Systematic Review and Meta-Analysis

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Anlotinib, a novel TKI, as a third-line or further-line treatment in patients with advanced non-small cell lung cancer in China

A systemic review and meta-analysis of its efficacy and safety

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Abstract

Purpose: In this meta-analysis and systemic review, we focused on the effectiveness and safety of anlotinib in patients with advanced non-small cell lung cancer(NSCLC).

Methods: The databases of PubMed, EMBASE, Cochrane Library, CNKI, Wanfang, and CBM were searched by 2 investigators up to April 2020. Titles and abstracts of all records were screened and eligible publications were retrieved in full. Review Manager (version 5.2, Cochrane Library) was used for data analysis. The outcomes of interest were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse event (TRAE). Data was pooled for quantitative analysis and the effect size was reported as hazard ratio for survival outcomes and odds ratio (OR) for safety outcomes, both with a random-effects model.

Results: A sum of 1480 patients were included in 11 trials ranging from 2018 to 2020. Substantial improvements of PFS, OS, and DCR were observed in patients treated with anlotinib alone or in combination with other conventional treatment. Accompanied TRAE included statistically significant higher risk for hypertension (OR = 11.05, 95% confidence interval [CI] = 7.85–15.55, $P < .001$), hepatic dysfunction (OR = 1.96, 95% CI = 1.29–2.68, $P < .001$), diarrhea (OR = 2.20, 95% CI = 1.17–4.16, $P < .05$), and hemoptysis (OR = 2.59, 95% CI = 1.71–3.93, $P < .01$).

Conclusions: Our study suggested that anlotinib as maintenance therapy for advanced NSCLC patients is associated with prolonged PFS and OS as well as DCR improvement, but it was accompanied by increased risk of TRAE, such as hypertension, hepatic dysfunction, diarrhea and hemoptysis. Although much effort has been made to clinical trials of anlotinib, further studies are warranted to provide more convincing evidence.

Abbreviations: CI = confidence interval, DCR = disease control rate, LC = lung cancer, NSCLC = non-small cell lung cancer, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RCTs = randomized controlled trials, TKIs = tyrosine kinase inhibitors, TRAE = treatment-related adverse event.

Keywords: advanced non-small cell lung cancer, anlotinib, systemic review and meta-analysis, TKI, tyrosine kinase inhibitors

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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1. Introductions

Worldwide, lung cancer (LC) remains the top leading cause of cancer-related deaths with a 5-year survival rate of less than 20%.[1,2] Non-small cell lung cancer (NSCLC), usually found to be at advanced stage when firstly diagnosed, constitutes the largest proportion of lung cancer cases (approximately 80%–85%).[3] It was reported that LC patients with stage IV had a 1-year survival rate of just 15% to 19% compared with 81% to 85% for stage I.[4] Data have shown that LC deaths in China, which accounts for one fifth of the world's population, are more than one third of the world total number of LC deaths.[5,6]

Historically, the Food and Drug Administration approved standard regime for advanced NSCLC is platinum doublet chemotherapy.[7] However, the choice of platinum-based doublet has generally been influenced by the histologic subtype.[8] In recent years, immunotherapy combined with chemotherapy has been recommended as the first-line agent in metastatic LC. Researchers have certified that the combination of programmed cell death-1/programmed death ligand-1 inhibitors and chemotherapy as a promising therapeutic option for advanced NSCLC.[9]

Accumulated evidences have confirmed that multi-target antiangiogenic-tyrosine kinase inhibitors (TKIs), one of the

antiangiogenic agents, combined with chemotherapy, targeted therapy and immunotherapy can confer a significant overall survival (OS) benefit to NSCLC patients.[10,11]

Anlotinib, as a novel TKI, has been approved by the China National Medical Products Administration for patients in China since 2018. According to data from clinical trials, anlotinib has brought a statistically and clinically significant improvement in survival among patients with advanced NSCLC who have progressed on at least 2 lines of prior systemic chemotherapies.[12] Therefore, in this systemic review and meta-analysis, we focused on the effectiveness and safety of anlotinib on advanced NSCLC patients.

2. Materials and methods

2.1. Search strategy

Two authors searched PubMed, EMBASE, Cochrane Library, CNKI, Wanfang, and CBM databases (up to April 2020) without any language restrictions. Search terms included "Anlotinib," "AL-3818," "lung cancer," " lung carcinoma," "lung neoplasm," "NSCLC". In addition, we also checked each reference listed in the included studies, all related review and guidelines to include any previously ignored papers.

This systematic review has been registered in PROSPERO, the registration ID is CRD42020180480.

2.2. Participants

2.2.1. Inclusion criteria.

1. Age between 18 and 80 years old.
2. Randomized controlled trials (RCTs);
3. The study population consisted of patients with histologically or cytologically proved stage IIIB or IV NSCLC;
4. The study contained an intervention group: Anlotinib or in combination with other conventional treatment, and a control group: Placebo or other conventional treatment;
5. at least one of the following outcomes: disease control rate (DCR), progression-free survival (PFS), OS and treatment related adverse event (TRAE) were reported.

2.2.2. Exclusion criteria.

1. Age $\leq$18 or $\geq$80 years old.
2. not RCTs;
3. The patients in the study were not histologically or cytologically proved to be stage IIIB or IV NSCLC;
4. The intervention group was not anlotinib or combination of anlotinib and other conventional treatment;
5. incomplete outcomes were reported;
6. The number of patients in any arm was less than 15.

2.3. Outcome measures

The following outcomes were reported: DCR, PFS, OS and treatment-related toxicities (adverse event grade $\geq$3, TRAEs).

2.4. Risk of bias assessment

Two authors assessed the risk of bias of each eligible study using the Cochrane risk of bias tool which was advised by the Cochrane Handbook as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The judgment of each domain had 3 options (low risk, unclear risk, and high risk). Two authors independently assessed the risk of eligible studies. We solved all disagreements occurring in assessing the risk of each eligible study.

