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Efficacy and safety of EGFR-TKIs for non-small cell lung cancer

A meta-analysis of randomized controlled clinical trials

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Abstract

Background: We conducted this meta-analysis based on updated literature and research to compare the efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as treatments for patients with non-small cell lung cancer (NSCLC).

Methods: A literature search was conducted using PubMed, Embase, Medline and Web of Science databases to perform a systematic literature search based on random control trials. In these articles, EGFR-TKIs were compared with placebos, chemotherapy, or whole-brain irradiation as treatments for NSCLC. In this research, a meta-analysis of the literature was performed to produce a combined risk ratio (RR) with a 95% confidence interval (CI) for progression-free survival (PFS), overall survival (OS), and adverse events. The data were synthesized with Review Manager 5.3 software, which was used to manage the process.

Results: There were 15 random control trials included in the study, involving 4249 patients in total. There was evidence that EGFR-TKIs can significantly prolong OS (RR: 0.87, 95% CI: 0.75–1) and PFS (RR: 0.75, 95% CI: 0.66–0.86) in NSCLC patients. There was an increase in the incidence of adverse events after treatment with EGFR-TKI, including diarrhea (RR: 0.18, 95% CI: 0.10–0.26), infection (RR: 0.09, 95% CI: 0.02–0.16), and rash (RR: 0.37, 95% CI: 0.22–0.51).

Conclusions: It has been shown that EGFR-TKIs prolong OS and PFS in patients with NSCLC. NSCLC patients may benefit from EGFR-TKIs as an important treatment option in order to prolong their survival.

Abbreviations: AEs = adverse events, CI = confidence interval, EGFR = epidermal growth factor receptor, EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, RCTs = random control trials, RR = risk ratio, TKIs = tyrosine kinase inhibitors, WBI = whole-brain irradiation.

Keywords: chemotherapy, EGFR-TKI, NSCLC, RCT

1. Introduction

Worldwide, lung cancer is the leading cause of cancer-related deaths among people of all ages.[1] As the leading cause of cancer-related deaths worldwide, lung cancer poses a significant threat to human health, and it is estimated that nearly 1.4 million people die from lung cancer every year. Due to the many concomitant medical conditions associated with localized disease, it continues to be difficult for a substantial proportion of patients to undergo curative resection procedures in order to cure their cancer.[2] In many cases, patients suffer from advanced stages of the disease when they are diagnosed. This

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Participants' informed consent: We explained the purpose, process, risks and benefits of the study to all individuals involved in the study orally or in writing, and obtained their informed consent. Participants have the right to know that their participation is voluntary and can withdraw from the study at any time. Assessment and management of potential risks: We assessed the potential risks that may be involved in the study during the project design stage and took appropriate measures to reduce or manage these risks. We guarantee that participants will not suffer any physical or psychological harm because of participating in the study. Research data use: We will strictly abide by the principles of legality and transparency in data use to ensure the correct use and interpretation of research data. We will try our best to avoid data misunderstanding and abuse, and only use the data for research purposes. The purpose of this statement is to ensure the ethical compliance of research projects and protect the rights and privacy of participants. If you have any further questions or doubts, please feel free to contact us.

The authors have no conflicts of interest to disclose.

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

This research project has been approved by the Institutional Ethics Committee of Ganzhou People's Hospital and operated in strict accordance with ethical standards. In this study, we respect and protect the rights and privacy of participants and ensure the confidentiality of their personal information.

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is the primary cause of the high mortality rate associated with this disease. According to current chemotherapy options, such as platinum-based therapy, there seems to have been a plateau in the efficacy of current chemotherapy options.[3] A common genomic alteration in non-small cell lung cancer (NSCLC) is the presence of mutations that sensitize the epidermal growth factor receptor (EGFR) gene. Approximately 15% of lung adenocarcinomas in the United States and 22% to 64% of lung adenocarcinomas in Asian patients exhibit these markers.[4] As a result of the recent development of efficient EGFR tyrosine kinase inhibitors (TKIs), there are now 5 different agents that can be used to treat advanced NSCLC with common EGFR-sensitizing mutations available on the market: erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib. There are several types of TKIs that are available on the market today, including 1st-generation, 2nd-generation, and 3rd-generation agents. Afatinib and osimertinib, 2 TKIs of the 3rd-generation and 2nd-generation, respectively, have shown some persistent activity in the treatment of some uncommon mutations in the EGFR.[5] There have been a series of studies examining the efficacy of EGFR-TKIs as an adjuvant treatment for resected NSCLC due to their improvement in response rates and a significantly enhanced survival rate compared to doublet chemotherapy in advanced NSCLC.[6] In spite of this, subsequent randomized controlled trials (RCTs) gave contradictory results when compared to placebo treatment or adjuvant chemotherapy for patients with operable NSCLC in which EGFR-TKIs were used at adjuvant stages, suggesting that adjuvant treatment could improve the prognosis for patients with operable NSCLC.[6]

We performed this updated meta-analysis in order to summarize the efficacy and safety of EGFR-TKIs in the treatment of NSCLC based on updated data and new evidence in order to further improve the treatment strategy and management of these patients with resected NSCLC in the future.

