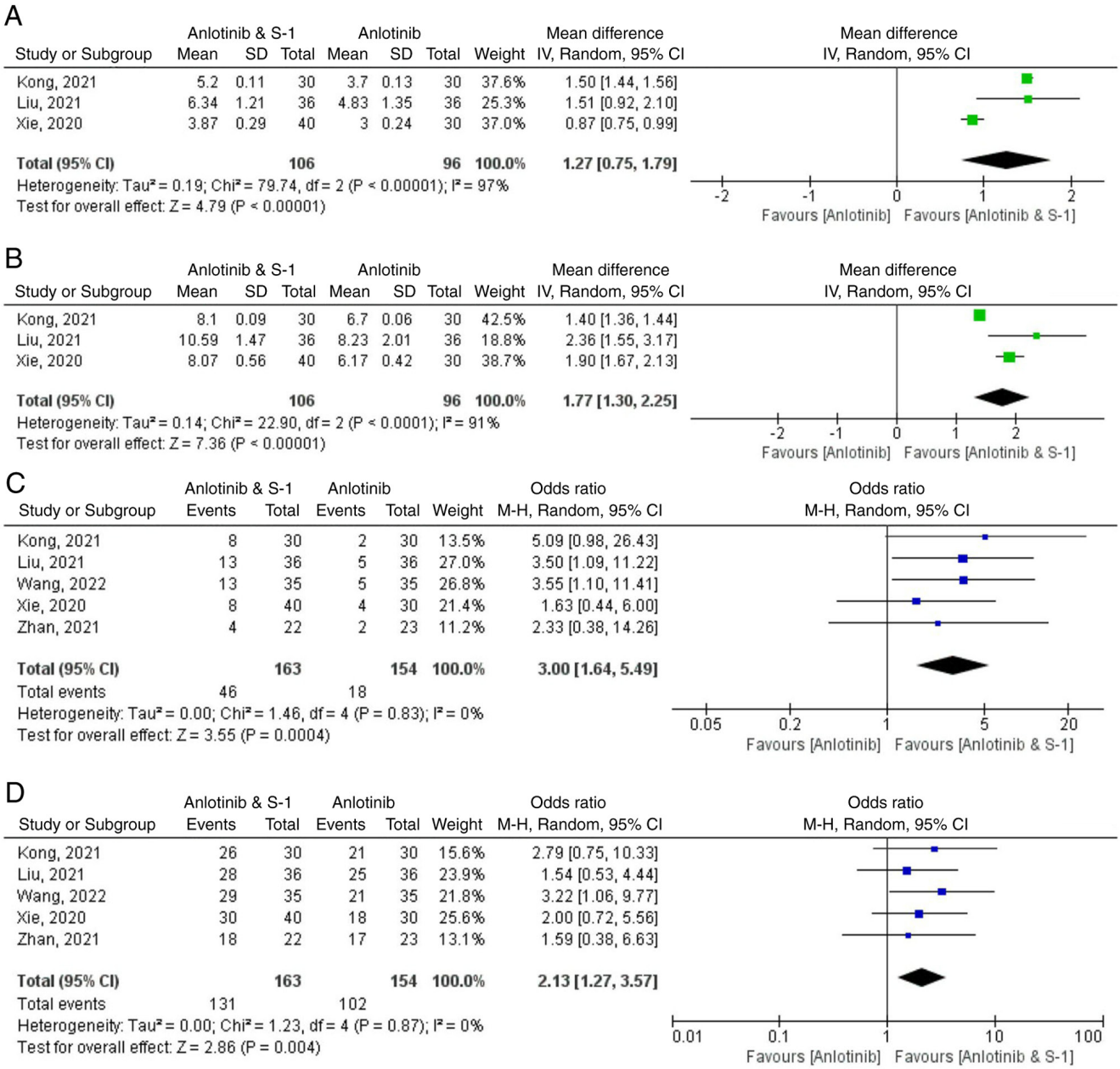

Figure 3. Forest plots depicting the outcomes of the included studies. (A) Progression-free survival, (B) Overall survival, (C) Overall response rate and (D) Disease control rate. Study weights for continuous data are shown in green and study weights for dichotomous data are shown in dark blue. IV, Inverse Variance; M-H, Mantel-Haenszel.

a comprehensive systematic review and meta-analysis to evaluate the efficacy and safety profile of combining anlotinib with S-1 compared to anlotinib alone in patients with advanced NSCLC. To the best of our knowledge, the present study was the first meta-analysis to compare anlotinib combined with S-1 vs. anlotinib alone in patients with advanced non-small cell lung cancer using the PubMed, Embase, Web of Science, Cochrane Library, CMB and CNKI databases. Therefore, the results detailed in the present study were innovative and novel.