2.5. Study selection and data collection

Two authors independently searched the articles for inclusion, as described. Titles and abstracts of all records were screened and eligible publications were retrieved in full. Hand searching of reference lists of relevant studies and reviews was used to identify additional articles. Differences in judgment during the selection process were settled by discussion and consensus. The methodological quality of the studies was assessed independently by 2 authors using the Jadad scale, and the study quality was settled by consensus.

2.6. Quality assessment

Improved Jadad scale was applied to assess the quality of RCTs including randomization, blinding of participants, personnel, outcome assessors, incomplete outcome data, and other threats to validity.[13] Four to 7 points represent for high quality, while 1 to 3 points for low quality.

2.7. Statistical analysis and data synthesis

Review Manager (version 5.2, Cochrane Library) was used for statistical analysis. Six researchers participated in this work: 2 conducted the data extraction independently, 2 conducted the data synthesis independently, and 2 carried out the data analysis to resolve any discrepancies, and ensure the accuracy of results. The heterogeneity of the included studies was analyzed by using I^2, and if data shows high level of heterogeneity ($I^2 > 50\%$), subgroup analyses was performed to investigate the sources by age, the histological types, EGFR mutation or the side effects, etc. If more than ten articles were included, a meta-regression analysis was performed to further explore the potential effects of the heterogeneity and confounders on the outcomes.

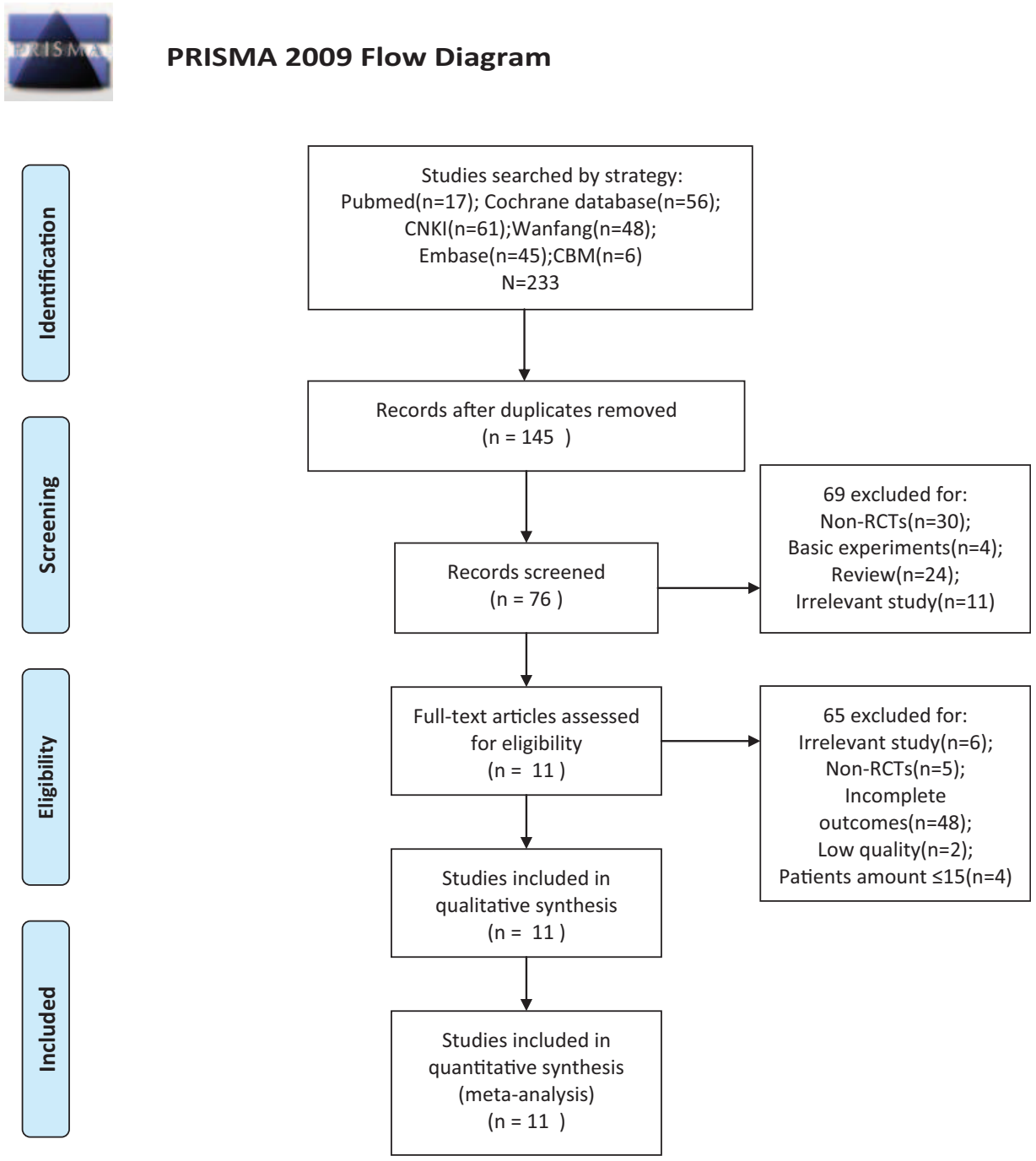
2.8. Ethical approval and patient consent

The ethical approval and informed patient consent were stated explicitly in the part of study design and patients of the original articles of all the included studies.

3. Results

3.1. Description of studies

The flow diagram was depicted as in Figure 1. Totally, 233 studies were initially searched by strategy and hand from the above 6 electronic databases (Fig. 1). After removal of 88 duplicate studies, 145 articles were left for screening. After reviewing by the titles and abstracts, we excluded 69 studies, including 30 non-RCTs, 4 basic experiments, 24 reviews, and 11 irrelevant studies. We retrieved the full texts of 76 articles for further evaluations, of which 65 studies were excluded, including 6 irrelevant studies, 5 non-RCTs, 48 incomplete outcomes, 2 low quality and sample size of 1 arm $\leq$15 (n=4). In the end, a total of 11 articles were included for this review.[14–25]



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For more information, visit www.prisma-statement.org.

Figure 1. Guidelines flow diagram of the included studies.