2. Methods

2.1. Research in the literature

An independent literature review and screening were conducted by 2 experienced investigators focused on the comparison of EGFR-TKIs to other treatments for the treatment of patients with NSCLC from the available databases: Web of Science, PubMed, Embase, and Medline. It was necessary for the literature search to be conducted based on the following key terms: "NSCLC" and "EGFR" and "tyrosine kinase inhibitor" and "randomized controlled trials." To resolve any dissonance between the results and expectations, further consultation was conducted to resolve the issue. We included articles in this review if they met the following inclusion criteria: patients were diagnosed with NSCLC; research designs were randomized controlled trials comparing EGFR-TKIs with other treatments; the following outcomes were reported: progression-free survival (PFS), overall survival (OS), and adverse events (AEs). During the screening, the following articles were excluded: these include letters, comments, editorials, protocols, replies, reviews, meta-analyses, guidelines, etc; one or more case reports or case series with a limited number of patients; there were no data available in the full-text review. The literature screening process was conducted using Endnotes throughout the period when articles were screened. An international prospective review systematic review protocol has been registered for this meta-analysis.

2.2. Extraction of data

Based on the included articles, the following information was collected: the author, the year of publication, the mutant status of the EGFR, the size of the sample, the underlying age group, interventions, and results. We collected the following raw statistics for data synthesis: the rate ratio and 95% confidence interval (CI) for PFS, OS, and AEs in the experimental group (EGFR-TKIs) and control group (other treatments), respectively, and the number of AEs in each group. Data were extracted from each article independently by 2 authors and recorded. There was a dissonance between the results of the literature search and the method described by the 3rd author in the literature search section that was used to resolve the dissonance. Table 1 summarizes all of the extracted data.

2.3. Definitions

As part of this meta-analysis, the following definitions of PFS and OS were used to incorporate the RR of all included studies with subtle differences in definitions of PFS and OS. Specifically, PFS refers to the period from the moment the baseline assessment or therapy began until the moment when the subjective disease deteriorated or died. The OS was defined as the period of time that elapsed between the start of treatment or the baseline assessment and the date of death as the time of treatment ended. AEs that occurred during treatment were evaluated and recorded in both groups and compared.

2.4. Statistical analyses

Based on the results obtained using Review Manager 5.3 software, the risk of bias summary and the risk of bias graph were developed by the Nordic Cochrane Center, Copenhagen, Denmark, in accordance with the Cochrane Collaboration 2014. The RRs for PFS and OS were calculated using the inverse variance method and expressed as percentages. This study was deemed statistically significant if $P \leq .05$ was used as the threshold. There was a 2-sided test for all P values and 95% CIs. A chi-squared test was used to test for heterogeneity in the sample. There were 2 types of models used in this study: a random-effects model was used if there was significant heterogeneity ($P < .05$ or $I^2 > 50\%$) to reduce the impact of heterogeneity on the results, and a fixed-effects model when there was no significant heterogeneity. Using the funnel plot, we determined whether or not there was publication bias. To assess the methodological quality of the included studies, the Cochrane Handbook for Systematic Reviews of Interventions risk of bias tool was used. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, incomplete dates, selective reporting bias were all examined. As can be seen in the above-mentioned bias, high risk, unclear risk, and low risk were characterized by their respective risks.

3. Results

3.1. The characteristics of the studies

As a result of the initial search in the database, a total of 2084 articles were identified. The titles and abstracts were checked and 1525 articles were found to be irrelevant, reviews, case studies, and basic research articles conducted in vitro were excluded from the review. There were 67 articles included in the review, out of which 52 articles were excluded because they were not RCTs and lacked data based on the full-text review. There were 15 studies containing a total of 4249 patients who met the inclusion criteria at the end. All the trials included in this review evaluated and compared the efficacy and safety of EGFR-TKIs in the treatment of NSCLC compared to placebos and chemotherapy. It is important to note that out of the 15 studies, 4 included Erlotinib, 4 involved Gefitinib, 2 involved Anlotinib, 2 involved Osimertinib, 1 involved Icotinib, and

Table 1

A description of the characteristics of the trials that were included in the meta-analysis.

