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Meta-analysis

First-line therapeutic strategy for patients with advanced non–small cell lung cancer with Leu858Arg epidermal growth factor receptor mutations: a Bayesian network meta-analysis

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Abstract

Aim: The objective of this network meta-analysis was to determine the most useful first-line therapeutic strategy for patients with advanced (IIIB/IV or relapsed) non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Leu858Arg or EGFR 19del mutations.

Methods: PubMed, the Web of Science, Medline, and reports of the top three world cancer conferences (WCLC, ESMO, and ASCO) were searched for appropriated randomized controlled studies (RCTs) discussing the use of various generations of tyrosine kinase inhibitors (TKIs; gefitinib, erlotinib, icotinib, afatinib, dacomitinib, osimertinib, aumolertinib), chemotherapy [pemetrexed-based chemotherapy (PC), non-pemetrexed-based chemotherapy (NPC)], and different combined therapies (osimertinib plus bevacizumab, afatinib plus cetuximab, erlotinib plus bevacizumab, erlotinib plus ramucirumab, gefitinib plus apatinib, gefitinib plus PC, and gefitinib plus pemetrexed) to treat patients with advanced NSCLC with EGFR Leu858Arg or 19del mutations. OpenBugs and Stata software were used to analyze the data.

Results: We included 21 studies with 16 arms (including 2479 cases with EGFR Leu858Arg mutations and 3325 cases with EGFR 19del mutations). Among patients with NSCLC with EGFR Leu858Arg mutations, compared with the first-generation TKIs (such as gefitinib), the second- or third-generation TKIs [dacomitinib: hazard ratio (HR) = 0.63; 95% confidence index (CI) = (0.45, 0.89); osimertinib: HR = 0.63; 95% CI = (0.42, 0.97)] showed significant benefits in improving progression-free survival (PFS), as did afatinib plus cetuximab [HR = 1.98; 95% CI = (1.01, 3.95)], erlotinib plus bevacizumab [HR = 1.79; 95% CI = (1.22, 2.62)], and erlotinib plus ramucirumab [HR = 1.62; 95% CI = (1.07, 2.48)]. In terms of overall survival (OS), these 16 arms showed no significant differences between each other ($p > 0.05$). Among patients with NSCLC with EGFR 19del mutations, compared with the first- or second-generation TKIs (such as gefitinib and afatinib), aumolertinib [*versus* gefitinib: HR = 0.39; 95% CI = (0.28, 0.55) *versus* afatinib: HR = 0.53; 95% CI = (0.35, 0.84)] and osimertinib [*versus* gefitinib: HR = 0.40; 95% CI = (0.32, 0.51) *versus* afatinib: HR = 0.53, 95% CI = (0.38, 0.79)] showed significantly beneficial effects. Among these first-line therapeutic strategies for patients with EGFR Leu858Arg mutations, the combination of afatinib and cetuximab ranked as the best to prolong PFS (33.0%). For NSCLC patients with 19del mutations, however, osimertinib plus bevacizumab was the best at prolonging PFS (84.3%).

Conclusion: For NSCLC patients with EGFR Leu858Arg mutations, the second-generation TKIs, the third-generation TKIs, and the combined treatments showed better efficacy than the first-generation TKIs for PFS. There were, however, no significant differences between each group for OS.

Keywords: epidermal growth factor receptor, meta-analysis, non–small cell lung cancer, tyrosine kinase inhibitors

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Introduction

Lung cancer contributed to over 130,000 deaths in 2020.[1] The use of targeted therapies and immunotherapies has increased the 5-year survival rate of non–small cell lung cancer (NSCLC) to over 15%, even reaching 50%.[2–5] The overall prevalence of epidermal growth factor receptor (EGFR) mutations is 49.1% for Asian patients and 12.8% among European patients with NSCLC.[6] For patients with EGFR-mutant NSCLC, the standard treatment is tyrosine kinase inhibitors [TKIs; first generation (gefitinib, erlotinib, and icotinib), second generation (afatinib and dacomitinib), and third generation (osimertinib and aumolertinib)], which improved overall survival (OS) and were recommended by the National Comprehensive Cancer Network (NCCN) NSCLC guidelines.[7] Furthermore, the combination of TKIs with other therapies (e.g. chemotherapy, bevacizumab, ramucirumab, and apatinib) also showed beneficial results for survival.[8–13]

Among patients with EGFR mutations, 42% are Leu858Arg mutations.[14] Rosell *et al*[15] reported that erlotinib significantly improved progression-free survival (PFS) compared with chemotherapy in EGFR 19del-mutated NSCLC instead of the Leu858Arg-mutated subgroup. Studies also proved that when treated using various generations of EGFR TKIs, patients with NSCLC with EGFR Leu858Arg mutations experienced worse clinical outcomes than those with 19del mutations.[16–18]

In 2019, Zhao *et al.*[19] conducted a network meta-analysis and performed a subgroup analysis of Leu858Arg mutations. The result showed that among the Leu858Arg subgroup, gefitinib plus pemetrexed-based chemotherapy (PC) was the best strategy to improve PFS, and dacomitinib was the most promising regimen to prolong OS. To date, several multicenter studies (including ACTIVE,[8] SWOG 1403,[20] BEVERLY,[21] WJOG9717L,[22] and AENEAS[23]) have shown impressive results. In this study, we collected data from patients with Leu858Arg or 19del mutations and clarified the efficacy of different antitumor agents among them.

Methods

This meta-analysis follows the PRISMA reporting guidelines. Two investigators independently searched PubMed, Web of Science, MEDLINE, and the latest reports from world lung cancer conferences [World Conference of Lung Cancer (WCLC), European Society for Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO)] for appropriate studies about using various EGFR TKIs and combined therapies in NSCLC with EGFR Leu8585Arg mutations. For example, in PubMed, we used the following keywords: 'EGFR' and 'NSCLC', and the study type was restricted as 'randomized controlled trial' or 'clinical trial.' Up to 29 November 2021, we found 1491 studies after deleting duplicates, and we finally included 21 randomized controlled trials (RCTs; including 2479 cases with EGFR Leu858Arg mutations and 3325 cases with EGFR 19del mutations). These enrolled studies contained 16 therapeutic arms [aumolertinib, osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, icotinib, osimertinib plus bevacizumab, afatinib plus cetuximab, erlotinib plus bevacizumab, erlotinib plus ramucirumab, gefitinib plus apatinib, gefitinib plus PC, gefitinib plus pemetrexed, PC, and non-pemetrexed-based chemotherapy (NPC)][8–11,13,15,20,24–35] (Figure 1).