In previous years, the exploration of antiangiogenic drugs in combination with chemotherapy has shown considerable progress in lung cancer treatment. A number of clinical trials have demonstrated that integrating antiangiogenic drugs with conventional chemotherapy can reduce drug resistance and significantly improve treatment efficacy (21-23,36,37). The present study did not retrieve data from the included literature on the cost-effectiveness of combination therapy with anlotinib compared with other therapies, such as single-agent chemotherapy or anlotinib single-agent targeted therapy. Therefore, the present study discussed the therapeutic difference between efficacy and adverse reactions caused by anlotinib combined with S-1 and anlotinib alone.

The findings from the present study highlighted significant improvements in OS, PFS, ORR and DCR in patients treated with anlotinib combined with the S-1 group, compared with those treated with anlotinib alone. Specifically, the combination therapy extended mPFS and mOS by 1.27 months and 1.77 months, respectively, when compared with the anlotinib alone group. These results highlighted the promising potential of this regimen in the treatment of patients with advanced

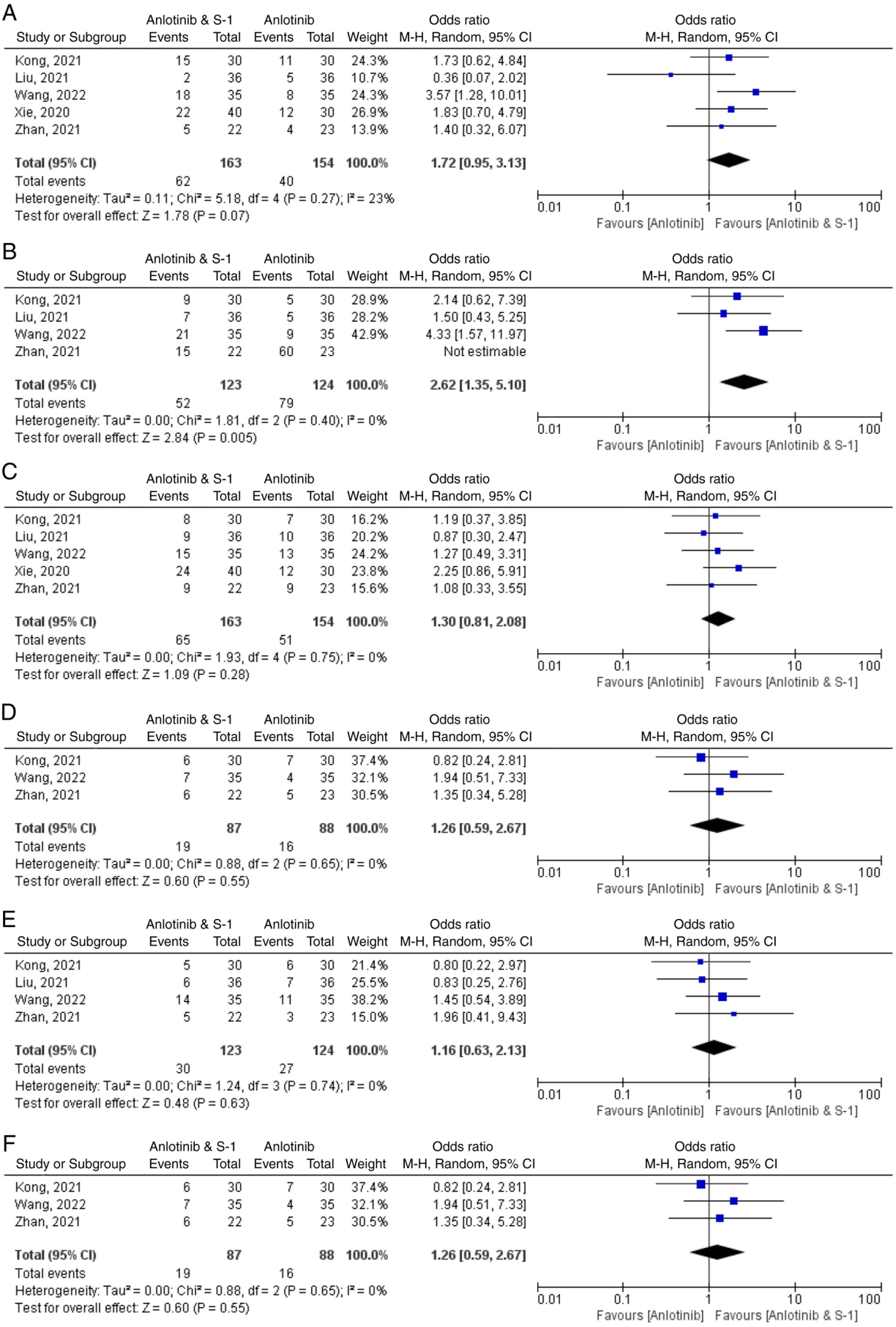

Figure 4. Forest plot illustrating adverse reactions associated with the treatment regimens. (A) Gastrointestinal adverse reactions, (B) Bone marrow suppression, (C) Hypertension, (D) Fatigue, (E) Proteinuria, (F) Hepatic and renal insufficiency and (G) Functional hand-foot syndrome. Study weights for dichotomous data are shown in dark blue. M-H, Mantel-Haenszel.

NSCLC. Compared with single-agent chemotherapy, the mOS and mPFS achieved with anlotinib combined with the S-1 group showed a notable increase. These results indicated that the combination of anlotinib and S-1 yielded favorable clinical outcomes compared with the single agent chemotherapy. In China, anlotinib, in combination with chemotherapy, has been studied for the treatment of advanced NSCLC. A retrospective study compared the efficacy of anlotinib with chemotherapy compared with that of chemotherapy alone. These results showed that the DCR of the combination group was significantly higher than that of the chemotherapy alone group (78% vs. 51%, respectively) and the mPFS of the combination group was 1.5 months longer than that of the chemotherapy alone group (5.0 months vs. 3.5 months) (38). These results suggest that anlotinib combined with chemotherapy can improve clinical efficacy. In another retrospective study by Meng *et al* (39), anlotinib combined with chemotherapy was compared with bevacizumab combined with paclitaxel and carboplatin for the treatment of advanced lung adenocarcinoma. The results showed that the ORR and DCR of anlotinib combined with chemotherapy and bevacizumab combined with chemotherapy were significantly better compared with those of chemotherapy alone and that the ORR and DCR of the anlotinib group were higher compared with those of the bevacizumab group. Collectively, the aforementioned studies suggest that anlotinib combination therapy offers enhanced clinical benefits compared with chemotherapy, immunotherapy or targeted therapy alone.

