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BIM deletion polymorphism predicts poor response to EGFR-TKIs in nonsmall cell lung cancer

An updated meta-analysis

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Abstract

Background: A germline deletion in BIM (B cell lymphoma-2-like 11) gene has been shown to impair the apoptotic response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in vitro but its impact on response to EGFR-TKIs in patients of nonsmall cell lung cancer (NSCLC) remains controversial.

Methods: Eligible literature were searched and screened. Objective response rate (ORR) and disease control rate (DCR) were extracted and aggregated with odds ratio (OR). Hazard ratio (HR) and 95% confidence interval (CI) for progression-free survival (PFS) and overall survival (OS) were extracted and aggregated based on random-effect model.

Results: Fourteen studies including 2694 NSCLC patients were eligible. Individuals harboring BIM deletion polymorphism had inferior ORR (OR = 0.49, 95% CI: 0.34–0.70, $P < .001$), inferior DCR (OR = 0.50, 95% CI: 0.30–0.84, $P = .009$). Patients with BIM deletion had shorter OS despite of the heterogeneity between countries (in subgroup of South Korea and Taiwan, HR = 1.34, 95% CI: 1.18–1.53, $P < .001$; in subgroup of other countries, HR = 2.43, 95% CI: 2.03–2.91, $P < .001$). The pooled analysis of PFS showed great heterogeneity ($I^2 = 79\%$). All the reported characteristics did not account for the heterogeneity. However, 2 subgroups could be obtained through sensitivity analysis. In one subgroup, patients with BIM deletion polymorphism had shorter PFS (HR = 2.03, 95% CI: 1.71–2.40, $P < .001$), while in the other subgroup, no significant difference was observed (HR = 0.92, 95% CI: 0.79–1.06, $P = .25$).

Conclusion: NSCLC patients with BIM deletion polymorphism show poor ORR, DCR, and OS after EGFR-TKIs treatment. BIM deletion polymorphism indicates poor response to EGFR-TKIs, and it could be used as a predictor to identify those who would benefit from EGFR-TKIs in NSCLC patients.

Abbreviations: BIM = B cell lymphoma-2-like 11, CI = confidence interval, CML = chronic myeloid leukemia, ECOG = Eastern Cooperative Oncology Group, DCR = disease control rate, EGFR = epidermal growth factor receptor, HR = hazard ratio, NSCLC = nonsmall cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, TKIs = tyrosine kinase inhibitors.

Keywords: BIM deletion polymorphism, nonsmall cell lung cancer, response, tyrosine kinase inhibitor

1. Introduction

Nonsmall cell lung cancer (NSCLC) is a kinase-driven cancer, in which, epidermal growth factor receptor (EGFR), a common kind of tyrosine kinase, can bind to extracellular ligands and transfer a phosphate group from ATP to the tyrosine residues of target proteins to regulate survival of cancer cells.[1] EGFR-tyrosine kinase inhibitors (TKIs) can compete with ATP to bind to the intracellular catalytic domain of tyrosine kinase and consequently inhibit the process of cross-phosphorylation.[2] EGFR-TKIs, such as gefitinib, erlotinib, and afatinib, are widely used for treatment of EGFR-mutant NSCLC.[3] Despite high response rates with first-line EGFR-TKIs, a considerable portion of EGFR-mutant NSCLC patients develop acquired resistance after 9 to 18 months of treatment.[4,5] Approximately 30% of EGFR-mutant NSCLC patients displayed intrinsic resistance to EGFR-TKIs.[5,6]

Pro-apoptotic protein BIM (also known as B cell lymphoma-2-like 11) is a BH3-only protein of the BCL-2 family. The BH3 domain can bind and regulate the antiapoptotic bcl-2 proteins (bax, bak) to promote apoptosis.[7] Activation of BIM is essential for apoptosis triggered by EGFR-TKIs in EGFR-mutant NSCLC.[8–10] A 2903-bp germline deletion polymorphism in intron 2 of BIM gene was found in chronic myeloid leukemia (CML) and EGFR-mutant NSCLC in 2012.[11] BIM deletion polymorphism results in the generation of alternatively spliced isoforms of BIM that lack the crucial BH3 domain, thus impairs the apoptotic response to TKIs and confers NSCLC cells

Editor: Yan Li.