Inclusion and exclusion criteria

The inclusion criteria comprised the following: (1) RCTs discussing first-line therapeutic strategies for patients with advanced NSCLC with EGFR Leu858Arg or EGFR 19del mutations, (2) primary outcome: PFS, and (3) only published in English. The exclusion criteria comprised the following: (1) review, retrospective research, case report, study with nonrandomized controlled designs; (2) single-arm studies; and (3) insufficient data in the articles.

Data extraction and risk of bias assessment

Two authors independently reviewed the identified abstracts and selected articles for full review. The third reviewer addressed the discrepancies. For each selected publication, the following baseline and study characteristics were extracted: first author, publication year, country, participant characteristics, total number of patients in the experiment and control groups, age of the patients in each group, other baseline characteristics, and the treatment dose of each group in these studies (Table 1). The primary outcome was PFS of selected NSCLC patients with EGFR Leu858Arg mutations. The secondary outcomes included OS of EGFR Leu858Arg mutations and PFS and OS of EGFR 19del mutations.

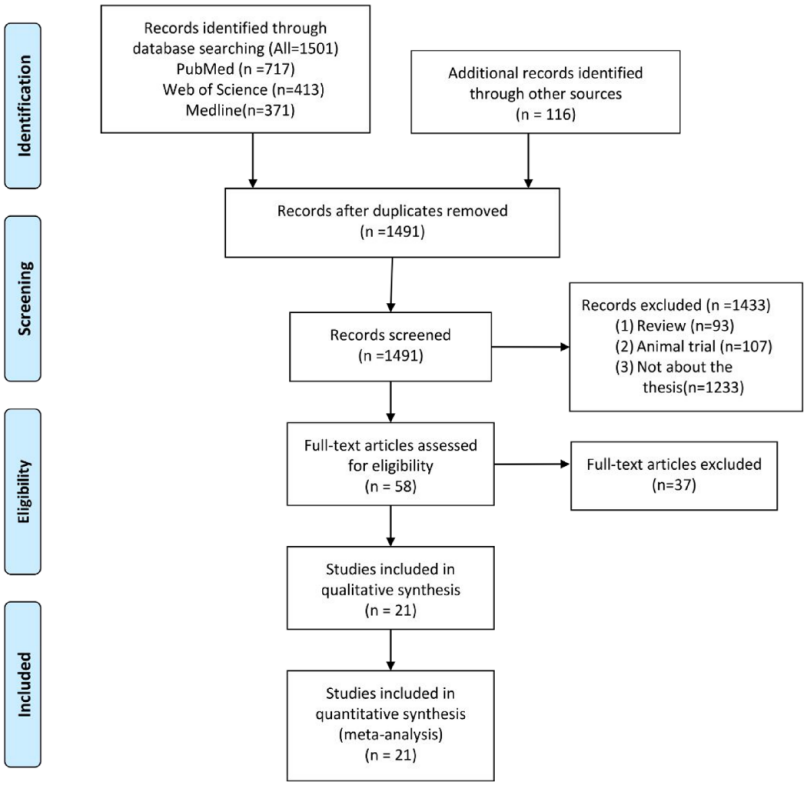

Figure 1. Flow diagram of the selection process of the included studies.

Statistical analysis

We pooled the data and used the hazard ratio (HR) and its associated confidence interval (CI) for the dichotomy outcome: PFS and OS of selected patients with EGFR Leu858Arg- or 19del-mutated NSCLC. All statistical analyses were performed using OpenBugs (version 3.2.3) and Stata (version 15.1; StataCorp LLC, College Station, Texas, USA). The results were calculated based on Bayesian algorithm.

Results

This study included 21 studies (2479 subjects with EGFR Leu858Arg mutations and 3325 subjects with EGFR 19del mutations).[8–11,13,15,20–35] The network maps of the various therapeutic arms for the results of PFS and OS of EGFR Leu858Arg mutations are shown in Figures 2 and 3, respectively.

For the PFS of patients with NSCLC with EGFR Leu858Arg mutations, compared with the first-generation TKIs (such as gefitinib and erlotinib), some of the second- or third-generation TKIs, such as dacomitinib [*versus* gefitinib: HR = 0.63; 95% CI = (0.45, 0.89) *versus* erlotinib: HR = 0.63; 95% CI = (0.41, 0.98)], osimertinib [*versus* gefitinib: HR = 0.51; 95% CI = (0.39, 0.67) *versus* erlotinib: HR = 0.51; 95% CI = (0.39, 0.67)], and aumolertinib [*versus* gefitinib: HR = 0.60; 95% CI = (0.40, 0.90) *versus* erlotinib: HR = 0.60; 95% CI = (0.38, 0.98)], showed significantly better beneficial effects. In addition, compared with gefitinib, afatinib plus cetuximab [HR = 1.98; 95% CI = (1.01, 3.90)], erlotinib plus bevacizumab [HR = 1.69; 95% CI = (1.18, 2.41)], and erlotinib plus ramucirumab [HR = 1.62; 95% CI = (1.06, 2.47)] also showed increased PFS. Compared with NPC, the other therapeutic strategies showed significantly improved PFS. For OS, however, none of the first-line therapeutic strategies showed significant differences between each of the groups (Table 2).

For the PFS of patients with EGFR 19del-mutated NSCLC, compared with the first- and second-generation TKIs (such as gefitinib, erlotinib, icotinib, and afatinib), the third-generation TKIs such as aumolertinib [*versus* gefitinib: HR = 0.39; 95% CI = (0.28, 0.55) *versus* erlotinib: HR = 0.45; 95% CI = (0.30, 0.68) *versus* icotinib:

Table 1. Baseline characteristics of the enrolled studies.