3.2. Characteristics of included studies

As shown in Table 1, a total of 1,480 NSCLC patients were included from year 2018 to 2020 with 1 phase II studies and 3 phase III studies. The baseline characteristics of the included trials were comparable between the intervention groups with the comparator groups. As to the histology of NSCLC, 8 trials referred to the Adenocarcinoma, 5 referred to the squamous cell carcinoma while 5 referred to the other types.

The chemotherapy regimens included anlotinib (12 mg/d from day 1–14 for 21 d/cycle (n = 7 trials); anlotinib plus pleural infusion chemotherapy with cisplatin (n = 2 trials); radiotherapy plus anlotinib (n = 1 trials); docetaxel 75 mg/m^2 for d1 plus anlotinib 12 mg/d from day 1 to 14 for 21 d/cycle (n = 1 trials).

Table 1

Characteristics of the included studies of the systematic review.

First author	year	Size	phase	Histology	Interventions (regimen, participants)	Comparators (regimen, participants)	Main outcomes	Jadad score
Han[1]	2018	117	II	Adenocarcinoma (n=104)/SCC (n=13)	anlotinib (12 mg per d, per os; d 1–14; 21 days per cycle, n=60)	Placebo (n=57)	①②③④	7
Han[2]	2018	439	III	Adenocarcinoma (n=336)/SCC (n=86)/others(n=15)	anlotinib (12 mg per d, per os; d 1–14; 21 d per cycle, n=296)	Placebo (n=143)	①②③④	7
Yue	2018	80	/	Adenocarcinoma (n=67)/Others (n=13)	Anlotinib + Pleural infusion chemotherapy with cisplatin (n=40)	Pleural infusion chemotherapy with cisplatin (n=40)	①③④	5
Zhou	2019	437	III	Adenocarcinoma (n=336)/SCC (n=86)/Others (n=15)	anlotinib (12 mg per d, per os; d 1–14; 21 days per cycle, n=294)	Placebo (n=143)	①③③④	5
Cheng	2019	50	/	Adenocarcinoma (n=17)/Others (n=3)	Anlotinib + Pleural infusion chemotherapy with cisplatin (n=25)	Pleural infusion chemotherapy with cisplatin (n=25)	①④	3
Dai	2019	40	/	Adenocarcinoma (n=21)/SCC (n=19)	anlotinib (12 mg per d, per os; d 1–14; 21 days per cycle, n=20)	Placebo (n=20)	①③③④	4
Yu	2019	66	/	Adenocarcinoma (n=66)	Docetaxel 75 mg/m^2 ivgtt d1+ anlotinib 12 mg per d, per os; d 1–14; 21 d per cycle, (n=33)	Docetaxel 75 mg/m^2 ivgtt d1, 21 days per cycle, (n=33)	①④	2
Huang, Cai	2020	40	/	/	Radiotherapy+ anlotinib (12 mg per day, per os; d 1–14; 21 d per cycle, n=20)	Radiotherapy (n=20)	①④	2
Jiang	2020	97	III	Adenocarcinoma (n=86)/SCC (n=8)/Others (n=3)	anlotinib (12 mg per d, per os; d 1–14; 21 d per cycle, n=67)	Placebo (n=30)	②③④	7
Huang, Li	2020	70	/	/	anlotinib (12 mg per d, per os; d 1–14; 21 d per cycle, n=35)	Platinum-based chemotherapy regimen (12 mg per d, d 1–14; 21 days per cycle, n=35)	①③③④	3
Wang	2020	44	/	/	anlotinib (12 mg per d, per os; d 1–14; 21 d per cycle, n=22)	Placebo (n=22)	②③④	4

① DCR = disease control rate, ③ PFS = progress free survival, ③ OS = overall survival, ④ AE = adverse events, SCC = squamous cell carcinoma.

Regarding the regimens of comparators, the placebo was used in 6 trials, pleural infusion chemotherapy with cisplatin was used in 2, radiotherapy was used in 1, docetaxel was used in 1, and platinum-based chemotherapy regimen was used in 1.

Additionally, it provided information of the outcomes data. For DCR outcomes, 9 trials reported; 7 trials reported PFS outcomes; 8 studies reported OS outcomes; besides, 11 studies reported the treatment related adverse events.

3.3. Risk of bias in individual study

Results of the risk of bias are showed in Figure 2A and Figure 2B.

3.3.1. Random sequence generation. All the studies were at low risk of bias for using a computer random number generator or random number table method.

3.3.2. Allocation concealment. Seven trials were analyzed to be at low risk of bias for reporting allocation concealment or the allocation method having no influence on the results. Four studies did not mention allocation concealment being judged to be at unclear risk of bias.

3.3.3. Blinding of participants and personnel. Nine trials set up placebo arm and reported blinding of patients and study personnel being judged to be at low risk of bias. Two studies were judged to be at unclear risk of bias for not mentioning it.

3.3.4. Blinding of outcome assessors. Eleven studies were judged to be at low risk of bias for setting up placebo arm or blinding the data collectors or being analyzed to have little possible to break the blinding.

3.3.5. Incomplete outcome data. Patients in all the 11 studies were reported to complete the whole course of treatment being judged to be at low risk of bias.

3.3.6. Selective reporting. Ten trials were not registered anywhere and provided no information of the selective report, to be judged to be at unclear risk of bias while 1 remained to be unclear.

