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Research Article

Efficacy and Safety of Pemetrexed and Gefitinib in the Treatment of Non-Small-Cell Lung Cancer: A Meta-Analysis

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Object. This study is aimed at evaluating the efficacy and safety of pemetrexed and gefitinib in the treatment of non-small-cell lung cancer (NSCLC). *Methods*. Databases, including PubMed, the Cochrane Library, Embase, CNKI, and Web of Science, were applied to search for randomized controlled trials (RCTs) about the use of pemetrexed and gefitinib in the second-line treatment of locally advanced and metastatic NSCLC from database foundation to April 2020. Meta-analysis was conducted using the RevMan 5.3 software. Primary outcomes included progression-free survival (PFS) and overall survival (OS), and secondary outcomes included objective response rate (ORR), disease control rate (DCR), and all grades of drug-related adverse events (AEs). *Results*. Totally, 14 RCTs and 1,334 patients were involved in the study. The results of meta-analysis showed that compared with pemetrexed, gefitinib was not superior in improving ORR ($P = 0.21$), DCR ($P = 0.52$), PFS ($P = 0.41$), and OS ($P = 0.79$). Subgroup analysis showed that in patients with mutant EGFR ($P = 0.08$) and wild-type EGFR ($P = 0.80$), both pemetrexed and gefitinib produced a similar effect on PFS. In terms of safety, the incidence of rash ($P < 0.00001$) and diarrhea ($P = 0.0005$) in the gefitinib group was significantly higher than those in the pemetrexed group, while the occurrence of neutropenia ($P = 0.01$) and fatigue ($P = 0.02$) was significantly lower. *Conclusion*. Gefitinib and pemetrexed showed similar efficacy and safety, regardless of the type of EGFR. Both gefitinib and pemetrexed can be used as conventional drugs for the second-line treatment of locally advanced and metastatic NSCLC.

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) is the most common type, accounting for about 80%-85% of all lung cancers [2]. Most patients diagnosed with NSCLC are in advanced stage or locally advanced metastatic period. Platinum-based chemotherapy is used as the standard first-line chemotherapy regimen at present for advanced NSCLC [3], but it can only take effect on 30%-40% of patients and contribute to a median survival time of only 8 to 11 months [4]. Compared with the optimal supportive treatment, platinum-based chemotherapeutics can improve patient's overall survival (OS) and progression-free survival (PFS). However, most patients will develop drug resistance after several periods of platinum-based first-line chemotherapy, on which occasion second-line chemotherapy is recommended [5]. At present, second-line chemotherapeutics mainly include docetaxel, pemetrexed, and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) (gefitinib and erlotinib) [6]. This study is aimed at comparing the efficacy and safety of pemetrexed and gefitinib in the treatment of NSCLC.

Pemetrexed is a new antifolate drug, and its combination with platinum drugs (cisplatin or carboplatin) has been widely recognized as the mainstay in first-line chemotherapy of NSCLC. Pemetrexed works by disrupting folic-acid-dependent metabolic processes that are critical to cancer cells. Gefitinib is one of the first-generation reversible EGFR-TKIs, and it is usually used in second-line or third-line treatment for advanced NSCLC [7]. In a phase II clinical trial, gefitinib was identified to have a significant antitumor

effect on progressive NSCLC or on NSCLC with brain metastasis [8], with good tolerance [9]. However, it was also reported that gefitinib could not increase the OS and disease-free survival (DFS) of NSCLC patients, and more toxic reactions occurred in patients [10]. In recent years, some scholars have probed into the efficacy and safety of gefitinib and pemetrexed in the second-line treatment of advanced NSCLC, yet most of the conclusions are different and the sample size is relatively small.

This study comprehensively compared the efficacy and safety of gefitinib and pemetrexed in the second-line treatment of locally advanced and metastatic NSCLC with a systematic evaluation method. We hope that this study can provide more evidences for the rational choice of second-line drugs in the treatment of locally advanced and metastatic NSCLC.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria

2.1.1. Type. Randomized controlled trials (RCTs).

2.1.2. Objective

(1) Patients who were diagnosed with locally advanced and metastatic (stage III b or IV) NSCLC by pathology or cytology

(2) Patients who had undergone at least one course of platinum-based chemotherapy but failed

(3) Patients who had at least one measurable focus

(4) Patients who had an ECOG PS score of 0-2

(5) Patients who had no obvious contraindications to chemotherapy

2.1.3. Interventions. Gefitinib was given by oral in the test group, while pemetrexed was given for systemic chemotherapy in the control group.

2.1.4. Outcome Index

(1) Objective response rate (ORR): according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [11], ORR is divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). ORR = (CR + PR)

(2) Disease control rate (DCR): DCR = (CR + PR + SD)

(3) Progression-free survival (PFS): time (months) from the start of treatment to disease progression or the last follow-up visit without progression

(4) Overall survival (OS): time (months) from the start of treatment to death due to any cause

(5) Adverse events (AEs) of all grades: according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 of the National Cancer Institute [12], drug-related AEs include rash, diarrhea, neutropenia, and fatigue