Previous studies have reported the pharmacological mechanisms underlying the combined administration of anlotinib, with studies showing the effect of anlotinib on tumor blood vessels (40-43). Tumor blood vessels are often characterized by pericyte shedding, abnormal basement membranes and increased vascular leakage, which leads to inadequate blood perfusion, increased interstitial fluid pressure, difficulty in drug delivery and persistent hypoxia (40). Anlotinib functions by inhibiting tumor angiogenesis, thereby reducing nutrient supply to tumors. Moreover, it promotes a process known as tumor vascular matrix reprogramming. This mechanism involves enhancing the integrity of tight junctions in tumor endothelial cells, which increases pericyte coverage around blood vessels and facilitates vascular normalization to improve blood vessel morphology and enhance tumor blood perfusion. This ultimately leads to the restoration of normal tumor interstitial fluid pressure and an increased distribution of chemotherapy and other drugs in the tumor tissue for a more effective antitumor effect. Therefore, anlotinib can improve the antitumor effects of chemotherapy drugs, targeted drugs or immune checkpoint inhibitors and enhance tumor tissue distribution of drugs (41-43). Previous studies reported that anlotinib combined with S-1 was superior when compared with anlotinib alone in the treatment of advanced NSCLC, which suggests that anlotinib improves the distribution of anti-tumor drugs in tumor tissues and enhances the anti-tumor effect (29-33). The advantages of combination therapy with anlotinib still require further elucidation through additional clinical studies. The efficacy of anlotinib combined with other antineoplastic drugs and whether the adverse reactions of the combination drugs are controllable warrants further study. Additional studies are required to determine any efficacy advantages and potential adverse reactions caused by anlotinib combined with other antineoplastic drugs, such as chemotherapy drugs or immune checkpoint inhibitors, compared with other antineoplastic drugs alone. Furthermore, the specific use and medication management of the combination drugs in clinical practice (such as drug dosage selection, management of adverse drug reactions, formulation of treatment cycles, etc.) still need a large number of clinical trials and practice to accumulate experience in the treatment of advanced tumors with anlotinib, in order to form robust evidence-based medical guidelines to inform clinical practice.