This work was supported by the Weifang Technology Development Program (grant number 2018YX030), the Medical Science Development Program of Shandong Province (grant number 2018WS058), and the National Natural Science Foundation of China (81502469).

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:10(e14568)

Received: 20 November 2018 / Received in final form: 9 January 2019 / Accepted: 25 January 2019

http://dx.doi.org/10.1097/MD.0000000000014568

intrinsically resistant to TKIs in vitro.[11] Accumulating articles about the impact of BIM deletion polymorphism on response to EGFR-TKIs in NSCLC patients have been published. However, the results were contradictory. Some studies showed that NSCLC patients harboring BIM deletion polymorphism had inferior response to EGFR-TKIs than those with BIM wild after TKIs treatment,[11–20] while others argued that there was no difference in response to EGFR-TKIs in NSCLC patients with and without BIM deletion polymorphism.[21–24]

In order to obtain an objective and consistent conclusion, we conducted this comprehensive analysis to demonstrate the impact of BIM deletion on response to EGFR-TKIs in NSCLC patients.

2. Materials and methods

2.1. Ethic statement

This meta-analysis was performed based on previously published studies, ethical approval was not necessary.

2.2. Literature search

A comprehensive literature search was conducted in the database PubMed and Embase using the subject headings and text words of the following terms: BIM ("BCL2L11," "B-cell lymphoma-like 11," "BCL-2-like 11"), TKI ("Tyrosine kinase inhibitor," "gefitinib," "erlotinib," "afatinib"), and NSCLC ("Non-Small Cell Lung Cancer," "Nonsmall Cell Lung Cancer," "non-small cell lung cancer," "Lung Adenocarcinoma") dating up to October 1, 2018. Manual retrieval was performed to obtain relevant studies by reviewing all the reference in the eligible studies. This study was approved by the Institution Ethics Commission of Weifang Medical University.

2.3. Eligibility criteria

Eligible literatures were identified in accordance with the following inclusion criteria: (1) Prospective or retrospective studies concerning the impact of BIM deletion polymorphism on response to EGFR-TKI therapy. (2) Studies in NSCLC patients with or without EGFR mutations. (3) Response data in studies were available. (4) Published full texts were available. However, review articles, systematic reviews, meta-analyses, and case studies were excluded.

2.4. Data extraction

Objective response rate (ORR), disease control rate (DCR), and overall survival (OS) were the primary outcomes and progression-free survival (PFS) was the second outcome for this meta-analysis. For ORR, the cases of events were extracted by response rate multiplied by number of patients with BIM deletion polymorphism or with BIM wild. For DCR, the cases of events were extracted by DCR multiplied by number of patients with BIM deletion polymorphism or with BIM wild. For OS and PFS, hazard ratios (HRs) and 95% confidence interval (CI) of patients with BIM polymorphism compared to those with BIM wild in EGFR-TKI-treated NSCLC were extracted. If HR and 95% CI for PFS or OS were not given in the study, the data were extracted from Kaplan–Meier curve by the method of Tierney.[25] Data from all eligible studies were extracted independently by 2 investigators. Any disagreement was discussed with the third investigator to reach a consensus.

2.5. Statistical analysis

Statistical analysis was performed using Revman 5.3 (The Nordic Cochrane Center, the Cochrane collaboration, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX) and pooled odds ratios (ORs) for ORR and DCR were calculated by Mantel–Haenszel method with fixed-effect model, and pooled HRs for PFS and OS with 95% CIs were calculated by inverse variance method with random-effect model. Statistical significance was set at a 2-sided $P < .05$. A forest plot was applied for display of results.