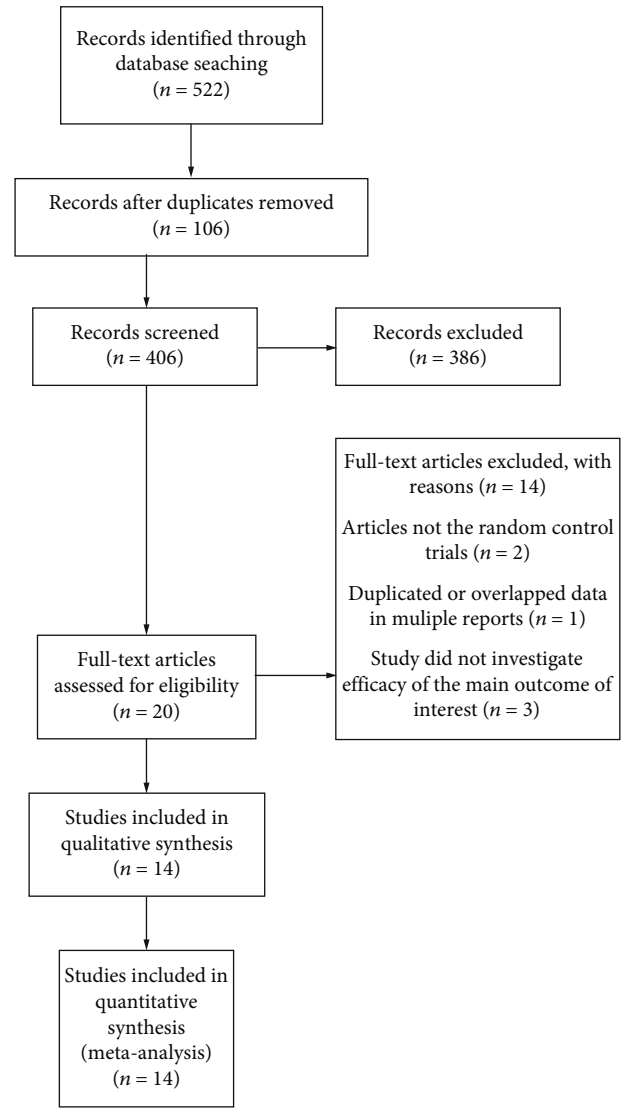


Figure 1: Flow chart for literature screening.

2.1.5. Exclusion Criteria

(1) Non-English or non-Chinese literature

(2) Repeatedly published literature

(3) Patients who had already been treated by pemetrexed or gefitinib or other micromolecular TKIs

(4) Patients who had been treated by gefitinib or pemetrexed as first-line treatment or maintenance treatment

(5) Patients who had other small cell lung cancers or other malignant tumors

2.2. Search Strategies. Databases including PubMed, the Cochrane Library, Embase, CNKI, and Web of Science were searched to find RCTs about the use of pemetrexed and

Table 1: Primary characteristics of the eligible studies in more detail.

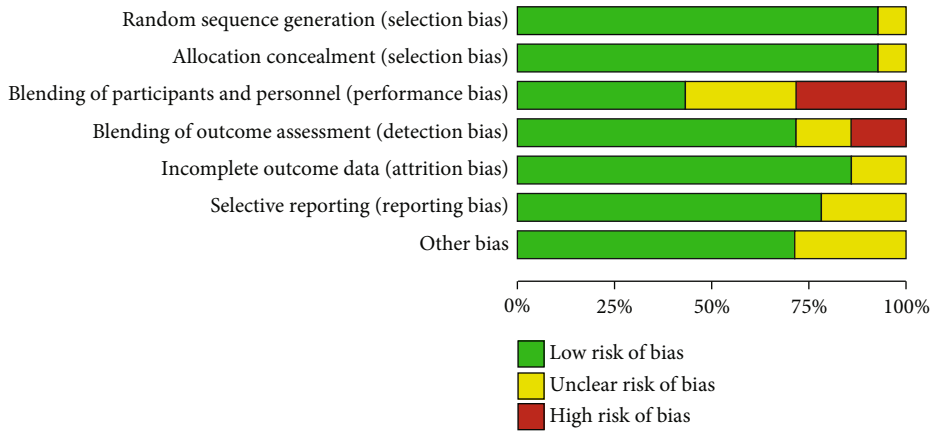
Author	Year	Country	Treatment	No. of patients	Gender (male/female)	Median age	Median follow-up time	Outcomes
Hong J	2010	Korea	C: pemetrexed	20	17/3	62	12.1 months	ORR, DCR, PFS, OS, AE
			T: gefitinib	20	9/11	61		
Sun JM	2012	Korea	C: pemetrexed	67	10/57	64	15.9 months	ORR, PFS, OS, AE
			T: gefitinib	68	10/58	58		
Dai HY	2013	China	C: pemetrexed	23	14/9	61	NR	ORR, DCR, PFS, AE
			T: gefitinib	23	15/8	62		
Zhou Q	2014	China	C: pemetrexed	76	47/29	55.9	10.6 months	ORR, DCR, PFS, OS, AE
			T: gefitinib	81	54/27	57.5		
Kim YS	2016	Korea	C: pemetrexed	47	33/14	64	60.6 months	ORR, DCR, PFS, OS, AE
			T: gefitinib	48	35/13	67		
Xu YH	2015	China	C: pemetrexed	94	NR	NR	NR	ORR, DCR, AE
			T: gefitinib	94	NR	NR		
Lin L	2016	China	C: pemetrexed	48	36/12	57	25 months	ORR, DCR, PFS, OS, AE
			T: gefitinib	53	29/24	59		
Liu XM	2015	China	C: pemetrexed	22	13/9	61.3	NR	ORR, DCR, PFS, AE
			T: gefitinib	20	13/7	62.3		
Song TT	2015	China	C: pemetrexed	60	36/24	54.9	NR	ORR, DCR, AE
			T: gefitinib	60	38/22	55.7		
Wang MQ	2012	China	C: pemetrexed	38	25/13	63.3	NR	ORR, DCR, AE
			T: gefitinib	37	23/14	64.2		
Zhang DG	2016	China	C: pemetrexed	55	30/25	65	NR	ORR, DCR, AE
			T: gefitinib	50	17/33	67		
Zhang J	2012	China	C: pemetrexed	40	26/14	NR	6 months	ORR, DCR, AE
			T: gefitinib	40	19/21	NR		
Zhang YH	2009	China	C: pemetrexed	32	13/15	56	NR	ORR, DCR, AE
			T: gefitinib	35	12/23	58		
Zhao LH	2013	China	C: pemetrexed	41	NR	NR	NR	ORR, DCR, AE
			T: gefitinib	42	NR	NR		

NR: no report; T: treatment group; C: control group; ORR: overall response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; AE: adverse event.