Study	Country and participants	Number of subjects (group A *versus* group B)	Age (group A *versus* group B)	Sex (group A *versus* group B)	Group A	Group B	Histopathological classification
AENEAS	China, multicenter	214 *versus* 215 (all) 74 *versus* 74 (Leu858Arg)	59 (32–78) *versus* 62 (25–81)	37.4% *versus* 37.2% (All)	Aumolertinib 110 mg/d	Gefitinib 250 mg/d	Adenocarcinoma (98.1% *versus* 98.1%)
WJOG9717L	Japan, multicenter	61 *versus* 61 (all) 26 *versus* 25 (Leu858Arg)	67 (41–86) *versus* 66 (29–85)	39.4% *versus* 37.7% (all)	Osimertinib 80 mg/d Bevacizumab 15 mg/kg, q3w	Osimertinib 80 mg/d	Nonsquamous NSCLC
BEVERLY	Italy, multicenter	80 *versus* 80 (all) 34 *versus* 32 (Leu858Arg)	65.9 (57.9–71.8) *versus* 67.7 (60.7–73.6)	35% *versus* 37.5% (all)	Erlotinib 150 mg/d plus bevacizumab 15 mg/kg, q3w	Erlotinib 150 mg/d	Nonsquamous NSCLC
NEJ009	Japan, multicenter (47 centers)	170 *versus* 172 (all) 69 *versus* 67 (Leu858Arg)	64.8 ± 7.8 *versus* 64.0 ± 8.4 (all)	32.9% *versus* 37.2% (all)	Gefitinib 250 mg/d combined with carboplatin AUC 5 and pemetrexed 500 mg/m^2	Gefitinib 250 mg/d	Adenocarcinoma (98.8% *versus* 98.8%)
NEJ026	Japan, multicenter (69 centers)	114 *versus* 114 (all)	67 (61–73) *versus* 68 (62–73) (all)	37.0% *versus* 35.0% (all)	Erlotinib 150 mg/d plus bevacizumab 15 mg/kg	Erlotinib 150 mg/d	Adenocarcinoma (98% *versus* 100%) Large-cell carcinoma (1% *versus* 0%) Other (1% *versus* 0%)
WJTOG3405	Japan, multicenter (36 centers)	86 *versus* 86 (all) (Leu858Arg)	64.0 (34–74) *versus* 64.0 (41–75)	31.4% *versus* 30.2% (all)	Gefitinib 250 mg/d	Docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2) for 28 days	Adenocarcinoma (96.5% *versus* 97.7%) Adenosquamous carcinoma (0% *versus* 1.2%) Squamous-cell carcinoma (1.2% *versus* 0%) Non–small cell lung cancer; not otherwise specified (2.3% *versus* 1.2%)
Archer 1050	China, multicenter (71 centers)	227 *versus* 225 (all) (Leu858Arg)	62 (53–68) *versus* 61 (54–68) (all)	36% *versus* 44% (all)	Dacomitinib 45 mg/d	Gefitinib 250 mg/d	/
RELAY	Japan, multicenter (100 centers in 13 countries)	224 *versus* 225 (all) (Leu858Arg)	65 (57–71) *versus* 64 (56–70) (all)	37% *versus* 37% (all)	Ramucirumab 10 mg/kg/2 weeks and erlotinib 150 mg/d	Erlotinib 150 mg/d	Adenocarcinoma (96% *versus* 97%) NSCLC not otherwise specified (4% *versus* 3%)
LUX-Lung 3	China, multicenter (133 centers in 25 countries)	230 *versus* 115 (all) 91 *versus* 47 (Leu858Arg)	61.5 (28–86) *versus* 61 (31–83)	36.1% *versus* 33.0% (all)	Afatinib 40 mg/d	Cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2)	Adenocarcinoma (100% *versus* 100%)

(Continued)

Table 1. (Continued)

Study	Country and participants	Number of subjects (group A *versus* group B)	Age (group A *versus* group B)	Sex (group A *versus* group B)	Group A	Group B	Histopathological classification
LUX-Lung 7	South Korea, multicenter (64 centers in 13 countries)	160 *versus* 159 (all) 67 *versus* 66 (Leu858Arg)	63 (30–86) *versus* 63 (32–89)	43% *versus* 33% (all)	Afatinib 40 mg/d	Gefitinib 250 mg/d	/
FLAURA	USA, multicenter	279 *versus* 277 (all) 104 *versus* 103 (Leu858Arg)	64 (26–85) *versus* 64 (35–93)	36% *versus* 38% (all)	Osimertinib 80 mg/d	Gefitinib 250 mg/d or erlotinib 150 mg/d	Adenocarcinoma (99% *versus* 98%) Others (1% *versus* 2%)
EURTAC	Spain, multicenter	86 *versus* 87 (all) 29 *versus* 29 (Leu858Arg)	63.4 ± 11.0 *versus* 64.2 ± 9.2	33% *versus* 22% (all)	Erlotinib 150 mg/d	Cisplatin 75 mg/m^2 (carboplatin AUC 6) on day 1 plus docetaxel (75 mg/m^2 on day 1) or gemcitabine (1250 mg/m^2 on days 1 and 8)	Adenocarcinoma (95% *versus* 90%) Bronchoalveolar adenocarcinoma (0% *versus* 2%) Large-cell carcinoma (3% *versus* 1%) Squamous-cell carcinoma (1% *versus* 0%) Other (0% *versus* 7%)
LUX-Lung 6	China, multicenter (36 centers)	242 *versus* 122 (all) 92 *versus* 46 (Leu858Arg)	58 (49–65) *versus* 58 (49–62)	36% *versus* 32% (all)	Afatinib 40 mg	Gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 75 mg/m^2 on day 1 (3-week schedule for up to 6 cycles)	Adenocarcinoma (100% *versus* 100%)
ACTIVE	China, multicenter (36 centers)	157 *versus* 156 (all) 74 *versus* 73 (Leu858Arg)	57 (51–65) *versus* 60 (51–65)	42% *versus* 39.7% (all)	Gefitinib 250 mg/d plus apatinib 500 mg/d	Gefitinib 250 mg/d	Adenocarcinoma (98.1% *versus* 99.4%)
CTONG-0802	China, multicenter (22 centers)	83 *versus* 82 (all) 39 *versus* 33 (Leu858Arg)	57 (31–74) *versus* 59 (36–78)	41% *versus* 40% (all)	Erlotinib 150 mg/d	Up to 4 cycles of gemcitabine plus carboplatin	Adenocarcinoma (88% *versus* 86%) Non-adenocarcinoma (12% *versus* 14%)
CTONG-1509	China, multicenter	157 *versus* 154 (all) 75 *versus* 75 (Leu858Arg)	57 (33–78) *versus* 59 (27–77)	38.2% *versus* 37.7% (all)	Bevacizumab plus erlotinib	Erlotinib	Adenocarcinoma (100% *versus* 100%)
SWOG 1403	Canada, multicenter	83 *versus* 85 (all) 30 *versus* 31 (Leu858Arg)	65.5 (27.9–90.5) *versus* 66.3 (39.3–93.0)	29% *versus* 38%	Afatinib 40 mg orally daily plus cetuximab intravenously (IV) 500 mg/m	Afatinib 40 mg orally daily	Adenocarcinoma (96% *versus* 95%) Large-cell carcinoma (0% *versus* 1%) Squamous-cell carcinoma (4% *versus* 0%) Mixed (0% *versus* 2%)