Study	EGFR-mutant	Sample (T/C)	Age (T/C)	Intervention (T/C)	Outcomes
Cappuzzo et al[7]	EGFR-positive	438/451	60 (33–83)/60 (30–81)	Erlotinib: 150 mg/d; Placebo	PFS; OS; adverse events
Cufer et al[8]	NA	68/73	63.0 (34–85)/59.5 (29–83)	Gefitinib 250 mg/d; Docetaxel 75 mg/m^2	OS; PFS; adverse events
Han et al[9]	NA	60/57	55.2 ± 10.0/55.5 ± 9.1	Anlotinib (12 mg/d); Placebo	PFS; OS; adverse events
Lee et al[10]	NA	617/307	60 (20–85)/60 (21–84)	Vandetanib: 0–300 mg/d; Placebo	PFS; adverse events
Mitsudomi et al[11]	EGFR mutations (either the exon 19 deletion or L858R point mutation)	86/86	64 (34–74)/64 (41–75)	Gefitinib: 250 mg/d; Cisplatin (80 mg/m^2) plus docetaxel (60 mg/m^2)	PFS; adverse events
Mok et al[12]	EGFR T790M positive	279/140	62 (25–85)/63 (20–90)	Osimertinib: 80 mg once daily; Pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin or cisplatin (75 mg per square meter)	PFS; adverse events
Papadimitrakopoulou et al[13]	EGFR T790M-positive	279/140	62 (25–85)/63 (20–90)	Osimertinib: 80 mg once daily; Pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin or cisplatin (75 mg per square meter)	OS; adverse events
Si et al[14]	NA	294/143	56.8 (31–74)/57.9 (20–75)	Anlotinib: 12 mg once daily; Placebo	Adverse events
Wu et al[15]	NA	59/63	55 (33–73)/54 (30–77)	Erlotinib: 150 mg/d; Placebo	PFS; OS; adverse events
Yang et al[16]	EGFR-mutant	85/91	57 (51–64)/58 (48–63)	Icotinib: 125 mg 3 times per day; WBI	PFS; OS; adverse events
Yoshioka et al[17]	EGFR mutation (either exon 19 deletion (Del19) or L858R in exon 21)	88/89	NA	Gefitinib: 250 mg/d Cisplatin (80 mg/m^2 per day) plus Docetaxel (60 mg/m^2 per day)	PFS; OS
Yue et al[18]	EGFR mutation-positive	51/51	59 (50–66)/57 (51–61)	Erlotinib (150 mg once daily); Vinorelbine (25 mg/m^2) plus cisplatin (75 mg/m^2)	OS; adverse events;
Zhou et al[19]	EGFR mutation-positive	82/72	NA	Erlotinib: 150 mg daily; Chemotherapy (gemcitabine 1000 mg/m^2 and carboplatin [area under the curve = 5.0])	OS; PFS; adverse events
Tada et al[20]	EGFR mutation	116/116	64 (34–74)/64 (34–74)	Gefitinib (250 mg) once a day; Cisplatin (80 mg/m^2 on day 1) plus Vinorelbine (25 mg/m^2 on days 1 and 8)	OS
Zhong et al[21]	EGFR-mutant	111/111	58 (32–74)/60 (26–76)	Gefitinib (250 mg once daily); Vinorelbine (25 mg/m^2 on days 1 and 8) plus cisplatin (75 mg/m^2 on day 1)	OS

ORR = objective response rate, PFS = progression-free survival, WBI = whole-brain irradiation.

2 involved Vandetanib. It should also be noted that 8 studies included only patients with EGFR mutations, while 5 studies involved patients regardless of their EGFR mutation status. In Figure 1, we had a flow chart that illustrated how the study retrieval and data selection would be performed. A summary of the main characteristics of the studies included in the review can be found in Table 1. In addition, a summary of the main results of the meta-analysis of the included studies is presented in Table 2.

A summary of the results of the quality assessment can be found in Figure 2. The majority of studies (10 of 15) did not provide any data that could be used to assess selection bias (allocation concealment) in the studies. Three of the studies showed a low risk of performance bias due to the fact that participants and personnel were blinded, which may have contributed to the results. Attrition and reporting bias have been shown to be low risks in all studies.

3.2. Effects of EGFR-TKIs versus other therapy on OS and PFS

In a review of twelve randomized controlled trials, it was found that RRs and 95% CIs for OS were reported in patients with NSCLC who received EGFR-TKI combined with chemotherapy or whole-brain irradiation (WBI) alone or placebo, as illustrated in Figure 3. As a result of significant heterogeneity between studies, random-effects statistical models were run to analyze the results (I^2 = 76 %, P < .001). The results of our meta-analysis confirmed that EGFR-TKIs can significantly prolong the OS of patients with NSCLC, irrespective of gene mutation status, compared to the control group (RR: 0.87, 95% CI: 0.75–1).

Also, 8 RCTs have reported data on the RR and 95% CI for PFS after EGFR-TKIs are compared to placebos or adjuvant chemotherapy in addition to prior studies (Fig. 4). A meta-analysis of our findings showed that EGFR-TKIs have a significant impact on PFS compared to the control group (HR: 0.75, 95% CI: 0.66–0.86).

3.3. Adverse events associated with EGFR-TKIs versus other therapies

3.3.1. Diarrhea. During the evaluation of safety outcomes, all of these AEs were found to be relatively manageable in most cases. According to Figure 5, patients treated with EGFR-TKIs had a higher risk of diarrhea compared to the control group (RR: 0.18, 95% CI: 0.10–0.26). The heterogeneity in these studies was significant, so therefore, there was the need to conduct a random-effects statistical analysis (I^2 = 89.9%, P < .001).