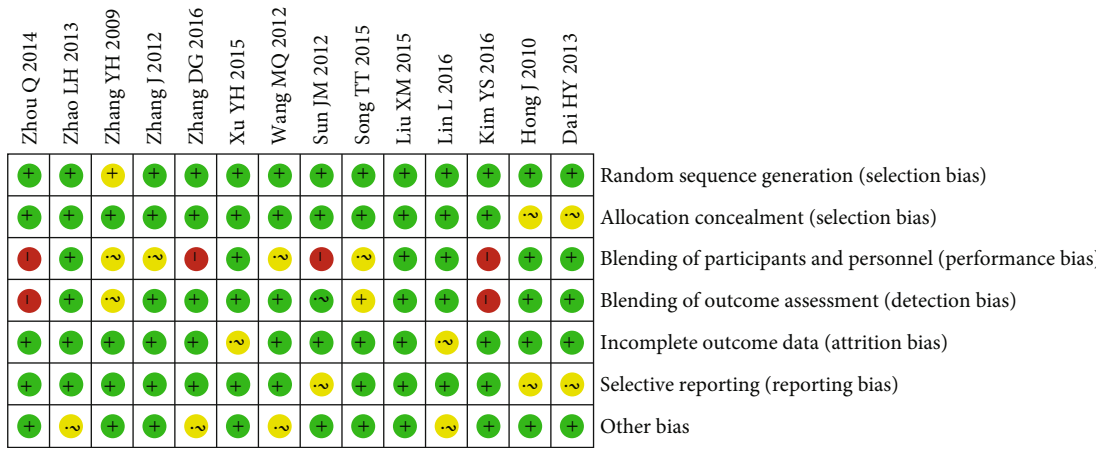
gefitinib in the second-line treatment of locally advanced and metastatic NSCLC from foundation to April 2020. The search was performed using free words and subject terms together. Retrieval keywords and related medical subject headings (MeSHs) are as follows: "gefitinib", "pemetrexed", and "non-small cell lung cancer". References from the conforming articles were also searched manually to check other related articles.

2.3. Literature Screening, Data Extraction, and Evaluation of the Risk of Bias for the Included Literature. Literature screening and data extraction were done by two researchers independently. The data were cross-checked, and if there was a discrepancy, they would discuss or ask for a third party. Data were extracted with a self-designed extraction form, including (1) basic information of the included literature, such as the first author and the published year; (2) baseline characteristics, such as case number, gender ratio, age, and follow-up time; and (3) outcome indexes and measurement data. The risk of bias for the included literature was evaluated by the bias risk assessment tool recommended in Cochrane 5.1.0 [13], including random sequence generation, allocation concealment, blind evaluation, incomplete result data, selective reporting, and other biases. Each quality item is classified as low risk, high risk, or unclear risk.

2.4. Statistics Analysis. Meta-analysis was conducted using RevMan 5.3. The odds ratio (OR) was used as the effect indicator for enumeration data, and the hazard ratio (HR) was used for measurement data. The effect size was provided with a point estimate value and a 95% confidence interval (CI). The chi-square test was used to study the heterogeneity of the study results (test standard, $\alpha = 0.1$), and the degree was quantitatively judged by I^2. If $I^2 \leq 50\%$ and $P \geq 0.1$, there is no statistical heterogeneity among the studies, and a fixed-effects model will be used for meta-analysis. Instead, the origin of the heterogeneity will be further explored and a random-effects model will be used for meta-analysis after obvious clinical heterogeneity is excluded. Obvious clinical heterogeneity was treated by subgroup analysis or sensitivity



(a) Overall risk of bias



(b) Risk of bias for each RCT

Figure 2: Cochrane's bias risk assessment.

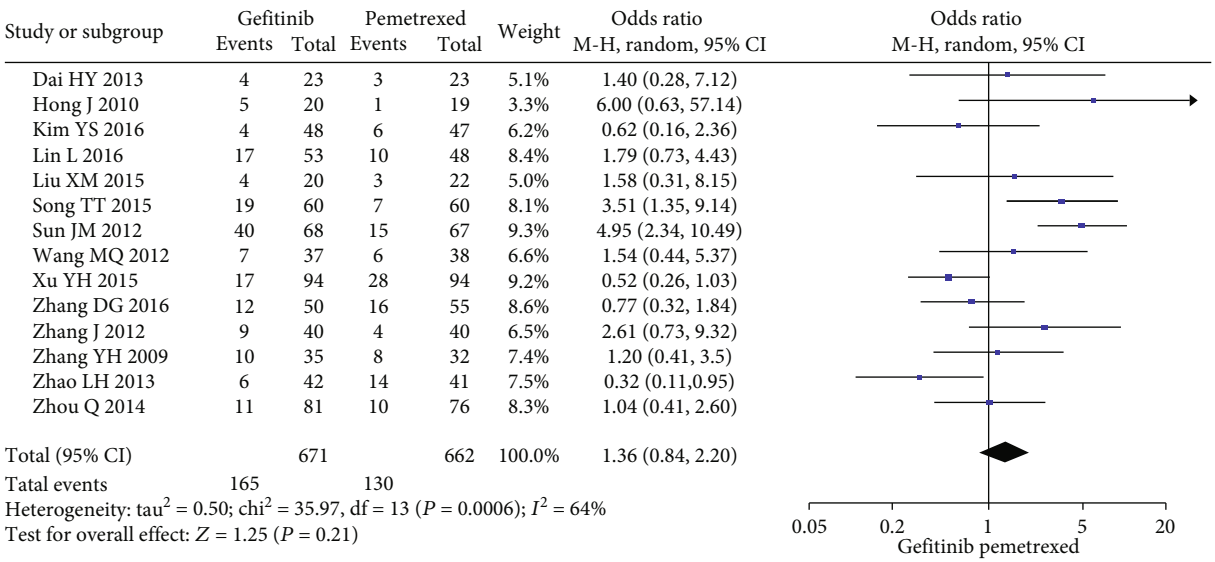


Figure 3: Comparison of ORR between the gefitinib group and the pemetrexed group.