A previous study by Kong (31) reported that the efficacy of anlotinib combined with S-1 was not significantly influenced by the previous lines of treatment received by patients, possibly because the mechanism of action of this combination is entirely independent of previous treatments. Furthermore, patients who have received prior antiangiogenic therapy or EGFR-TKI treatment can still derive benefits from continuing with anlotinib, which can effectively sustain treatment outcomes for patients with advanced NSCLC. Traditionally, an increase in the number of chemotherapy drugs used can lead to tumor cell drug resistance. Long-term exposure to chemotherapy may result in both functional and structural cross-resistance to different drugs, thus reducing the effectiveness of subsequent treatments (44). Xie *et al* (29) reported that by improving comorbidity management, patients' performance status scores may improve even after multiple lines of treatment failure, which could enable patients to receive systemic treatment again. These studies highlight the potential advantages of combining anlotinib and S-1 in clinical practice.

Data on adverse effects from a study of antirotinib combined with chemotherapy vs. chemotherapy (docetaxel, gemcitabine, vinorelbine or pemetrexel) in advanced NSCLC suggest that AEs is significantly more common in the combined treatment group compared with the chemotherapy alone group. The incidence of adverse events, such high blood pressure, hand, foot and skin reactions and hypothyroidism was significantly higher in the joint treatment group compared with the chemotherapy alone group. According to the CTCAE 5.0 classification of adverse events (divided into grade I, II, III and IV) (45), in the joint group, adverse reactions of grade III and grade IV are mainly bone marrow suppression and gastrointestinal reaction, but there were no statistically significant difference between the joint group and the anlotinib group (31,38). In general, most toxicity was limited to grades I or II and was both well-tolerated and controlled (38). The present systematic review of the adverse effects of anlotinib combined with S-1 vs. anlotinib alone highlighted that the anlotinib group experienced fewer gastrointestinal adverse reactions, bone marrow suppression, hypertension, fatigue, proteinuria, liver and kidney dysfunction and hand and foot dysfunction compared with the anlotinib combined with S-1 group. The differences between the bone marrow suppression and fatigue results of the two groups were statistically significant and demonstrated heterogeneity. S-1 is a cytotoxic chemotherapeutic agent and previous studies have reported that adverse reactions to S-1 mainly manifest in the blood and digestive systems. Adverse reactions observed with the combination therapy of