(Continued)

Table 1. (Continued)

Study	Country and participants	Number of subjects (group A *versus* group B)	Age (group A *versus* group B)	Sex (group A *versus* group B)	Group A	Group B	Histopathological classification
Cheng 2016 (NCT01469000)	China, multicenter	126 *versus* 65 (all) 52 *versus* 23 (Leu858Arg)	62.0 ± 9.4 *versus* 61.0 ± 9.5	35% *versus* 37% (all)	Gefitinib with pemetrexed	Gefitinib without pemetrexed	/
JO 25567	Japan, multicenter	75 *versus* 77 (all) 35 *versus* 37 (Leu858Arg)	67.0 (59–73) *versus* 67.0 (60–73)	40% *versus* 34%	Erlotinib 150 mg/d Bevacizumab	Erlotinib 150 mg/d	Adenocarcinoma (99% *versus* 99%) Large-cell carcinoma (0% *versus* 1%) Adenosquamous carcinoma (1% *versus* 0%)
COVINCE	China, multicenter	148 *versus* 137 (all) 68 *versus* 63 (Leu858Arg)	56 (35.3–73.7) *versus* 56 (30.5–76.9)	29.1% *versus* 30.8%	Icotinib	Cisplatin plus pemetrexed	Adenocarcinoma (100% *versus* 100%)
WJOG5108L	Japan, multicenter	279 *versus* 280 (all) 92 *versus* 80 (Leu858Arg)	68 (34–91) *versus* 67 (39–85)	45.5% *versus* 45.7%	Gefitinib 250 mg/d	Erlotinib 150 mg/d	Adenocarcinoma (100% *versus* 100%)

AUC, Area Under the Curve; NSCLC, non-small cell lung cancer.

HR = 0.22; 95% CI = (0.10, 0.50) *versus* afatinib: HR = 0.53, 95% CI = (0.35, 0.84)] and osimertinib (*versus* gefitinib: HR = 0.40; 95% CI = (0.32, 0.51) *versus* erlotinib: HR = 0.46; 95% CI = (0.37, 0.58) *versus* icotinib: HR = 0.23; 95% CI = (0.11, 0.50) *versus* afatinib: HR = 0.53, 95% CI = (0.38, 0.79)] showed significantly better beneficial effects. In addition, the third-generation TKIs also showed the trend of prolonged PFS compared with the combination therapies containing the first- and second-generation TKIs (Table 3). For OS, however, only osimertinib [*versus* gefitinib: HR = 0.69; 95% CI = (0.53, 0.90) *versus* erlotinib: HR = 0.67; 95% CI = (0.51, 0.88)] showed significantly better beneficial effects compared with those of the first-generation TKIs (such as gefitinib and erlotinib), among patients with EGFR 19del-mutated NSCLC (Table 3).

For EGFR Leu858Arg-mutated NSCLC, the first-line therapeutic strategies to prolong PFS were ranked as the follows: afatinib plus cetuximab was the best (30.3%), followed by gefitinib plus pemetrexed (13.6%), osimertinib plus bevacizumab (12.9%), icotinib (12.8%), osimertinib (12.4%), aumolertinib (6.1%), erlotinib plus ramucirumab (4.3%), erlotinib plus bevacizumab (3.6%), dacomitinib (2.7%), gefitinib plus apatinib (1%), gefitinib plus PC (0.3%), afatinib (4.0E-4), PC (6.667E-5), erlotinib (0%), gefitinib (0%), and NPC (0%) . To prolong OS, the first-line therapeutic strategies were ranked as follows: afatinib plus cetuximab was the best (27.7%), followed by erlotinib plus bevacizumab (23.4%), dacomitinib (18.9%), PC (11.9%), gefitinib plus PC (8.6%), icotinib (8.6%), NPC (0.7%), osimertinib (0.1%), afatinib (8.333E-4), erlotinib (7.667E-4), and gefitinib (0%) (Table 4).

For EGFR 19del-mutated NSCLC, the first-line therapeutic strategies to prolong PFS were ranked as the follows: osimertinib plus bevacizumab was the best (84.3%), followed by aumolertinib (11.0%), osimertinib (3.6%), erlotinib plus bevacizumab (0.4%), erlotinib plus ramucirumab (0.3%), dacomitinib (0.2%), gefitinib plus pemetrexed (0.1%), gefitinib plus PC (8.0E-4), gefitinib plus apatinib (6.0E-4), afatinib plus cetuximab (6.667E-5), afatinib (3.333E-5), erlotinib (0%), gefitinib (0%), icotinib (0%), PC (0%), and NPC (0%). To prolong OS, the first-line therapeutic strategies were ranked as follows: afatinib plus cetuximab was the best (33.1%), followed by gefitinib plus PC (30.1%), NPC