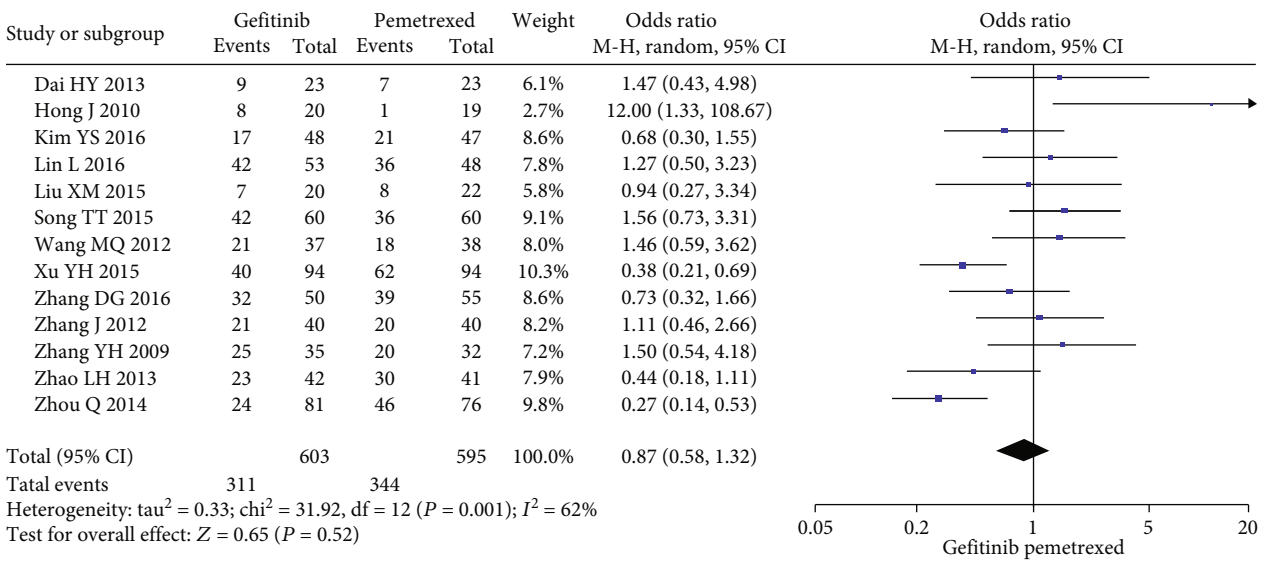


Figure 4: Comparison of DCR between the gefitinib and pemetrexed groups.

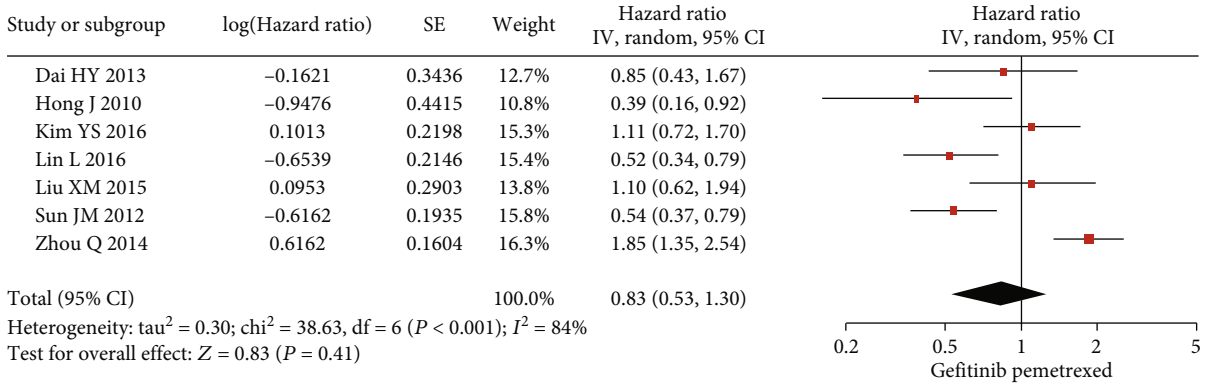


Figure 5: Comparison of PFS between the gefitinib and pemetrexed groups.

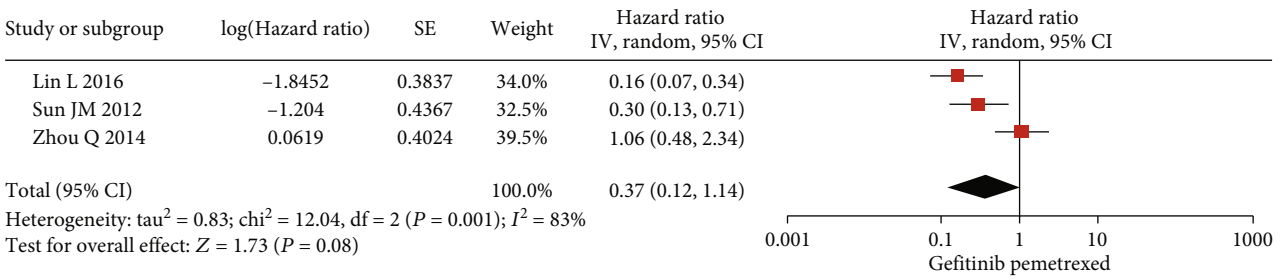


Figure 6: Comparison of PFS between the gefitinib and pemetrexed groups in the treatment of NSCLC with EGFR mutations.

analysis, or descriptive analysis only. In addition, potential publication bias was assessed via visual observation on the funnel plot. The test standard of meta-analysis was set to $\alpha = 0.05$.