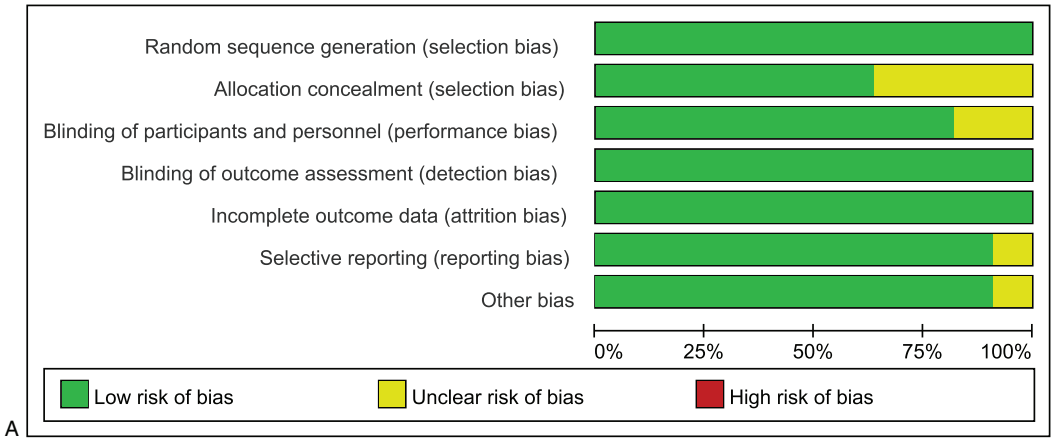
3.3.7. Other bias. Ten studies were judged to be at low risk of bias for being tested to be free of apparent other bias and 1 stayed unclear

3.4. PFS outcomes

An evident PFS improvement (mean difference=2.36, 95% confidence interval [CI]=1.64–3.08, $P<.01$ in Fig. 3A; hazard ratio=0.25, 95% CI=0.22–0.30, $P<.01$ in Fig. 3B) was observed in patients with anlotinib or combination of anlotinib and other conventional treatment, which significantly outperformed Placebo or other conventional treatment (Fig. 3). Notably, according to the result of the funnel plot in Figure 4 with a small degree of heterogeneity across the trials, a high quality of evidence and a strong recommendation were assigned to the pooled evidence of PFS.

3.5. OS outcomes

The regimen of anlotinib or combination of anlotinib and other conventional treatment for advanced NSCLC obviously led to a



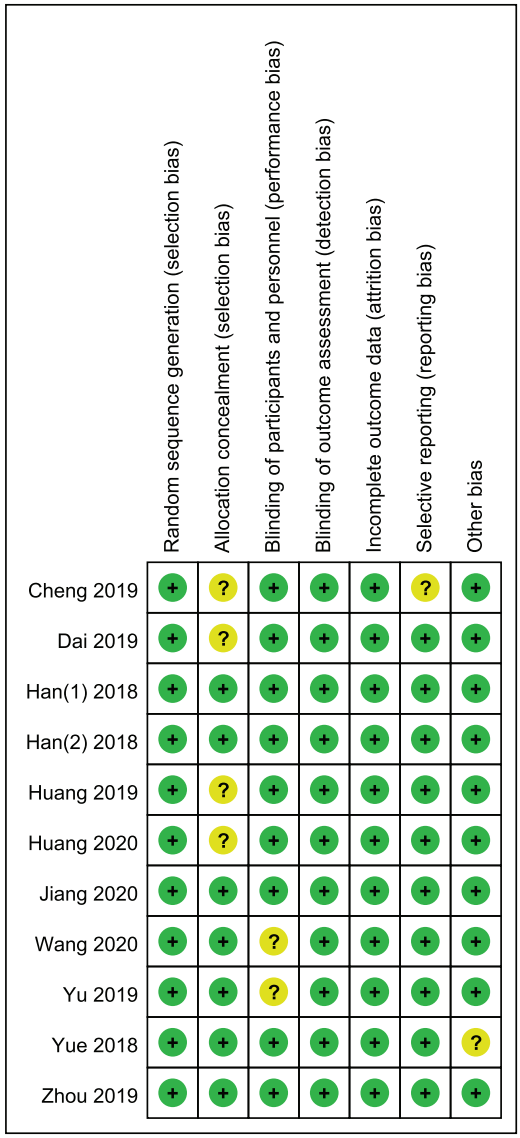


Figure 2. (A): Risk of bias graph; (B): Risk of bias summary: review of authors assessment about each risk of bias item for each included study. "+": low risk of bias; "?": unclear risk of bias; "−": high risk of bias.

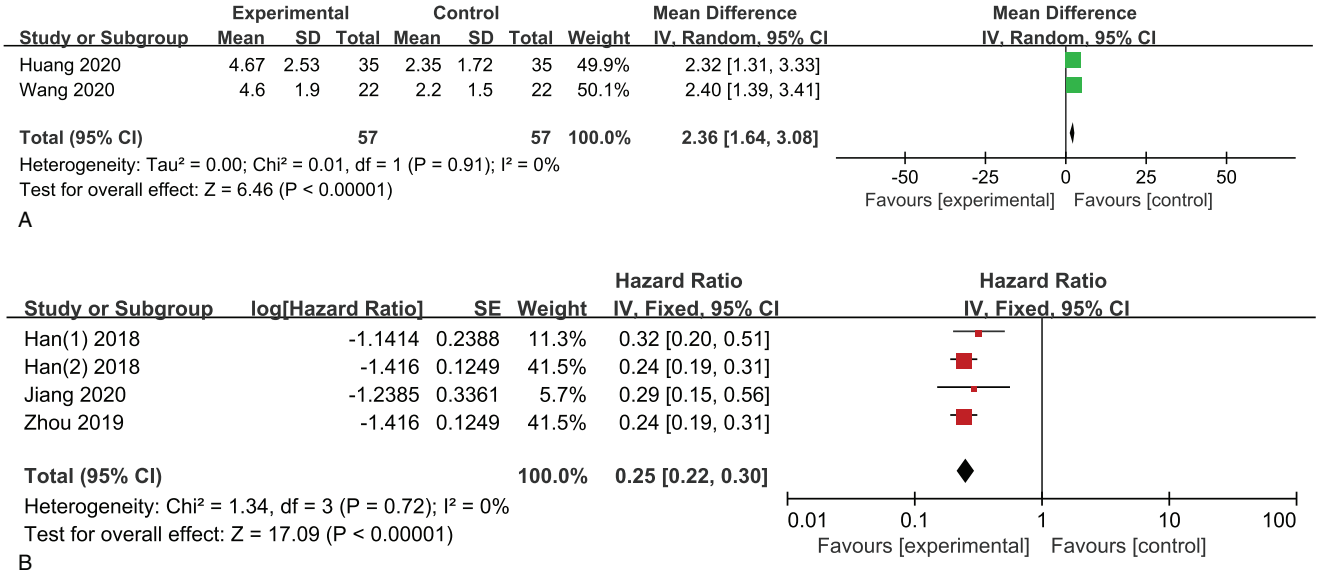


Figure 3. (A–B). Forest plot of the comparison of progression-free survival between experimental group and control group.

large improvement in OS (mean difference = 3.14, 95% CI = 1.83–4.45, $P < .001$ in Fig. 5A; hazard ratio = 0.70, 95% CI = 0.60–0.82, $P < .001$ in Fig. 5B) with slight heterogeneity across included trials (Fig. 6).