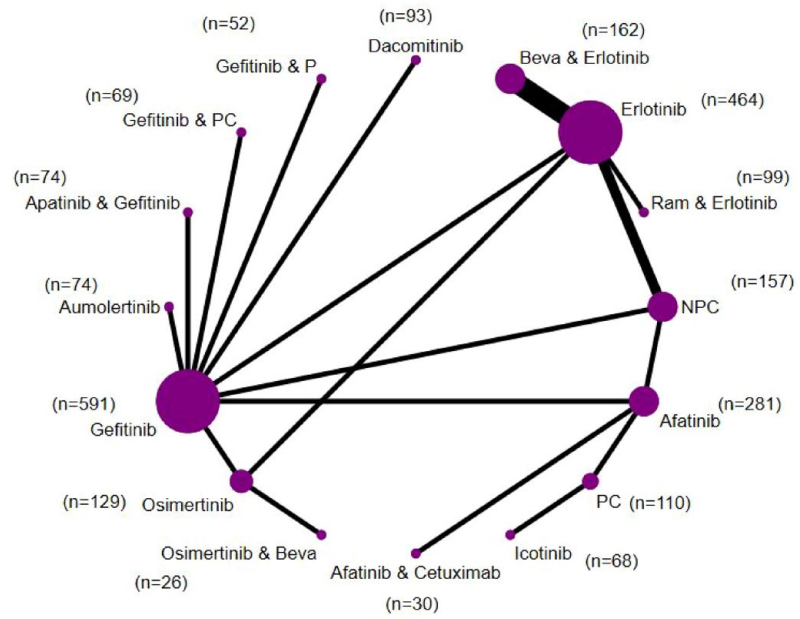

Figure 2. Network evidence of the comparisons for the different treatment strategies for patients with the EGFR LeuL858Arg mutation in terms of PFS.

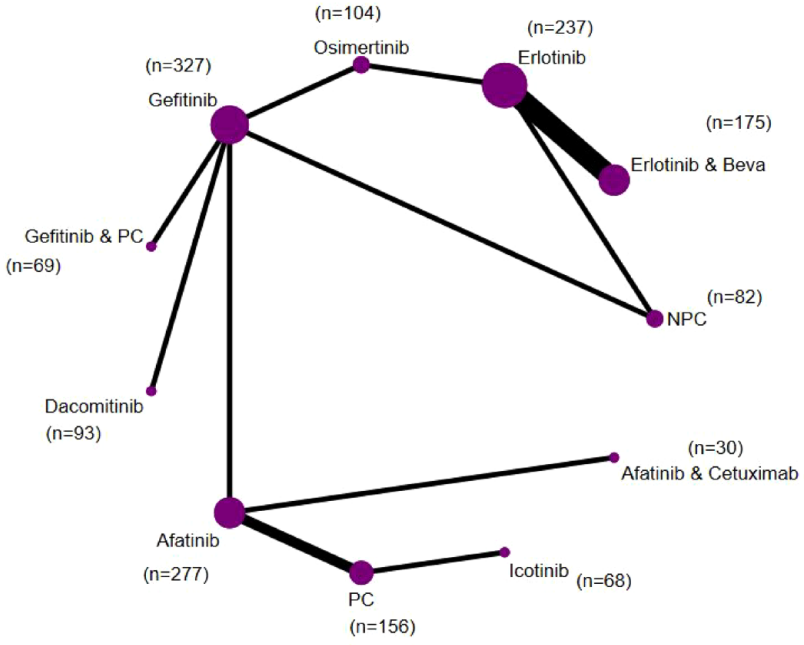

Figure 3. Network evidence of the comparisons for the different treatment strategies for patients with the EGFR LeuL858Arg mutation in terms of OS.

Table 2. The pooled comparisons shown as hazard ratios (with 95% confidence intervals) for progression-free survival (upper triangle) and overall survival (lower triangle) in patients with NSCLC with EGFR Leu858Arg mutations.