3. Results

3.1. Literature Screening and Basic Characteristics of the Literature Involved in the Study. Totally, 522 references were initially obtained, 116 duplicates were eliminated, and 14 RCTs were eventually involved in the study after further screening by reading the title, the abstract, and the whole text [14–27]. The screening procedure is shown in Figure 1. Totally, 1,334 patients were involved, with 671 in the test group and 663 in the control group. Among the 14 RCTs, 6 were written in English and 8 were in Chinese. The basic characteristics of the involved studies are listed in Table 1. In addition, the risk of bias for the included studies was

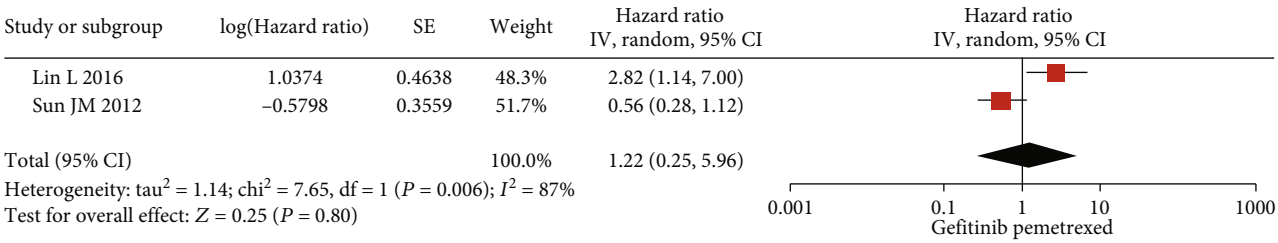


Figure 7: Comparison of PFS between the gefitinib and pemetrexed groups in the treatment of NSCLC with wild-type EGFR.

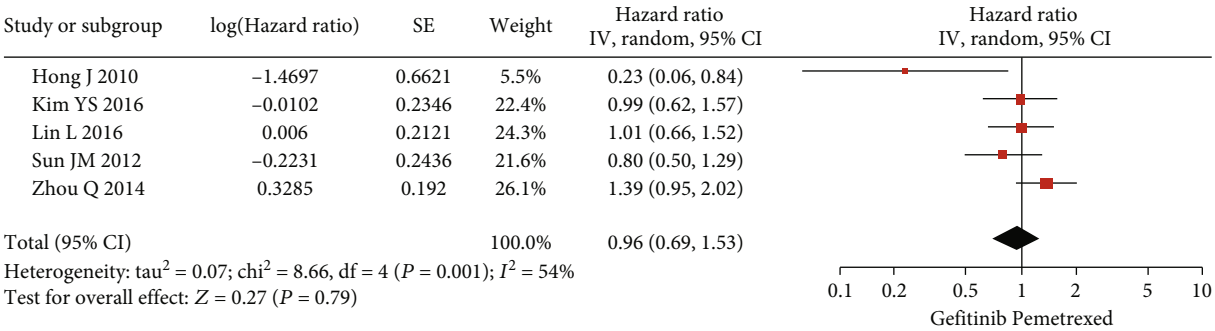


Figure 8: Comparison of OS between the gefitinib and pemetrexed groups.

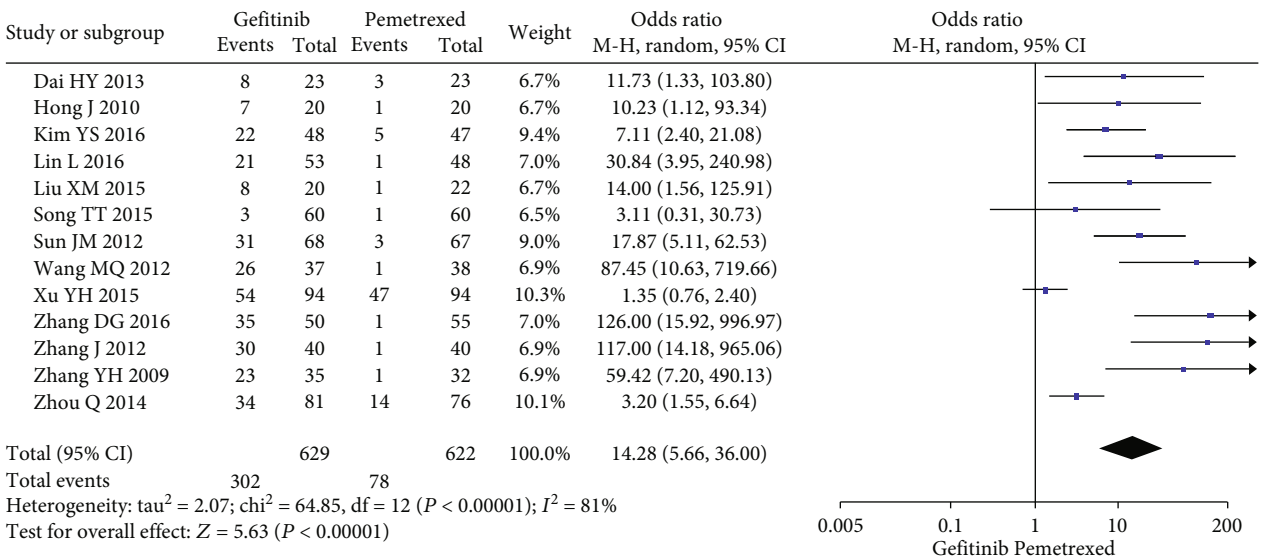


Figure 9: Comparison of rash occurrence rate between the gefitinib and pemetrexed groups.

assessed using Cochrane's bias risk assessment tool. Figure 2(a) shows the results of the overall risk of bias assessment, and Figure 2(b) shows the risk of bias for each included trial. The results showed that most of the included RCTs were of high quality.

3.2. Meta-Analysis

3.2.1. ORR. Fourteen RCTs were involved. The results of meta-analysis using a random-effects model showed that the difference in ORR between the gefitinib group and the pemetrexed group was not statistically significant (OR = 1.36, 95% CI (0.84, 2.20), $P = 0.21$), as shown in Figure 3.

3.2.2. DCR. Thirteen RCTs were involved. The results of the meta-analysis using a random-effects model showed that the difference in DCR between the gefitinib group and the pemetrexed group was not statistically significant (OR = 0.87, 95% CI (0.58, 1.32), $P = 0.52$), as shown in Figure 4.