3.6. DCR outcomes

An apparent DCR improvement (odds ratio [OR] = 6.50, 95% CI = 4.90–8.62, $P < .001$) (Fig. 7) showed that the method of using anlotinib to implement advanced NSCLC appeared more effective. Furthermore, no significant heterogeneity was represented across included trials (Fig. 8).

3.7. Treatment related adverse event (TRAE)

Overall, treatment related adverse events were proved to be more frequent in the experimental group (OR = 1.97, 95% CI = 1.43–2.72, $P < .001$). Specifically, significantly higher risk of TRAE for hypertension (OR = 11.05, 95% CI = 7.85–15.55, $P < .001$), hepatic dysfunction (OR = 1.96, 95% CI = 1.29–2.68, $P < .001$), diarrhea (OR = 2.20, 95% CI = 1.17–4.16, $P < .05$), hemoptysis (OR = 2.59, 95% CI = 1.71–3.93, $P < .01$) in intervention arm (Fig. 9) were observed.

However, no statistical significance was detected of leukopenia (RR = 1.12, 95% CI = 0.59–2.12, $P = .72$), nausea and vomiting (RR = 1.21, 95% CI = 0.82–1.78, $P = .34$), pulmonary infection

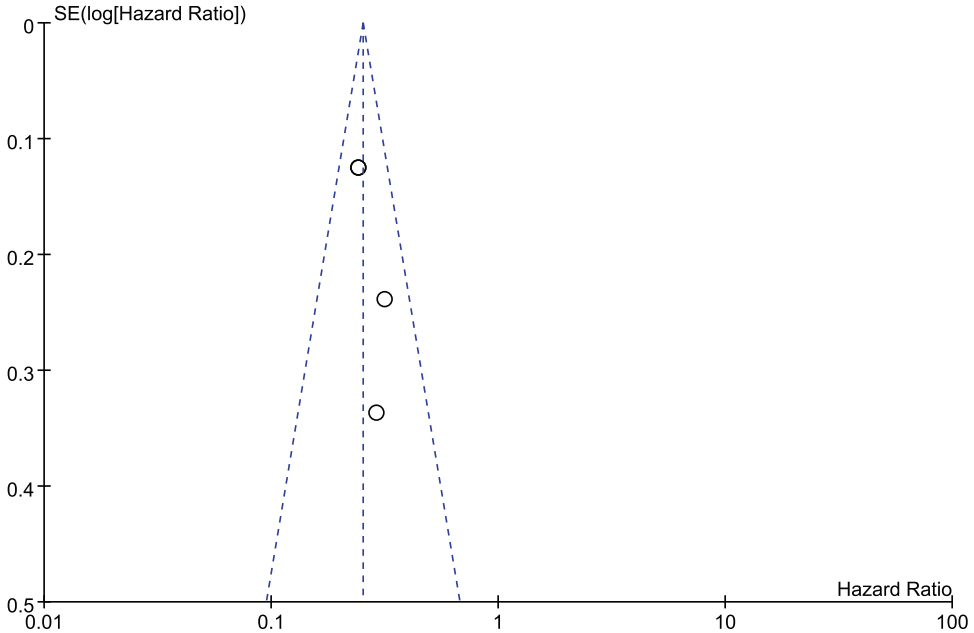


Figure 4. Funnel plot of the comparison of progression-free survival between experimental group and control group.

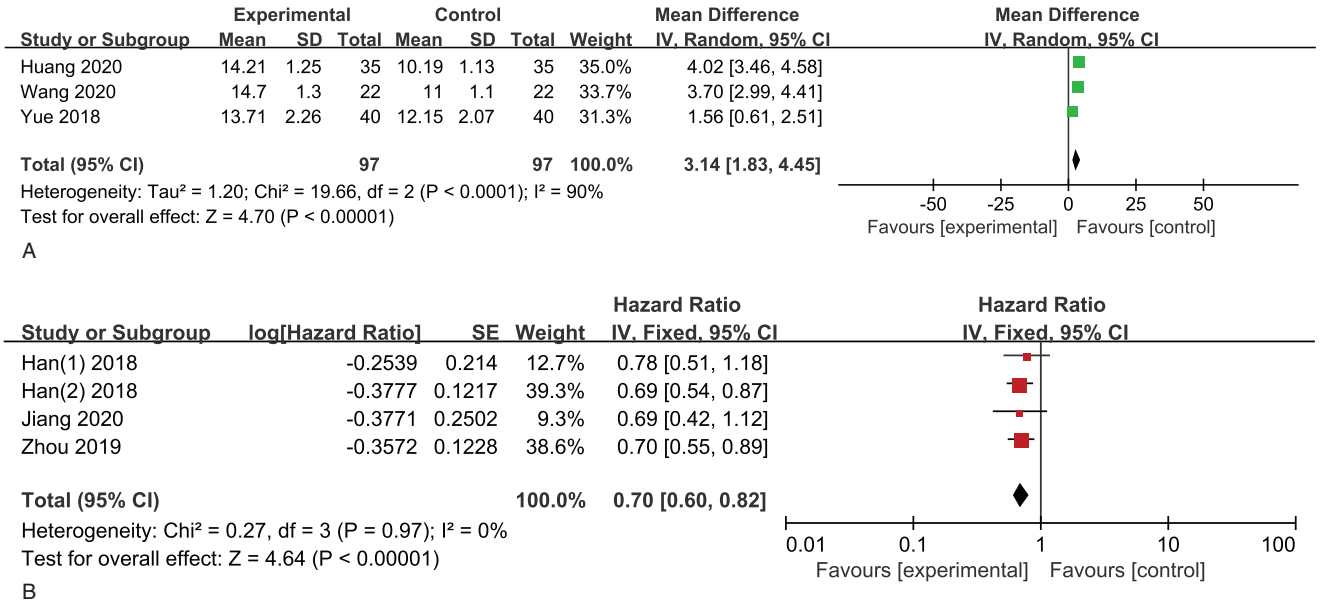


Figure 5. (A–B). Forest plot of the comparison of overall survival between experimental group and control group.