anlotinib and S-1 include bone marrow suppression, anorexia and fatigue and were mostly grade I and II reactions, with a low incidence of grade III reactions (46,47). This suggested that compared with anlotinib monotherapy, the incidence of adverse events is significantly increased in the combined therapy group compared with the chemotherapy alone group, primarily due to S-1 chemotherapy-related reactions involving the blood and digestive systems. No deaths were caused by adverse reactions in the anlotinib combined with S-1 group. This indicates that combination therapy did not significantly increase the incidence of adverse reactions. Most adverse reactions could be treated through drug intervention, with a few patients discontinuing treatment due to adverse reactions. For the majority of advanced NSCLC patients who are suitable for three-line treatment, the biggest challenge in completing treatment lies in the need for long-term systemic therapy, which may lead to repeated hospitalizations and intolerable drug side effects. Anlotinib and S-1 are both oral capsule preparations. The combination of anlotinib and S-1 can significantly improve patient convenience by allowing follow-up in outpatient clinics, reducing the need for repeated hospitalizations and enabling advanced cancer patients to reintegrate into society and family life, thereby enhancing their overall quality of life. Furthermore, oral anticancer drugs generally have lower severity and incidence of adverse reactions compared with intravenous antineoplastic drugs. For example, a study on the efficacy and adverse reactions of oral S-1 and intravenous fluorouracil (5-FU) in the chemotherapy of rectal cancer showed that S-1 can serve a similar clinical effect with 5-FU in the chemotherapy of advanced rectal cancer, as both S-1 and 5-FU are fluorouracil chemotherapeutic drugs. The two drugs cause few adverse reactions and patients exhibit good tolerance, therefore, both these drugs have value for clinical applications (48). The heterogeneity of mPFS was mainly derived from the study reported by Xie *et al* (29). The population included in this study included all patients with EGFR mutation-negative advanced squamous cell lung cancer at baseline, whereas the populations included in the other two studies included a mix of patients with EGFR mutation-positive status, lung adenocarcinoma and lung squamous cell carcinoma (30,31). Subgroup analyses of EGFR mutation status and lung cancer pathological types were not performed because detailed information was not available. The heterogeneity of mOS was mainly derived from Kong's study (31) and may be related to differences in regional economic development in China. Economic development is closely related to the survival rates of patients with cancer (49). The aforementioned study was conducted in Liaoning Province, China, whereas the other two studies were conducted in the Guangdong Province, China. As one of the most developed provinces in China, the Guangdong Province has a higher level of economic development than most other regions in China, including Liaoning Province (50), which may explain a number of differences observed between the Kong study and those of the other two studies.

The present study had some limitations. There were five studies included in this paper, of which three were prospective studies and two were retrospective studies. The sample size of the included studies was not calculated according to the response rate to anlotinib in the treatment of advanced non-small-cell lung cancer. According to the ORR (anlotinib combined with S-1 was designed to be ~30%) as the primary endpoint, the effective rate of anlotinib monotherapy was 9%, the two-sided α was 0.05 and the weight β was 80%. According to the 1:1 enrollment design, 52 patients were required for each group, so a meta-analysis comprised of five studies was required to include at least 520 patients. However, the actual sample size of the five studies was 317. Therefore, the sample size was small and it could be suggested that the subjects of the present study were not sufficiently representative and that there were some limitations in external validity. Systematic reviews based on small sample randomized controlled trials (RCTs) may lead to a greater risk of publication bias (51,52). Moreover, retrospective studies cannot guarantee that conditions other than intervention measures are the same, which may cause bias. A considerable part of the information in the present study was obtained from studies with an uncertain risk of bias. In addition, the included studies provided baseline data including patient demographics and NSCLC staging but did not analyze treatment outcomes related to patient demographics and NSCLC staging baseline data, which prevented the present study from conducting group analysis. As patient sex, age and condition (such as lung cancer classification, whether there is brain metastasis and gene mutation) were not explored in the included articles with respect to anlotinib S-1 treatment, the present study lacked access to certain data and was unable to consider other patient characteristics, such as sex, age or previous lung disease. In future research, there is a requirement to expand sample size, reduce bias and design a prospective multicenter RCT.

In summary, the present study suggested that combining anlotinib with S-1 may offer superior efficacy compared with anlotinib alone as a third- or later-line treatment for advanced NSCLC. In terms of adverse reactions, the combination therapy was generally well-tolerated. The present meta-analysis demonstrated that anlotinib combined with S-1 was superior to the anlotinib monotherapy recommended by the CSCO guidelines for NSCLC, which may provide clinicians with new ideas for the treatment of patients with advanced NSCLC, who have failed multiple lines of treatment. After the efficacy and adverse reactions of the dual drug combination and the single drug combination were analyzed, it could be suggested that further clinical trials with a larger sample size are required to promote the standardization and recommendation of the dual drug combination in the treatment of advanced NSCLC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HX and YL drafted the manuscript, HX, YL, WT and XY participated in the data review and collection for the study. XD conceived the study and reviewed and edited the manuscript. HX and XD confirm the authenticity of all the raw data. All authors read and approved the final version of the 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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