3.2.3. PFS and OS. Seven RCTs were involved to study patient's PFS. The results of meta-analysis using a random-effects model showed that there was no statistically

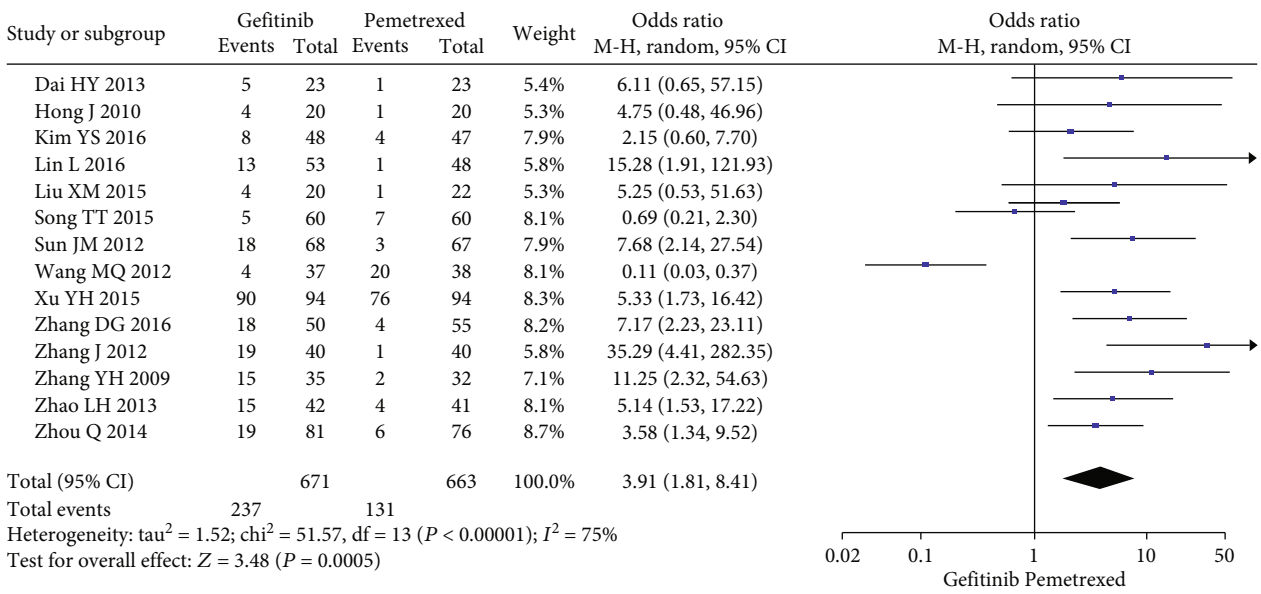


Figure 10: Comparison of diarrhea occurrence rate between the gefitinib and pemetrexed groups.

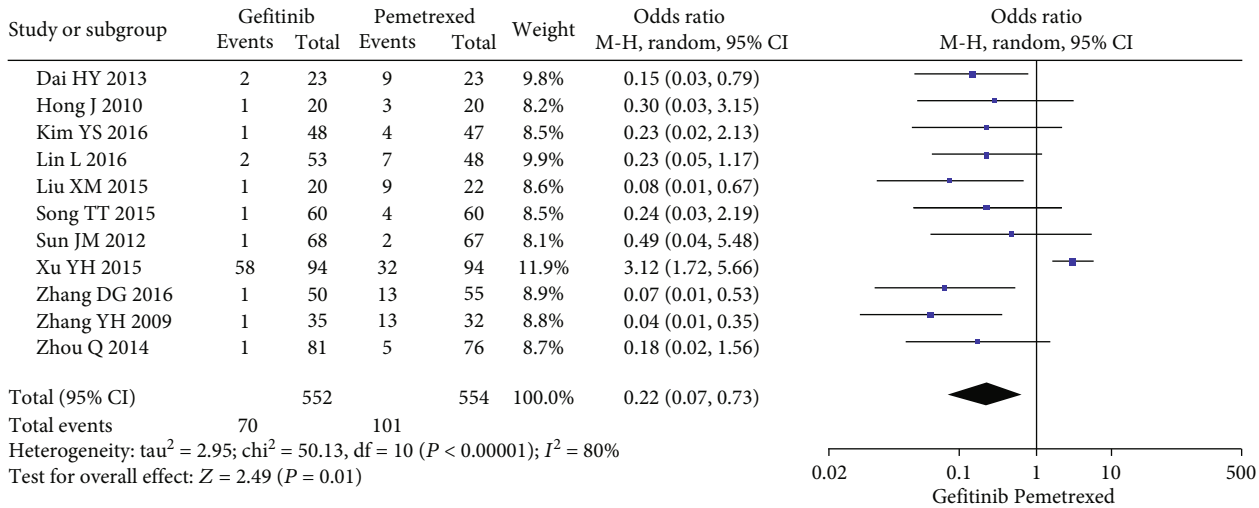


Figure 11: Comparison of neutropenia occurrence rate between the gefitinib and pemetrexed groups.

significant difference in PFS between the gefitinib group and the pemetrexed group (HR = 0.83, 95% CI (0.53, 1.30), $P = 0.41$) (Figure 5). In addition, subgroup analysis indicated that both gefitinib and pemetrexed showed a similar effect on PFS in patients with mutant EGFR (HR = 0.37, 95% CI (0.12, 1.14), $P = 0.08$) (Figure 6) and wild-type EGFR (HR = 1.22, 95% CI (0.25, 5.96), $P = 0.80$) (Figure 7). Five RCTs were involved to study patient's OS. The results of meta-analysis using a random-effects model showed there was no statistically significant difference in OS between the gefitinib group and the pemetrexed group (HR = 0.96, 95% CI (0.69, 1.33), $P = 0.79$) (Figure 8).