3.3.2. Infection. As a result of EGFR-TKIs, infection incidence rates increased significantly (RR: 0.09, 95% CI: 0.02–0.16) for the group. As shown in Figure 6, the empirical results relating to the use of EGFR-TKIs compared to controls in NSCLC were

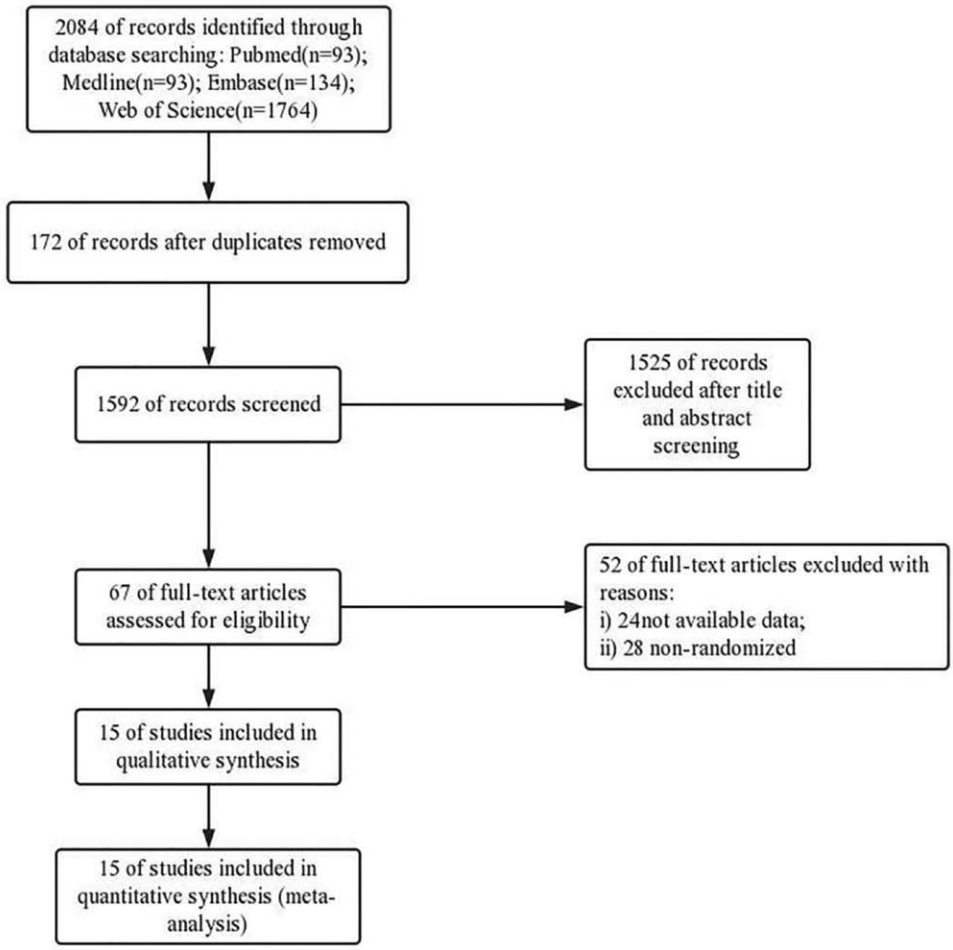

Figure 1. A flow chart showing the inclusion and exclusion of studies in the systematic review and meta-analysis.

Table 2

Summary table of meta-analysis results.

		Test for heterogeneity			Results of meta-analysis	
Outcomes (chemotherapy vs placebo)	**No. trials**	***P***	***I²***	**Effect model**	**Effect size (95% CI)**	***P***
OS	12[8–19]	<.001	76%	Random-effect model	RR: 0.87 (0.75–1.00)	.050
PFS	8[7–12,15,16]	<.001	89%	Random-effect model	RR: 0.75 (0.66–0.86)	<.001
Diarrhea	10[7–12,14–16,18]	<.001	89%	Random-effect model	RR: 0.18 (0.10–0.26)	<.001
Infection	9[7–9,11–15,18]	<.001	87%	Random-effect model	RR: 0.09 (0.02–0.16)	.010
Rash rates	9[7–12,15,16,18]	<.001	96%	Random-effect model	RR: 0.37 (0.22–0.51)	<.001

OS = overall survival, PFS = progression-free survival.

compared between the 2 groups. Since the studies showed a considerable degree of heterogeneity, random-effects statistical models were conducted on the data (I^2 = 87 %, P < .001) in order to analyze the data.

3.3.3. Rash. There was a significant rash rate associated with the use of EGFR-TKIs when compared to chemotherapy or a placebo (RR: 0.37, 95% CI: 0.22–0.51). A substantial amount of heterogeneity was observed among the studies, which is why we generated a random-effects statistical model (I^2 = 96%, P < .001) to investigate the results (Fig. 7).

3.3.4. Publication bias. The results of the analyses of OS and diarrhea are shown in Figure 8 and 9 and 10 articles, respectively, were included in both analyses. Publishing bias was assessed using funnel plots. The funnel plots had obvious symmetry. However, there was no evidence of publication bias.