(RR = 1.49, 95% CI = 0.79–2.8, $P = .22$), and dyspnea (RR = 1.41, 95% CI = 0.92–2.17, $P = .12$) between 2 groups(Fig. 9).

As was detected in the funnel plot of the comparison of TRAE, the use of anlotinib did not lead to significant heterogeneity across included trials (Fig. 10).

4. Discussion

4.1. Summary of main findings

In this article, the efficacy and safety of anlotinib as maintenance therapy for advanced NSCLC patients was analyzed and reported from 11 randomized controlled trials. Our results suggest evident PFS, OS, DCR improvement in patients with anlotinib or combination of anlotinib and other conventional treatment.

Despite of apparent efficiency, higher risk of TRAE significantly increased for anlotinib arm, such as: hypertension, hepatic dysfunction, diarrhea and hemoptysis. However, the possibility of leukopenia, nausea and vomiting, pulmonary infection and dyspnea are comparable in 2 arms.

4.2. Applicability of the current evidence

This meta-analysis results will hopefully serve as useful feedback information for maintenance regimen of advanced NSCLC patients.

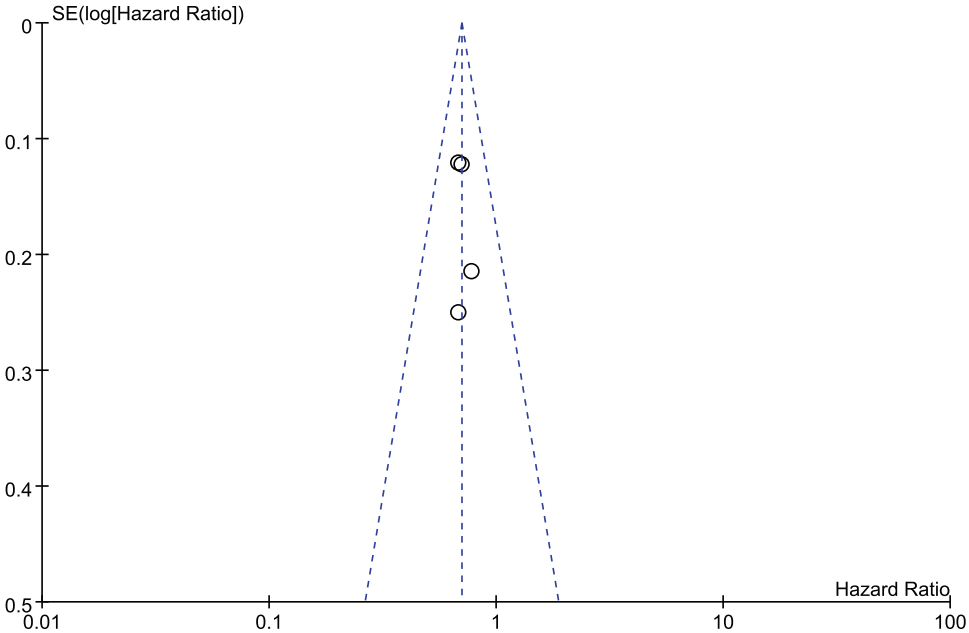


Figure 6. Funnel plot of the comparison of overall survival between experimental group and control group.

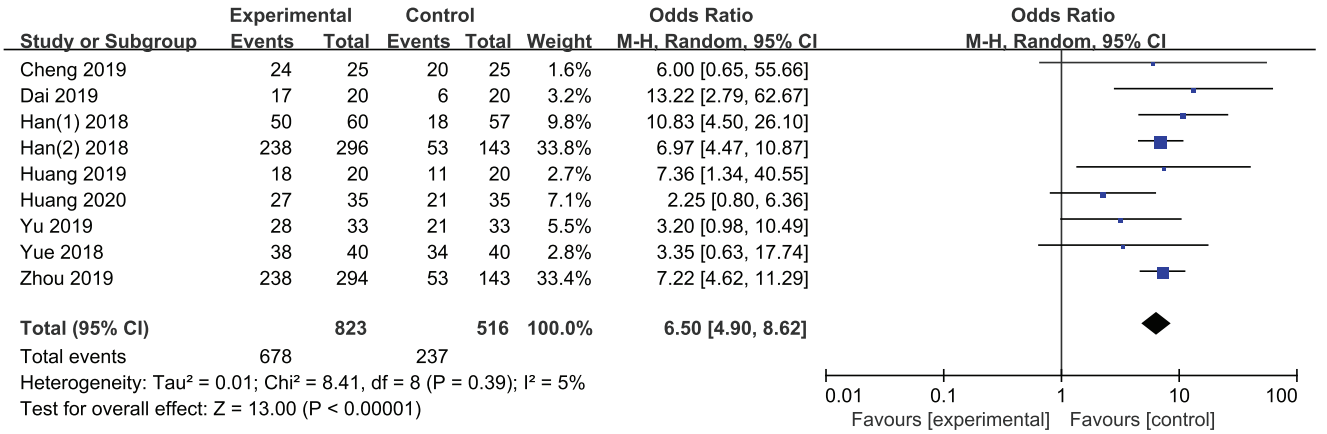


Figure 7. Forest plot of the comparison of disease control rate between experimental group and control group.