3.2.4. Occurrence Rate of Rash. Thirteen RCTs were involved. The results of meta-analysis on a random-effects model showed that the occurrence rate of rash in the gefitinib group was markedly higher than that in the pemetrexed group and the difference was statistically significant (OR = 14.28, 95% CI (5.66, 36.00), $P < 0.00001$) (Figure 9).

3.2.5. Occurrence Rate of Diarrhea. Fourteen RCTs were involved. The results of meta-analysis on a random-effects model showed that the occurrence rate of diarrhea in the gefitinib group was markedly higher than that in the pemetrexed group and the difference was statistically significant (OR = 3.91, 95% CI (1.81, 8.41), $P = 0.0005$) (Figure 10).

3.2.6. Occurrence Rate of Neutropenia. Eleven RCTs were involved. The results of meta-analysis on a random-effects model showed that the occurrence rate of neutropenia in the gefitinib group was markedly lower than that in the

Study or subgroup	Gefitinib Events	Gefitinib Total	Pemetrexed Events	Pemetrexed Total	Weight	Odds ratio M-H, random, 95% CI
Dai HY 2013	1	23	8	23	6.5%	0.09 (0.01, 0.75)
Hong J 2010	1	20	6	20	6.3%	0.12 (0.01, 1.14)
Kim YS 2016	10	48	21	47	11.8%	0.33 (0.13, 0.80)
Lin L 2016	5	53	8	48	10.5%	0.52 (0.16, 1.72)
Liu XM 2015	1	20	10	22	6.5%	0.06 (0.01, 0.56)
Sun JM 2012	15	68	14	67	12.2%	1.07 (0.47, 2.44)
Xu YH 2015	89	94	71	94	11.3%	5.77 (2.09, 15.93)
Zhang DG 2016	11	50	23	55	12.0%	0.39 (0.17, 0.92)
Zhang YH 2009	7	35	16	32	11.0%	0.25 (0.08, 0.74)
Zhou Q 2014	8	81	23	76	11.9%	0.25 (0.10, 0.61)
Total (95% CI)		492		484	100.0%	0.41 (0.19, 0.87)
Total events	148		200			

Heterogeneity: tau^2 = 1.03; chi^2 = 38.22, df = 9 ($P < 0.0001$); I^2 = 76%
Test for overall effect: $Z = 2.34$ ($P = 0.02$)

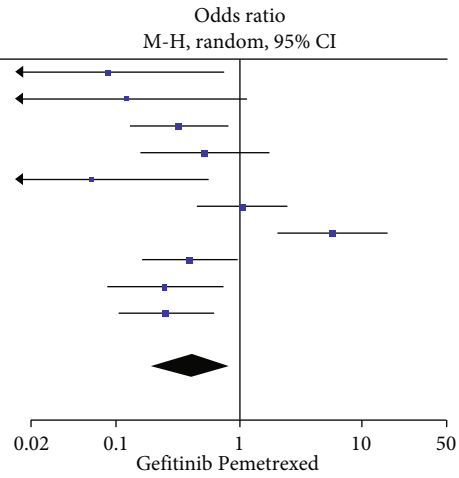


Figure 12: Comparison of fatigue occurrence rate between the gefitinib and pemetrexed groups.

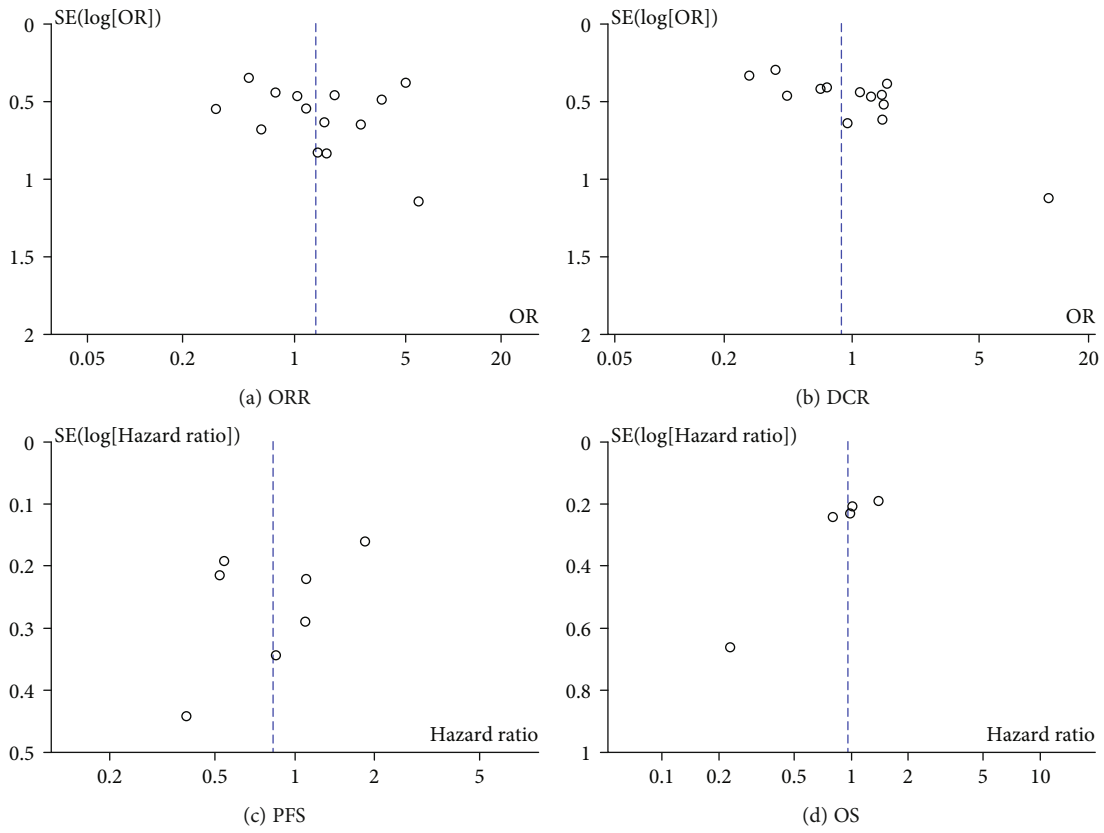


Figure 13: Funnel plots.

pemetrexed group and the difference was statistically significant (OR = 0.22, 95% CI (0.07, 0.73), $P = 0.01$) (Figure 11).