4. Discussion

Based on the results of our current meta-analysis, EGFR-TKIs are able to significantly prolong OS and PFS in patients with NSCLC. Further, there has been an increase in the frequency of AEs including diarrhea, infection, and rash as a result of EGFR-TKIs.

Currently, it has been controversial whether EGFR-TKIs could be used as a treatment for operable NSCLC patients despite the fact that they have been a controversial topic for decades. Studies in the past and recently have reported conflicting results

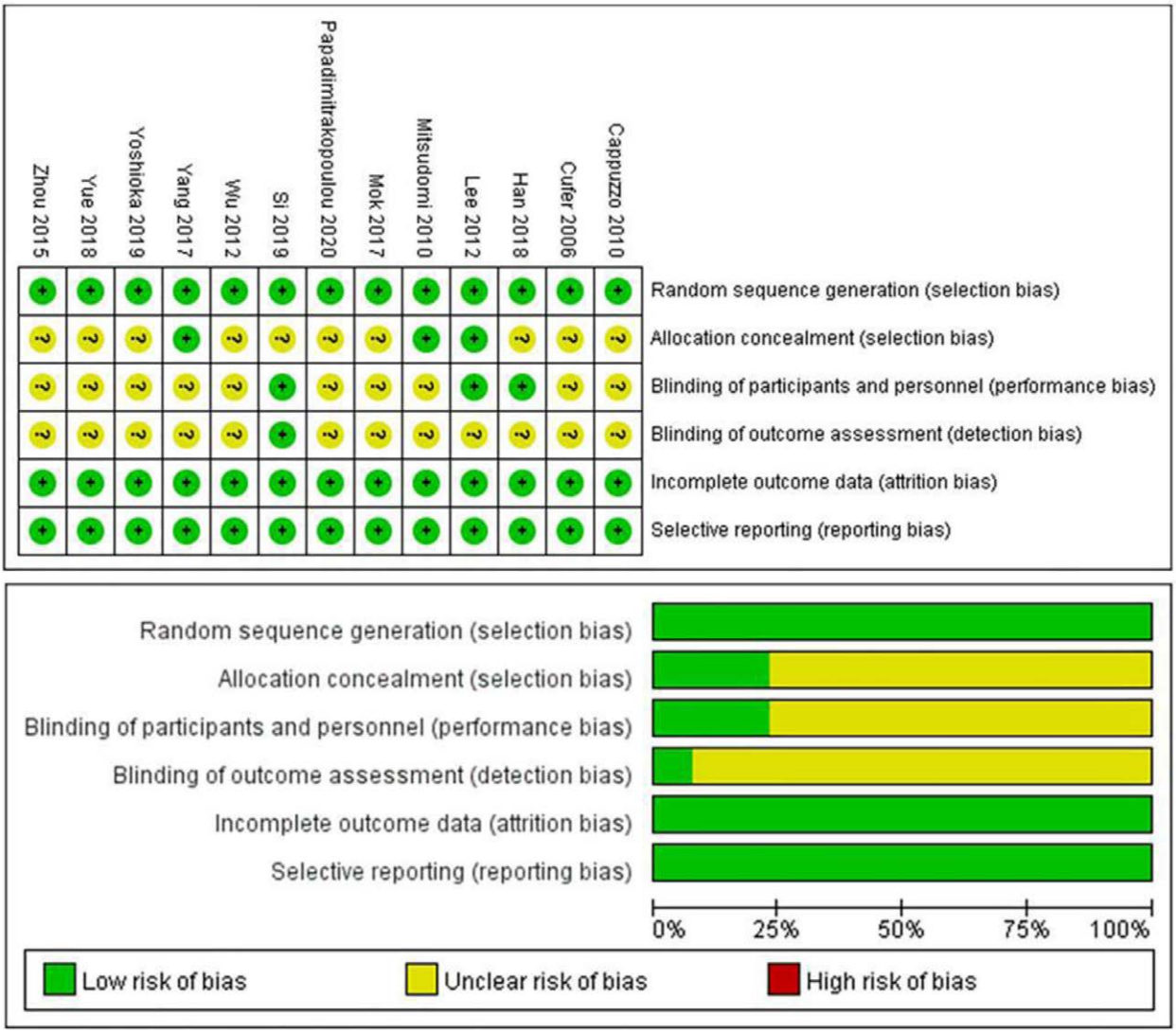

Figure 2. Quality assessment of included studies.