For heterogeneity evaluation, chi-squared tests and I^2 inconsistency statistics were used. A significant heterogeneity was considered when $P_H < .10$. I^2 values of 0% to 24.9%, 25% to 49.9%, 50% to 74%, and 75% to 100% were considered as none, low, moderate, and high heterogeneity, respectively.[26,27] Sensitivity analysis was performed to estimate stability of overall effect by omitting each eligible study or changing combination model. Publication bias was evaluated by Begg funnel plot and asymmetry of funnel plot was considered as an existence of publication bias.[28]

2.6. Meta-regression

Meta-regression was performed to assess the effect of the following given characteristics in the original articles on lnHR for PFS: gender (female vs. male), smoking history (without vs. with), Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs. 2–4), pathology (adenocarcinoma vs. non-adenocarcinoma), clinical stage (III B vs. IV, relapse), EGFR mutation (exon19 vs. L858R), TKI type (gefitinib vs. erlotinib, afatinib), and line of TKI treatment (first vs. second or more).

3. Results

3.1. Eligible studies

Three hundred forty-five records were identified using the search strategy, and 85 duplicated articles, 216 unrelated articles, 11 conference abstracts of the same original articles, 7 articles concerning BIM mRNA expression levels, 6 conference abstracts with data unavailable, 2 articles concerning the effect of other therapy, 1 article concerning lung cancer susceptibility, 1 in vitro study, 1 meta-analysis, and 1 report were excluded. Finally, 14 studies were eligible. ORR and DCR were available in 8 and 7 studies, respectively. PFS was available in 14 studies, and OS was available in 6 studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram was shown in Fig. 1.

3.2. Study characteristics

A total of 14 articles including 2 prospective studies and 12 retrospective studies with 2694 patients were included in this meta-analysis. Among them, 13 studies were in Asian populations and 1 study was in Latin American population. Gefitinib, erlotinib, and afatinib were investigated in 13, 11, and 2 studies, respectively. TKIs were used as first-line therapy in 3 studies, first-line or more-line therapy in 11 studies (Table 1).

3.3. ORR analysis

Eight studies including 1012 patients were pooled for ORR analysis. $P_H = .16$, $I^2 = 33\%$, indicating low heterogeneity of