Anlotinib is the first China National Medical Products Administration-approved drug for patients with advanced NSCLC following at least 2 lines of chemotherapy in China.[12] Besides, single agent anlotinib has been approved by the China Food and Drug Administration as a third-line treatment for advanced NSCLC patients.[26] According to research, anlotinib has demonstrated a clinically significant OS and PFS prolongation of advanced lung cancer patients.[27] What is more, as an orally administered anti-angiogenesis inhibitor, anlotinib displayed manageable toxicity, long circulation, and broad-spectrum antitumor potential for advanced lung cancer patients with low KPS scores.[28]

For anlotinib, hypertension is one of the independent protective factors. Research demonstrated that anlotinib, a potent multi-tyrosine kinases inhibitor (TKI), could suppress blood vessels sprout and micro vessel density by inhibiting on VEGF/PDGF-BB/FGF-2-induced angiogenesis, causing the risk of hypertension indirectly.[29]

Diarrhea was reported as TRAE in many pre-approval clinical trials. An animal experiment suggested that the major absorption sites for oral anlotinib were probably the stomach and duodenum. Anlotinib, just as many other approved TKIs, demonstrated pH-dependent hydrophilicity and lipophilicity. While, in the jejunum and the ileum with pH 6.5, the aqueous solubility appeared to be too low to provide adequate absorption, thus causing the issue of diarrhea.[30]

As is reported, hepatic dysfunction is one of the serious TRAE in clinical trials with TKIs. Mitochondrial dysfunction is regarded to play a central role in induction of hepatotoxicity. Research certified that the main mechanisms of drug-induced liver injury were based on the production of reactive metabolites generated by phase I oxidation reactions, immunological and/or alterations in mitochondrial function.[31,32]

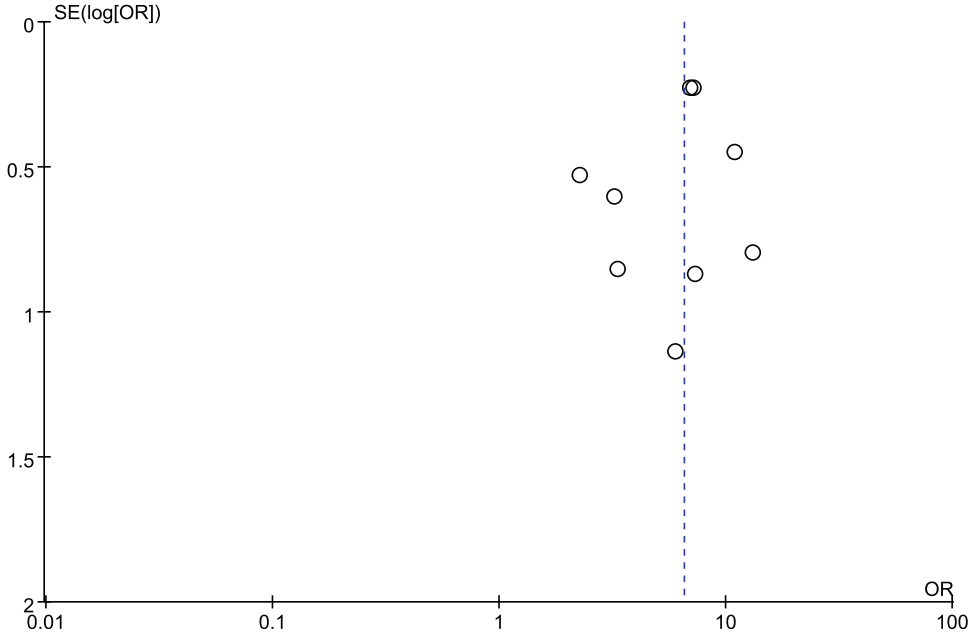


Figure 8. Funnel plot of the comparison of disease control rate between experimental group and control group.