regarding the clinical effectiveness of EGFR-TKIs in resected NSCLC.[22] There are no significant survival benefits reported in resected patients with NSCLC treated with erlotinib or gefitinib compared to patients without erlotinib or gefitinib.[20,23] The final median OS of the ADJUVANT trial did not show any significant differences between the gefitinib and vinorelbine plus cisplatin groups for total survival.[21] Erlotinib, gefitinib, and icotinib are all associated with 5.7 to 13.1 months of median progression-free survival when used as a 1st-line treatment, compared with 4.6 to 7.9 months of median PFS when used together.[24] While most 1st-generation EGFR-TKIs have demonstrated a significant OS benefit versus chemotherapy in the 1st-line setting, it is important to note that almost no patient has developed resistance to those agents after the 1st-line setting. There are a number of factors that could influence the final OS. Depending on the severity of the disease recurrence or metastasis, treatment options were markedly different, including chemotherapy, radiation, immunotherapy, surgery, continuation of the same EGFR-TKI or switching to another generation of EGFR-TKI, the best supportive care or waiting and watching. This meta-analysis found that EGFR-TKIs outperformed chemotherapy or placebo in improving OS and PFS in patients with NSCLC, regardless of their mutation status. When compared with other treatments, EGFR-TKIs lead to greater improvements in PFS and OS. Most of the comparisons range from moderate to substantial heterogeneity, so it is important to keep that in mind. This heterogeneity may be due to a number of reasons, one of which is that the number of comparative studies conducted is quite limited, as well as the diverse nature of the study populations.

An analysis of the AEs associated with EGFR-TKIs compared to chemotherapy and placebo. In our study, we found that significant AEs rates were observed in NSCLC patients receiving EGFR-TKIs. By binding covalently to the C797 residue of the EGFR family of proteins, the 3rd-generation EGFR-TKIs are specially designed to selectively inhibit the T790M mutation while sparing wild-type EGFR while also inhibiting mutations that activate the EGFR family of proteins. Due to its EGFR blockade specificity, it is expected to cause fewer side effects in the stomach and skin than wild-type EGFR blockade.[25] Despite the fact that AEs such as diarrhea and rash are commonly observed in the present meta-analysis, these effects rarely lead to severe side effects. The well-tolerance of EGFR-TKIs can be attributed to their low toxicity. There is also the possibility that this type of therapy could also be combined with other treatments, such as chemotherapy. A further investigation is still needed on the unresolved issues regarding EGFR-TKIs which need to be addressed.[26]

Furthermore, our analysis had a number of limitations. There was a shortcoming in the way that the experimental and control groups were defined, in that the control group included either

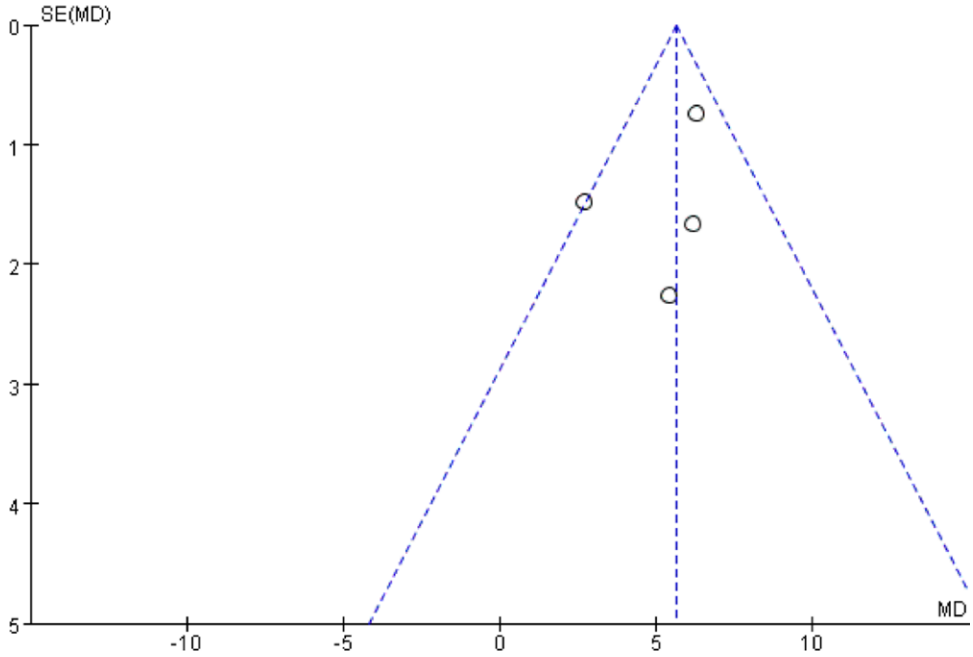

Figure 3. Comparison of OS between EGFR-TKIs and chemotherapy or placebo in patients with NSCLC. EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer, OS = overall survival.