3.2.7. Occurrence Rate of Fatigue. Ten RCTs were involved. The results of meta-analysis on a random-effects model showed that the occurrence rate of fatigue in the gefitinib group was markedly lower than that in the pemetrexed group and the difference was statistically significant (OR = 0.41, 95% CI (0.19, 0.87), $P = 0.02$) (Figure 12).

3.3. Publication Bias. Visually, the funnel plots were basically symmetrical (Figure 13), indicating that there was no publication bias in ORR, DCR, PFS, and OS.

4. Discussion

As a routine therapy for NSCLC, first-line chemotherapy can prolong a patient's lifetime to some extent, yet its efficacy in patients with advanced NSCLC is poor and patients always

have an unfavorable prognosis [28]. In recent years, with the emergence and development of molecular targeted therapies, studies found that molecular targeted therapy has increasingly shown its advantages in the treatment of lung cancer. In this study, we systematically evaluated the efficacy and safety of pemetrexed and gefitinib in the second-line treatment of locally advanced and metastatic NSCLC.

Pemetrexed is a multitargeted antimetabolite drug and a thymidylate synthase/dihydrofolate reductase inhibitor. It has a strong inhibitory effect on several folate-dependent enzymes. It can inhibit the synthesis of pyrimidine and purine by many methods, thus playing an antitumor role and reducing drug resistance [29]. Pemetrexed-based second-line therapy for advanced NSCLC was reported to have similar efficacy with docetaxel but have minor toxic and side effects [30]. In 2004, pemetrexed was approved to be used in second-line treatment for advanced NSCLC by the U.S. Food and Drug Administration. Gefitinib is a peroral micromolecular EGFR-TKI. It can inhibit the EGFR signaling pathway by competing with adenosine triphosphate (ATP) to bind to the catalyze zone of receptor tyrosine kinase, thus inhibiting cancer cell proliferation and promoting tumor cell apoptosis, ultimately mediating tumor growth and prolonging a patient's lifetime [31]. A phase III IPASS test verified that [32] gefitinib used in first-line therapy for advanced NSCLC can increase ORR and DCR and prolong PFS without severe AEs. However, gefitinib cannot be used in all patients with advanced NSCLC, and its efficacy is more obvious in the benefit population. Rosell and the fellows found when they screened EGFR mutations on 2,105 Spanish patients with lung cancer that the rate of EGFR mutation was high in nonsmoking and female patients with adenocarcinoma [33]. Women, Asians, nonsmokers, and patients with adenocarcinoma are now considered as the benefit populations of gefitinib treatment. The China Food and Drug Administration approved gefitinib for the first-line treatment of patients suffering from advanced NSCLC with EGFR-sensitive mutations on February 22, 2011. Notably, here, we found that for patients with EGFR mutation-positive NSCLC, gefitinib was not superior to pemetrexed in terms of PFS, which might be related to the predominance of the patients who smoked, had adenocarcinoma, had EGFR-sensitive mutation-negative NSCLC, or had unknown mutations in all included studies. In recent years, second-line therapy has become a hotspot in NSCLC research, and many scholars have explored the role of gefitinib as a second-line drug in the treatment of NSCLC. In order to compare the efficacy of gefitinib and docetaxel in patients with advanced NSCLC who had received first-line chemotherapy, Kim and fellows designed a phase III randomized trial (INTEREST) [34]. 1,466 patients from 24 countries and 149 hospitals were involved into this trial, and the results showed that gefitinib produced similar efficacy with docetaxel and there was no significant difference regarding OS and PFS between the two therapies. This trial identified the important role of gefitinib in the second-line treatment of NSCLC. A recent meta-analysis discussed the efficacy of gefitinib in the treatment of advanced NSCLC. The results showed that gefitinib may be more beneficial to patients with EGFR mutations compared with standard first-line or second-line chemotherapy or maintenance therapy [35]. Our study is mainly aimed at the gefitinib-based second-line treatment. However, in patients with EGFR mutations, compared with pemetrexed, gefitinib-based second-line treatment in locally advanced and metastatic NSCLC produced no benefit in PFS, while the differences in ORR, DCR, and OS between pemetrexed and gefitinib groups were not statistically significant, which is consistent with previous studies [36]. In addition, we found that in terms of AEs, the occurrence rate of rash and diarrhea in the gefitinib group was higher than that in the pemetrexed group, while the occurrence of neutropenia and fatigue in the gefitinib group was significantly lower than that of the pemetrexed group.

This study has some limitations. First of all, most studies included were conducted in China, and the results may not fully reflect the treatment situation in other countries, and the sample size is small. Second, in the included studies, there are biases in the length of follow-up time, treatment strategy, and time, which may cause the heterogeneity of clinical results to a certain extent. Although we conducted a subgroup analysis regarding the wild/mutant EGFR, there was still a large heterogeneity in the results, which may be related to the small cohort for EGFR mutations. Third, different first-line treatment methods may have an impact on final clinical outcomes. For example, a review discussed the necessity of EGFR-TKIs in first-line treatment for NSCLC, so as to provide the most effective therapeutic regimen in initial treatment [37]. Finally, meta-analysis is limited to the data provided by the original study authors. In some cases, information such as disease status, smoking status, and pathological subtype is incomplete and cannot be used for subgroup analysis.

In conclusion, gefitinib and pemetrexed for the treatment of locally advanced and metastatic NSCLC patients with failed first-line chemotherapy have similar efficacy and safety. In the future, more well-designed RCTs are needed for further verification.

Data Availability

The data used to support the findings of this study are included within the article. The data and materials in the current study are available from the corresponding author on reasonable request.

Consent

Consent is not applicable.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

Authors' Contributions

All authors contributed to data analysis and drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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