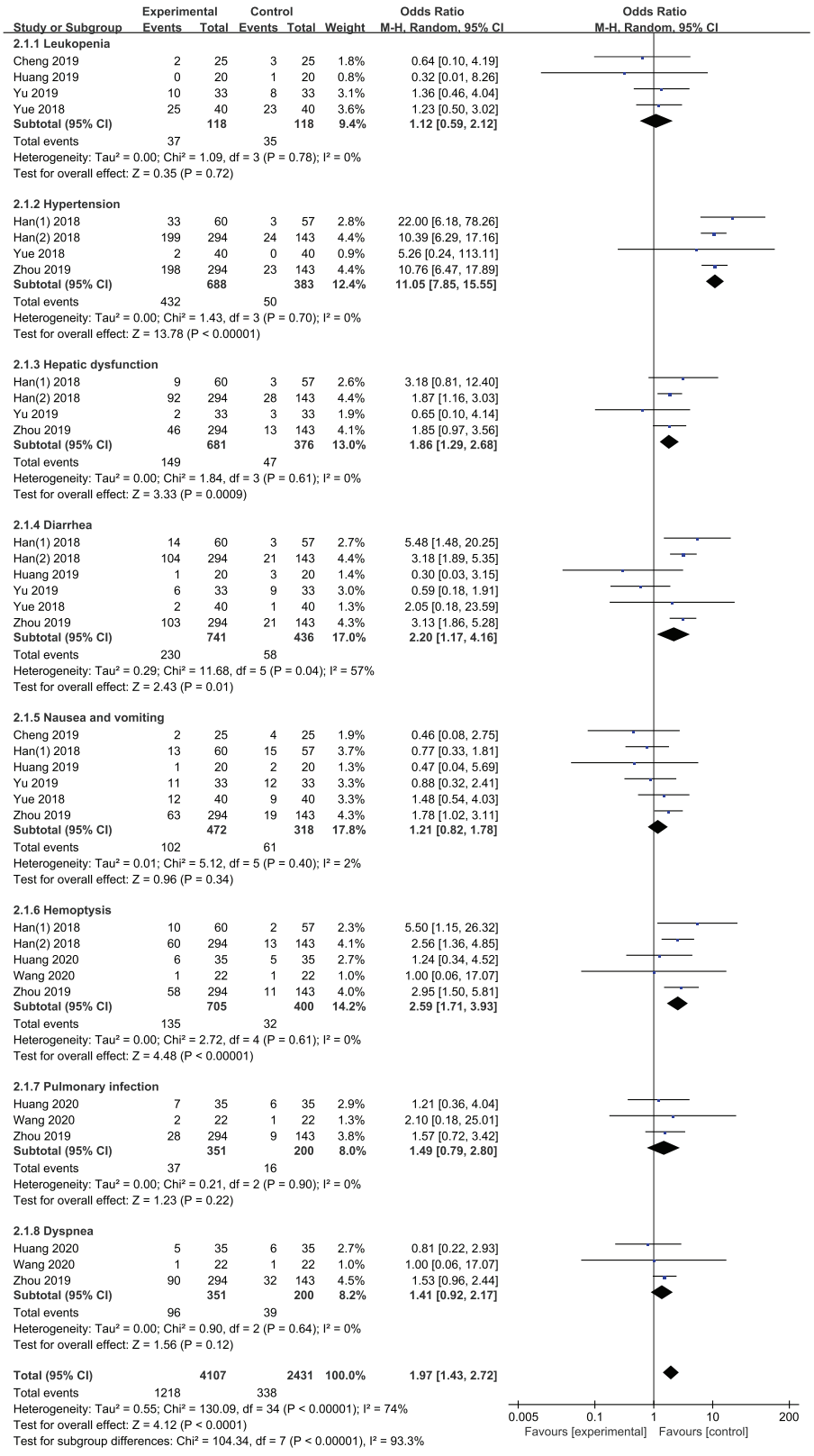


Figure 9. Forest plot of the treatment related adverse event between experimental group and control group.

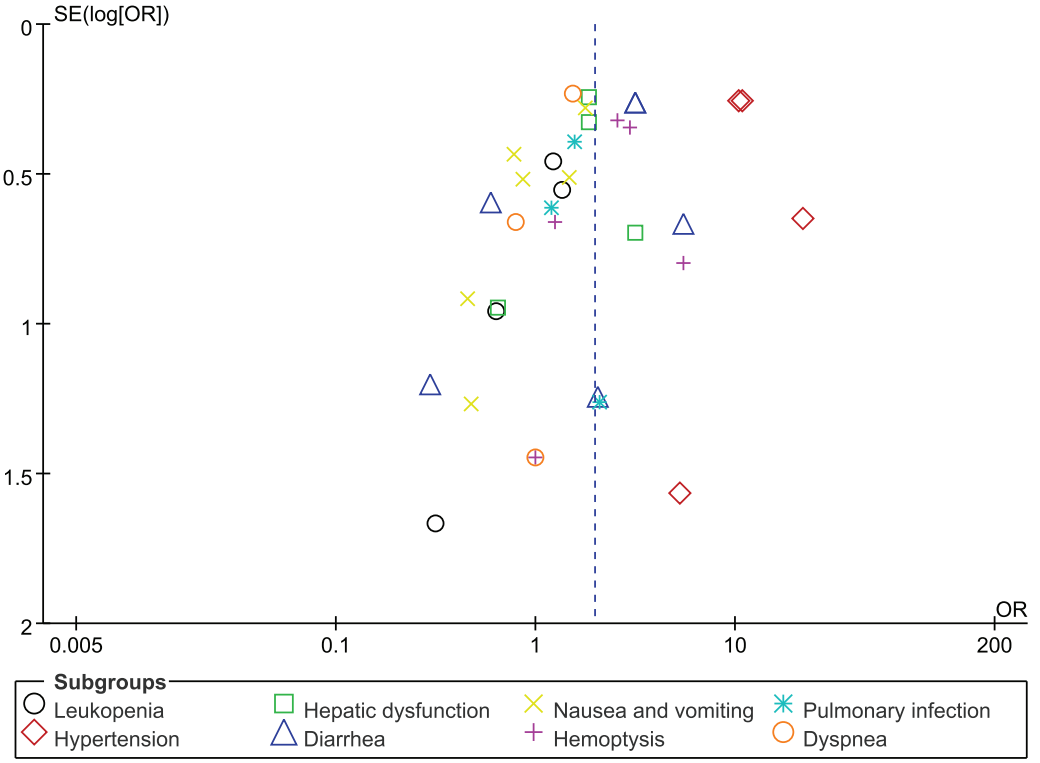


Figure 10. Funnel plot of the comparison of treatment related adverse event between experimental group and control group.

4.3. Limitations

The limitations of this study should be noted. First of all, the quality of the included trials were not high enough according to the Jada scores and risk of bias analysis. Second, the time to market is too short for researchers to carry out enough large-scale trials. The on-going or completed studies are mostly performed in China which may be limited of global reference value. Third, we did not perform subgroup analysis of survival factors such as age, pathological types, KPS score, EGFR mutation and so on, which need to be further explored.

5. Conclusion

Our study suggested that, anlotinib, as maintenance therapy for advanced NSCLC patients is associated with significantly prolonged PFS and OS as well as DCR improvement, but accompanied by increased risk of TRAE, such as hypertension, hepatic dysfunction, diarrhea and hemoptysis. Although much effort has been made for the clinical trials of anlotinib, existing limitations require further studies to provide more convincing clinical evidence.

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Conceptualization: Haiyong Ye, Zhengliang Cheng.
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Funding acquisition: Haiyong Ye, Kangning Liu, Zhengliang Cheng.
Investigation: Haiyong Ye, Zhaoyi Li.
Methodology: Haiyong Ye, Zhaoyi Li, Kangning Liu.
Software: Haiyong Ye, Zhaoyi Li, Kangning Liu.
Supervision: Haiyong Ye, Zhaoyi Li, Kangning Liu, Zhengliang Cheng, Feng Zhang.
Validation: Zhengliang Cheng.
Visualization: Zhaoyi Li, Kangning Liu.
Writing – original draft: Haiyong Ye, Zhaoyi Li, Kangning Liu.
Writing – review & editing: Haiyong Ye, Zhaoyi Li, Kangning Liu, Zhengliang Cheng, Feng Zhang.

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