Progression-free survival															
Overall survival	Aum	1.17 (0.73, 1.93)	0.95 (0.56, 1.62)	0.82 (0.49, 1.41)	0.60 (0.38, 0.98)	0.60 (0.40, 0.90)	0.94 (0.41, 2.24)	0.94 (0.41, 2.20)	1.18 (0.54, 2.62)	1.01 (0.59, 1.73)	0.97 (0.54, 1.75)	0.83 (0.47, 1.49)	1.03 (0.52, 2.07)	0.75 (0.43, 1.33)	0.60 (0.30, 1.25)	0.26 (0.15, 0.44)
	NA	Osi	0.81 (0.52, 1.26)	0.70 (0.46, 1.07)	0.51 (0.39, 0.67)	0.51 (0.39, 0.67)	0.80 (0.36, 1.81)	0.80 (0.40, 1.61)	1.00 (0.49, 2.08)	0.86 (0.59, 1.25)	0.82 (0.53, 1.28)	0.71 (0.43, 1.16)	0.88 (0.47, 1.64)	0.64 (0.39, 1.04)	0.51 (0.28, 0.98)	0.22 (0.15, 0.33)
	NA	1.38 (0.84, 2.28)	Dac	0.87 (0.54, 1.43)	0.63 (0.41, 0.98)	0.63 (0.45, 0.89)	0.98 (0.44, 2.29)	0.99 (0.44, 2.27)	1.24 (0.58, 2.68)	1.06 (0.64, 1.75)	1.02 (0.59, 1.77)	0.87 (0.51, 1.51)	1.09 (0.56, 2.11)	0.79 (0.47, 1.34)	0.63 (0.33, 1.27)	0.27 (0.17, 0.44)
	NA	1.07 (0.65, 1.76)	0.78 (0.45, 1.36)	Afa	0.72 (0.49, 1.07)	0.72 (0.52, 1.01)	1.14 (0.58, 2.24)	1.14 (0.51, 2.56)	1.43 (0.80, 2.56)	1.22 (0.76, 1.94)	1.17 (0.69, 1.97)	1.00 (0.59, 1.71)	1.24 (0.65, 2.40)	0.90 (0.54, 1.52)	0.73 (0.46, 1.17)	0.31 (0.22, 0.45)
	NA	1.02 (0.74, 1.40)	0.75 (0.43, 1.31)	0.95 (0.54, 1.66)	Erl	1.00 (0.78, 1.28)	1.56 (0.72, 3.47)	1.56 (0.74, 3.32)	1.97 (0.97, 4.01)	1.68 (1.30, 2.17)	1.61 (1.15, 2.27)	1.38 (0.86, 2.24)	1.72 (0.93, 3.18)	1.24 (0.78, 2.01)	1.00 (0.55, 1.88)	0.43 (0.31, 0.60)
	NA	0.98 (0.72, 1.33)	0.71 (0.48, 1.05)	0.91 (0.61, 1.34)	0.95 (0.64, 1.41)	Gef	1.57 (0.75, 3.41)	1.57 (0.75, 3.33)	1.98 (1.01, 3.90)	1.69 (1.18, 2.41)	1.62 (1.06, 2.47)	1.39 (0.92, 2.10)	1.72 (0.98, 3.03)	1.25 (0.83, 1.88)	1.01 (0.57, 1.83)	0.43 (0.31, 0.60)
	NA	1.18 (0.57, 2.46)	0.86 (0.40, 1.86)	1.10 (0.65, 1.89)	1.15 (0.54, 2.48)	1.21 (0.62, 2.35)	Ico	0.98 (0.35, 2.85)	1.23 (0.52, 3.04)	1.04 (0.48, 2.45)	1.00 (0.44, 2.43)	0.86 (0.38, 2.07)	1.07 (0.44, 2.80)	0.77 (0.34, 1.86)	0.64 (0.40, 1.03)	0.27 (0.13, 0.59)
	NA	NA	NA	NA	NA	NA	NA	Osi + Bev	1.23 (0.47, 3.46)	1.05 (0.49, 2.41)	1.00 (0.45, 2.38)	0.86 (0.38, 2.09)	1.07 (0.43, 2.82)	0.77 (0.34, 1.87)	0.63 (0.25, 1.66)	0.27 (0.13, 0.62)
	NA	1.32 (0.53, 3.28)	0.97 (0.38, 2.48)	1.23 (0.58, 2.63)	1.28 (0.51, 3.23)	1.35 (0.58, 3.16)	1.12 (0.45, 2.82)	NA	Afa + Cet	0.84 (0.41, 1.85)	0.80 (0.38, 1.83)	0.69 (0.32, 1.57)	0.86 (0.37, 2.12)	0.63 (0.29, 1.36)	0.50 (0.24, 1.09)	0.21 (0.11, 0.45)
	NA	1.37 (0.87, 2.15)	1.00 (0.53, 1.92)	1.28 (0.66, 2.42)	1.34 (0.97, 1.85)	1.41 (0.83, 2.36)	1.17 (0.51, 2.69)	NA	1.04 (0.39, 2.82)	Erl + Bev	0.96 (0.62, 1.47)	0.82 (0.48, 1.43)	1.02 (0.52, 2.01)	0.74 (0.43, 1.28)	0.60 (0.31, 1.18)	0.26 (0.17, 0.39)
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Erl + Ram	0.85 (0.48, 1.56)	1.06 (0.52, 2.16)	0.77 (0.43, 1.38)	0.62 (0.31, 1.28)	0.27 (0.17, 0.43)
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gef + Apa	1.25 (0.63, 2.47)	0.90 (0.51, 1.60)	0.73 (0.37, 1.48)	0.31 (0.19, 0.52)

(Continued)

Table 2. (Continued)

Progression-free survival																
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gef + P	0.73 (0.37, 1.43)	0.59 (0.27, 1.30)	0.25 (0.13, 0.47)		
NA		1.22 (0.73, 2.05)	0.89 (0.50, 1.57)	1.14 (0.64, 2.00)	1.19 (0.68, 2.10)	1.25 (0.83, 1.89)	1.04 (0.48, 2.23)	NA	0.92 (0.37, 2.33)	0.89 (0.46, 1.70)	NA	NA	NA	Gef + PC	0.81 (0.41, 1.64)	0.35 (0.21, 0.58)
NA	1.35 (0.74, 2.43)	0.98 (0.52, 1.85)	1.25 (0.92, 1.72)	1.31 (0.70, 2.46)	1.38 (0.84, 2.27)	1.14 (0.75, 1.75)	NA	1.01 (0.46, 2.31)	0.97 (0.48, 1.98)	NA	NA	NA	NA	1.10 (0.59, 2.08)	PC	0.43 (0.24, 0.76)
NA	1.00 (0.65, 1.53)	0.73 (0.41, 1.28)	0.93 (0.53, 1.63)	0.98 (0.65, 1.47)	1.03 (0.68, 1.54)	0.85 (0.39, 1.86)	NA	0.76 (0.30, 1.94)	0.73 (0.44, 1.23)	NA	NA	NA	NA	0.82 (0.47, 1.46)	0.74 (0.40, 1.43)	NPC

Afa, afatinib; Apa, apatinib; Aum, aumolertinib; Bev, bevacizumab; Cet, cetuximab; Dac, dacomitinib; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; NPC, non-pemetrexed-based chemotherapy; Osi, osimertinib; PC, pemetrexed-based chemotherapy; Ram, ramucirumab.

(18.8%), osimertinib (13.3%), dacomitinib (2.0%), afatinib (1.5%), icotinib (0.7%), erlotinib plus bevacizumab (0.5%), erlotinib (0%), gefitinib (0%), and PC (0%) (Table 4).

Discussion

The results of this study demonstrated that compared with the first-generation EGFR TKIs, the second-generation EGFR TKI (dacomitinib) and the third-generation EGFR TKIs (osimertinib and aumolertinib) showed significantly improved PFS in patients with NSCLC with EGFR Leu858Arg mutations. In addition, afatinib plus cetuximab was the best first-line therapeutic strategy for patients with NSCLC with EGFR Leu858Arg mutations. For patients with NSCLC with EGFR 19del mutations, the third-generation EGFR TKIs (osimertinib and aumolertinib) showed significantly improved PFS compared with that of the first- and second-generation EGFR TKIs (gefitinib, erlotinib, icotinib, and afatinib). In addition, to prolong PFS, osimertinib plus bevacizumab was the best first-line therapeutic strategy for patients with NSCLC with EGFR 19del mutations.

We assumed that using the third-generation TKIs combined with other therapies would be more beneficial than the other treatments for patients with NSCLC with EGFR Leu858Arg mutations. The results of the WJOG9717L study,[22] however, showed that the combination of osimertinib and bevacizumab did not achieve a better PFS than osimertinib alone in patients with NSCLC with EGFR Leu858Arg mutations. Apart from chemotherapy, various agents have been attempted in the dual therapy strategy, such as bevacizumab, ramucirumab, apatinib, and cetuximab.