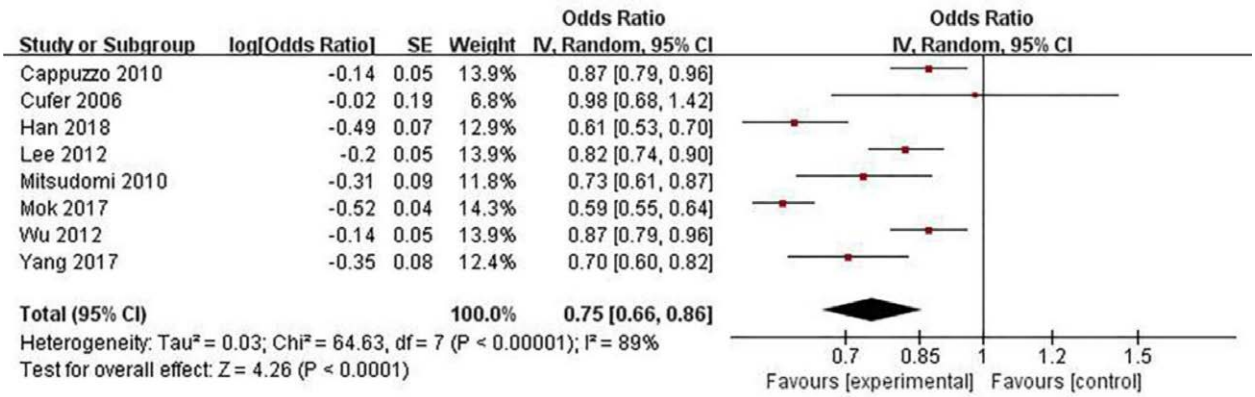

Figure 4. Comparison of PFS between EGFR-TKIs and chemotherapy or placebo in patients with NSCLC. EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer, PFS = progression-free survival.

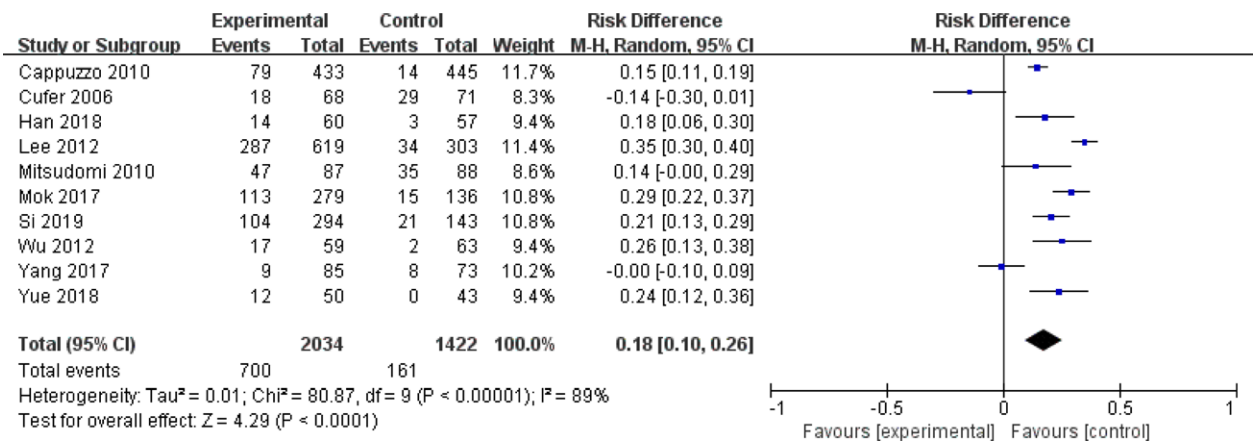

Figure 5. A comparison of diarrhea caused by EGFR-TKIs and chemotherapy or placebo in NSCLC patients was conducted. EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer.

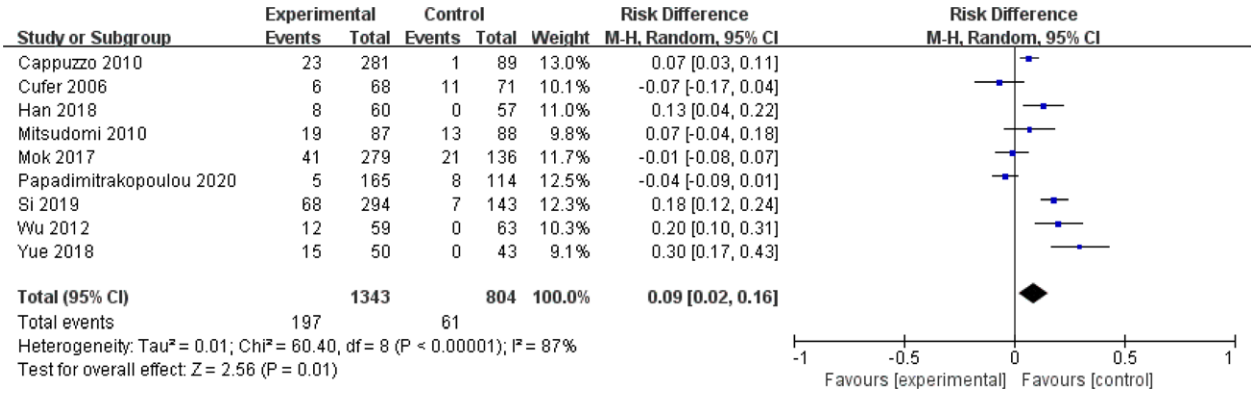

Figure 6. Comparison of infection between EGFR-TKIs versus chemotherapy or placebo in NSCLC patients. EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer.

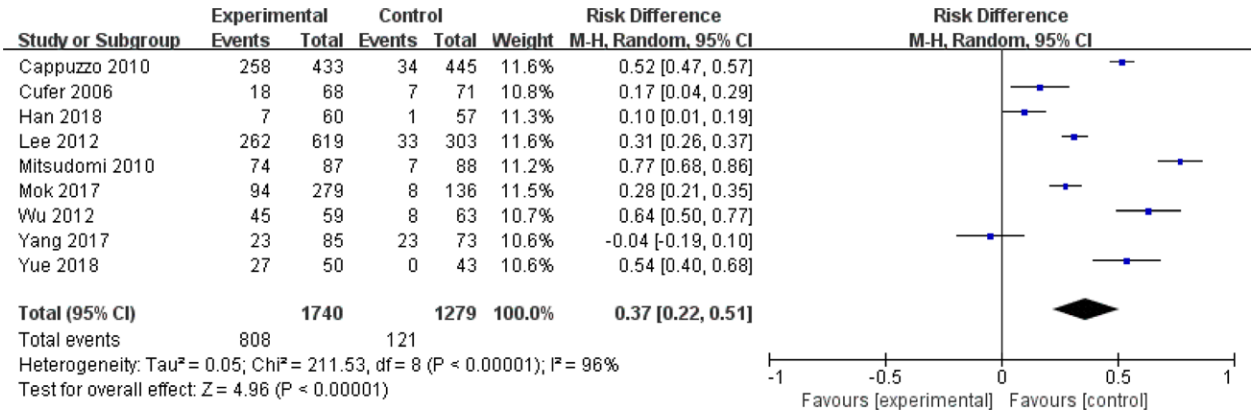

Figure 7. An analysis of rash rates associated with EGFR-TKIs and chemotherapy or placebo in patients with NSCLC. EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors, NSCLC = non-small cell lung cancer.

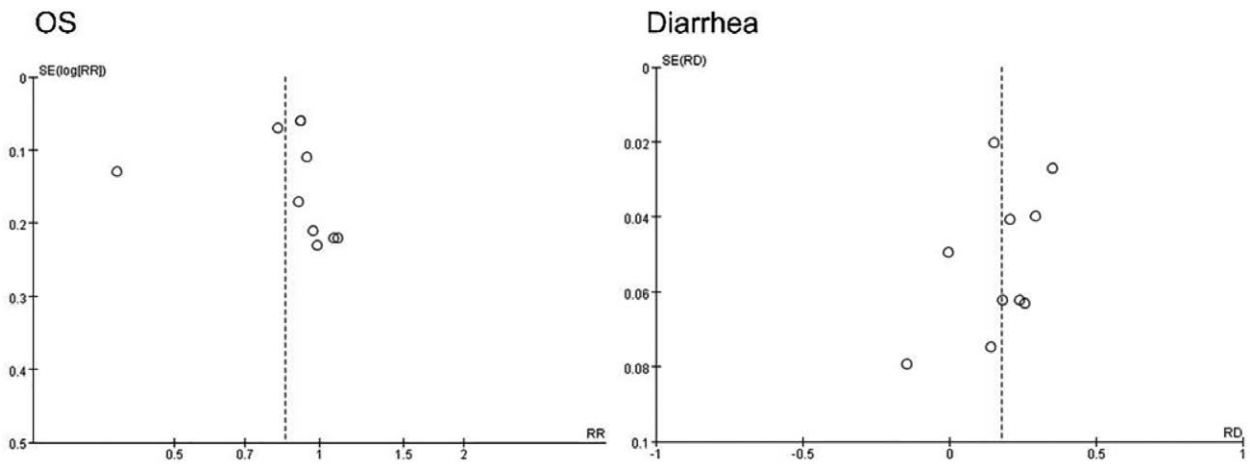

Figure 8. Publication bias analysis of the included studies.

placebo or adjuvant chemotherapy without any specific differentiation between them. The bias was reduced by comparing the interventions of experimental and control groups. Furthermore, this meta-analysis looked at both EGFR-TKIs from the 1st and 3rd generations. In addition, a small number of published articles focus on the effects of TKIs on the 3rd generation. Fourth, the study outcome might differ if there is a longer follow-up period. There has also been a lack of sufficient high-quality prospective clinical evidence to support the use of EGFR-TKIs as a therapy for patients with NSCLC. There is no firm standard of care and there is a clear heterogeneity between detection methodologies.

5. Conclusions

EGFR-TKI therapy significantly prolongs PFS and OS in patients with NSCLC based on our most recent analysis. EGFR-TKI treatment, however, was associated with an increase in AEs.

Author contributions

Conceptualization: Xiaoming Lai, Junlan Xiao.
Data curation: Xiaoming Lai, Jinlin Zeng, Zhijun Xiao, Junlan Xiao.
Formal analysis: Xiaoming Lai.
Funding acquisition: Xiaoming Lai.
Software: Xiaoming Lai.
Validation: Xiaoming Lai.
Visualization: Xiaoming Lai.
Writing – original draft: Xiaoming Lai, Junlan Xiao.
Writing – review & editing: Xiaoming Lai, Junlan Xiao.
Investigation: Jinlin Zeng, Zhijun Xiao, Junlan Xiao.
Methodology: Junlan Xiao.

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