Most tumor tissues show high expression of vascular endothelial growth factor (VEGF), which is associated with increased risk of metastasis and death.[36,37] Bevacizumab and ramucirumab are recombinant humanized monoclonal anti-VEGFR antibodies.[11,13] Previous studies demonstrated that bevacizumab plus chemotherapy could improve the PFS and OS in patients with NSCLC.[38,39] Apatinib, as a VEGFR2 TKI, targets the intracellular domain of the receptor and blocks signal transduction and can be orally administrated.[40] The theoretical basis of the combinations of TKIs and antivascular treatment was that the antivascular treatment could inhibit

Table 3. The pooled comparisons shown as hazard ratios (with 95% confidence intervals) for progression-free survival (upper triangle) and overall survival (lower triangle) in patients with NSCLC with EGFR 19del mutations.

Progression-free survival																
Overall survival	Aum	0.97 (0.65, 1.46)	0.71 (0.45, 1.11)	0.53 (0.35, 0.84)	0.45 (0.30, 0.68)	0.39 (0.28, 0.55)	0.22 (0.10, 0.50)	1.55 (0.70, 3.47)	0.43 (0.24, 0.81)	0.75 (0.47, 1.20)	0.69 (0.41, 1.16)	0.58 (0.35, 0.98)	0.58 (0.33, 1.02)	0.60 (0.36, 1.00)	0.15 (0.08, 0.29)	0.12 (0.07, 0.18)
	NA	Osi	0.73 (0.50, 1.07)	0.55 (0.38, 0.79)	0.46 (0.37, 0.58)	0.40 (0.32, 0.51)	0.23 (0.11, 0.50)	1.61 (0.82, 3.21)	0.45 (0.26, 0.78)	0.78 (0.56, 1.08)	0.71 (0.47, 1.06)	0.60 (0.38, 0.95)	0.60 (0.36, 0.99)	0.62 (0.39, 0.98)	0.15 (0.09, 0.28)	0.12 (0.08, 0.17)
	NA	0.78 (0.50, 1.23)	Dac	0.75 (0.50, 1.15)	0.63 (0.43, 0.93)	0.55 (0.41, 0.75)	0.31 (0.14, 0.69)	2.19 (1.01, 4.83)	0.61 (0.34, 1.12)	1.06 (0.68, 1.67)	0.97 (0.59, 1.61)	0.82 (0.50, 1.36)	0.82 (0.48, 1.41)	0.84 (0.52, 1.39)	0.21 (0.11, 0.40)	0.16 (0.11, 0.25)
	NA	0.83 (0.53, 1.29)	1.06 (0.64, 1.76)	Afa	0.84 (0.60, 1.18)	0.73 (0.55, 0.98)	0.42 (0.22, 0.81)	2.92 (1.35, 6.34)	0.81 (0.53, 1.24)	1.41 (0.93, 2.14)	1.29 (0.80, 2.08)	1.09 (0.67, 1.78)	1.09 (0.64, 1.86)	1.12 (0.69, 1.82)	0.28 (0.18, 0.44)	0.22 (0.16, 0.30)
	NA	0.67 (0.51, 0.88)	0.86 (0.52, 1.42)	0.81 (0.49, 1.33)	Erl	0.87 (0.69, 1.10)	0.49 (0.24, 1.06)	3.48 (1.69, 7.22)	0.97 (0.56, 1.68)	1.69 (1.33, 2.14)	1.54 (1.11, 2.13)	1.30 (0.83, 2.06)	1.30 (0.79, 2.15)	1.34 (0.86, 2.11)	0.33 (0.19, 0.59)	0.26 (0.19, 0.35)
	NA	0.69 (0.53, 0.90)	0.88 (0.61, 1.25)	0.83 (0.58, 1.17)	1.02 (0.72, 1.44)	Gef	0.57 (0.28, 1.19)	4.00 (1.94, 8.27)	1.11 (0.67, 1.86)	1.94 (1.39, 2.69)	1.77 (1.18, 2.63)	1.49 (1.01, 2.22)	1.49 (0.95, 2.34)	1.54 (1.04, 2.28)	0.38 (0.23, 0.66)	0.30 (0.22, 0.40)
	NA	0.59 (0.30, 1.15)	0.76 (0.37, 1.54)	0.71 (0.44, 1.18)	0.87 (0.44, 1.76)	0.86 (0.47, 1.58)	Ico	6.78 (2.54, 19.16)	1.90 (0.90, 4.22)	3.28 (1.58, 7.42)	2.99 (1.38, 6.98)	2.53 (1.16, 5.84)	2.52 (1.13, 6.04)	2.61 (1.21, 6.01)	0.66 (0.42, 1.07)	0.50 (0.25, 1.09)
	NA	NA	NA	NA	NA	NA	NA	Osi + Bev	0.27 (0.12, 0.71)	0.47 (0.23, 1.10)	0.43 (0.20, 1.04)	0.37 (0.16, 0.90)	0.36 (0.16, 0.92)	0.38 (0.17, 0.91)	0.09 (0.04, 0.25)	0.07 (0.04, 0.17)
	NA	0.99 (0.45, 2.22)	1.28 (0.55, 2.94)	1.20 (0.62, 2.34)	1.47 (0.65, 3.33)	1.45 (0.68, 3.06)	1.69 (0.74, 3.87)	NA	Afa + Cet	1.72 (0.97, 3.18)	1.57 (0.84, 3.03)	1.32 (0.70, 2.56)	1.33 (0.68, 2.65)	1.36 (0.73, 2.64)	0.34 (0.19, 0.64)	0.26 (0.16, 0.46)
	NA	0.67 (0.44, 1.01)	0.85 (0.47, 1.53)	0.81 (0.44, 1.44)	0.99 (0.72, 1.36)	0.97 (0.60, 1.56)	1.14 (0.53, 2.45)	NA	0.67 (0.28, 1.64)	Erl + Bev	0.91 (0.61, 1.36)	0.77 (0.46, 1.30)	0.77 (0.44, 1.36)	0.79 (0.48, 1.33)	0.20 (0.11, 0.37)	0.15 (0.10, 0.23)
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Erl + Ram	0.84 (0.48, 1.48)	0.84 (0.46, 1.54)	0.87 (0.50, 1.52)	0.22 (0.11, 0.42)	0.17 (0.11, 0.26)
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gef + Apa	1.00 (0.55, 1.81)	1.03 (0.59, 1.79)	0.25 (0.13, 0.51)	0.20 (0.12, 0.33)

(Continued)

Table 3. (Continued)

Progression-free survival															
	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Gef + P	1.03 (0.57, 1.86)	0.25 (0.13, 1.86)	0.20 (0.12, 0.34)
	NA	1.06 (0.66, 1.71)	1.35 (0.79, 2.31)	1.27 (0.75, 2.17)	1.57 (0.93, 2.66)	1.54 (1.03, 2.29)	1.80 (0.88, 3.68)	NA	1.06 (0.46, 2.45)	1.58 (0.86, 2.90)	NA	NA	NA	Gef + PC	0.25 (0.13, 0.49)	0.19 (0.12, 0.32)
	NA	0.49 (0.29, 0.82)	0.63 (0.35, 1.11)	0.59 (0.45, 0.78)	0.72 (0.42, 1.26)	0.71 (0.46, 1.11)	0.83 (0.55, 1.26)	NA	0.49 (0.24, 1.01)	0.73 (0.39, 1.38)	NA	NA	NA	0.46 (0.26, 0.83)	PC	0.77 (0.44, 1.36)
	NA	1.00 (0.67, 1.49)	1.28 (0.75, 2.17)	1.20 (0.71, 2.03)	1.48 (1.00, 2.19)	1.45 (0.98, 2.16)	1.70 (0.82, 3.52)	NA	1.00 (0.43, 2.35)	1.49 (0.91, 2.48)	NA	NA	NA	0.95 (0.54, 1.65)	2.05 (1.14, 3.72)	NPC

Afa, afatinib; Apa, apatinib; Aum, aumolertinib; Bev, bevacizumab; Cet, cetuximab; Dac, dacomitinib; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; NPC, non-pemetrexed-based chemotherapy; Osi, osimertinib; PC, pemetrexed-based chemotherapy; Ram, ramucirumab.

Table 4. Estimated probabilities of each treatment being the best for PFS and OS in patients with 21L858R and 19del mutations.

	Amu	**Osi**	**Dac**	**Afa**	**Erl**	**Gef**	**Ico**	**Osi + Bev**	**Afa + Cet**	**Erl + Bev**	**Erl + Ram**	**Gef + Apa**	**Gef + P**	**Gef + PC**	**PC**	**NPC**
PFS (21L858R)	0.061	0.124	0.027	4.0E-4	0	0	0.128	0.129	0.303	0.036	0.043	0.010	0.136	0.003	6.667E-5	0
OS (21L858R)	NA	0.001	0.189	8.333E-4	7.667E-4	0	0.086	NA	0.277	0.234	NA	NA	NA	0.086	0.119	0.007
PFS (19del)	0.110	0.036	0.002	3.333E-5	0	0	0	0.8425	6.667E-5	0.004	0.003	6.0E-4	0.001	8.0E-4	0	0
OS (19del)	NA	0.133	0.020	0.015	0	0	0.007	NA	0.331	0.005	NA	NA	NA	0.301	0	0.188

Afa, afatinib; Apa, apatinib; Aum, aumolertinib; Bev, bevacizumab; Cet, cetuximab; Dac, dacomitinib; Erl, erlotinib; Gef, gefitinib; Ico, icotinib; NPC, non-pemetrexed-based chemotherapy; Osi, osimertinib; PC, pemetrexed-based chemotherapy; Ram, ramucirumab.

tumor angiogenesis, thus improving the delivery of EGFR TKIs by vascular normalization.[41]

Anti-EGFR therapy resistant tumors contain T790M, exon 20 insertion, and EGFR amplification mutations. Using dual therapy comprising afatinib and cetuximab, Janjigian *et al.*[42] showed that patients with EGFR-mutant NSCLC with acquired resistance could achieve a response rate of about 30%, regardless of their T790M status. This demonstrated that the combination was beneficial to patients with T790M mutations. Second, Hasegawa *et al.*[43] demonstrated that EGFR exon 20 insertion mutations (typically resistant to EGFR TKIs) might respond well to the same combination. Mechanistically, dual inhibition of EGFR is probably useful in tumors that are dependent on signaling through the receptor, as EGFR TKIs bind to the intracellular domain of the receptor, whereas cetuximab binds extracellularly.

In addition, exon 21Leu858Arg mutations have a lower incidence of T790M mutations than 19del mutations. In some real-world studies, the authors reported that the frequency of the T790M mutation among patients with initial exon 19 deletion mutation was almost twice that in patients with 21Leu858Arg mutation,[44,45] which could benefit from using the third-generation TKIs. Therefore, therapies containing the third-generation EGFR TKIs are probably the best to treat patients with NSCLC with EGFR 19del mutations, but not those with 21Leu858Arg mutations.

There were, however, several limitations in our study. First, we could not identify some comutated genes (such as TP53 mutation) in the subjects included in our study, which contributes to a shorter PFS than in patients with wild-type *TP53*.[46] Second, the number of enrolled patients in some therapeutic arms was relatively small, which might have led to bias. Moreover, some updated studies included in our research were not published formally.

Conclusion

For patients with NSCLC with EGFR Leu858Arg mutations, afatinib plus cetuximab ranked as the best to prolong PFS. For patients with NSCLC with EGFR 19del mutations, however, osimertinib plus bevacizumab was the best to improve PFS. In the future, combined therapy containing the second-generation TKIs and other drugs (such as anti-VEGFR monoclonal antibodies) could be further tested to treat patients with NSCLC with EGFR Leu858Arg mutations.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Chongxiang Chen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

Chunning Zhang: Formal analysis; Software.

Huaming Lin: Formal analysis; Investigation; Validation.

Qianyin Liu: Formal analysis; Investigation; Software.

Limian Wu: Validation; Writing – review & editing.

Chengzhi Zhou: Conceptualization; Writing – review & editing.

Jiexia Zhang: Conceptualization; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The datasets used and/or analyzed in this study are available from the corresponding author upon request.

Data availability

All data generated or analyzed during this study are included in this published article.

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