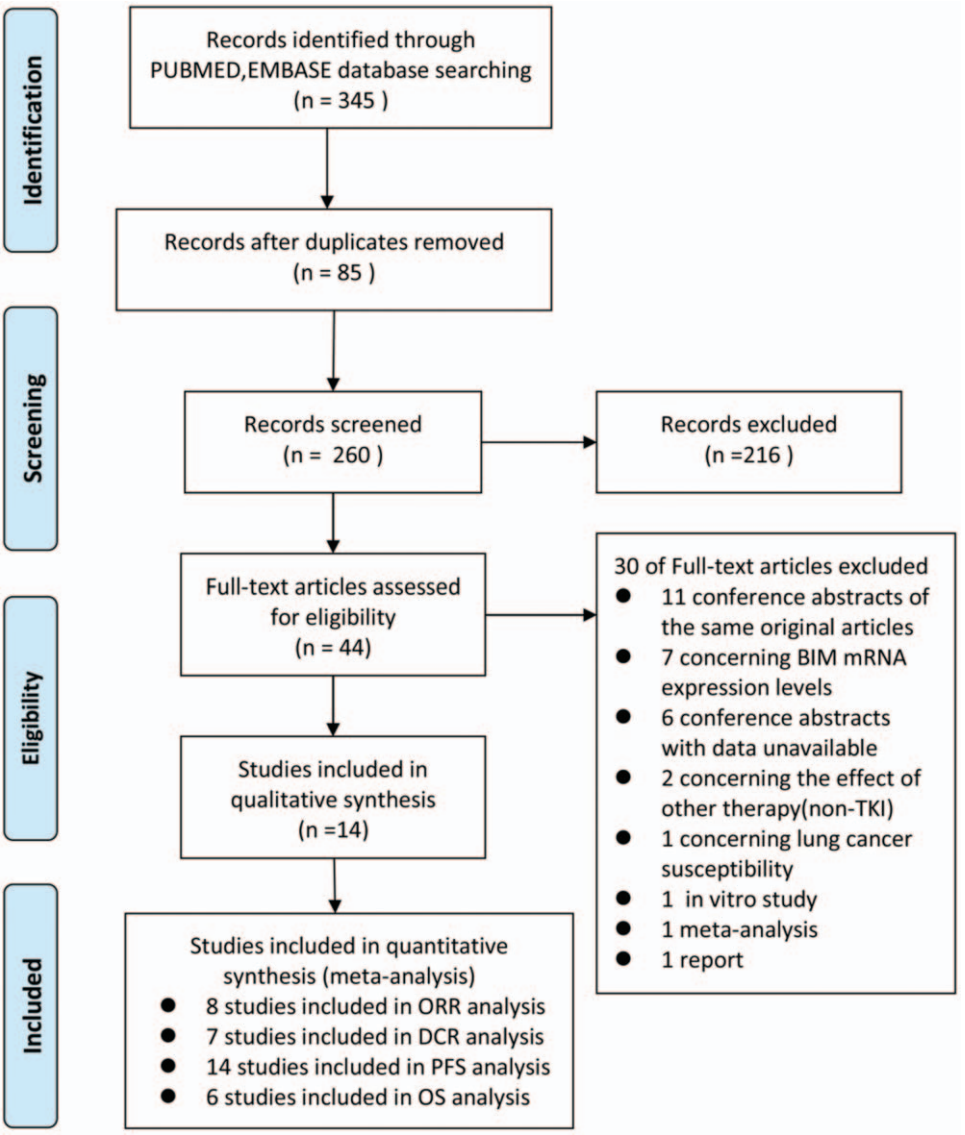

Figure 1. Flow diagram of eligible study selection.

Table 1

Characteristics of studies included for meta-analysis.

Study ID	Country/region	Study type	Cases	BIM deletion	Specimen	Clinical stage	TKI	Line of TKI therapy
Ng KP 2012[11]	Singapore	Retro	141	26	Tumor tissue or blood	IIIB, IV relapse	Gefitinib, erlotinib	First or more
Lee JK 2013[21]	South Korea	Retro	197	21	Tumor tissue	IIIB, IV relapse	Gefitinib, erlotinib	First or more
Zheng L 2013[12]	China	Retro	123	21	Blood	IIIB, IV	Gefitinib, erlotinib	Second or more
Isobe K 2014[13]	Japan	Retro	70	13	Tumor tissue or blood	IV relapse	Gefitinib, erlotinib	First or more
Lee JH 2014[14]	Taiwan	Pro	153	33	Blood	IIIB, IV	Gefitinib, erlotinib, afatinib	First
Zhao MC 2014[15]	China	Retro	352	45	Tumor tissue	IIIB, IV	Gefitinib, erlotinib	First or more
Zhong J 2014[16]	China	Retro	290	45	Blood	I, II, IIIA, IIIB, IV	Gefitinib, erlotinib	First or more
Lee JY 2015[22]	South Korea	Retro	205	32	Tumor tissue	IIIB, IV relapse	Gefitinib, erlotinib	First or more
Atsumi J 2016[17]	Japan	Pro	411	61	Blood	I, II, III	NA	First or more
Cardona AF 2016[18]	Colombia	Retro	89	14	Tumor tissue	IIIA, IIIB, IV	Gefitinib	First
Wu SG 2016[23]	Taiwan	Retro	327	52	MPE	IV	Gefitinib, erlotinib, afatinib	First or more
Qian K 2017[19]	China	Retro	85	14	Tumor tissue	IIIB, IV	Gefitinib, erlotinib, afatinib	First
Sun S 2017[24]	China	Retro	140	37	Blood	III, IV	Gefitinib, erlotinib	First or more
Yuan JP 2018[20]	China	Retro	111	73	Blood	IIIB, IV	Gefitinib	Second or more
Overall			2694	487 (18.08%)				

BIM = B cell lymphoma-2-like 11, MPE = malignant pleural effusion, NA = not available, Pro = prospective, Retro = retrospective, TKI = tyrosine kinase inhibitor.

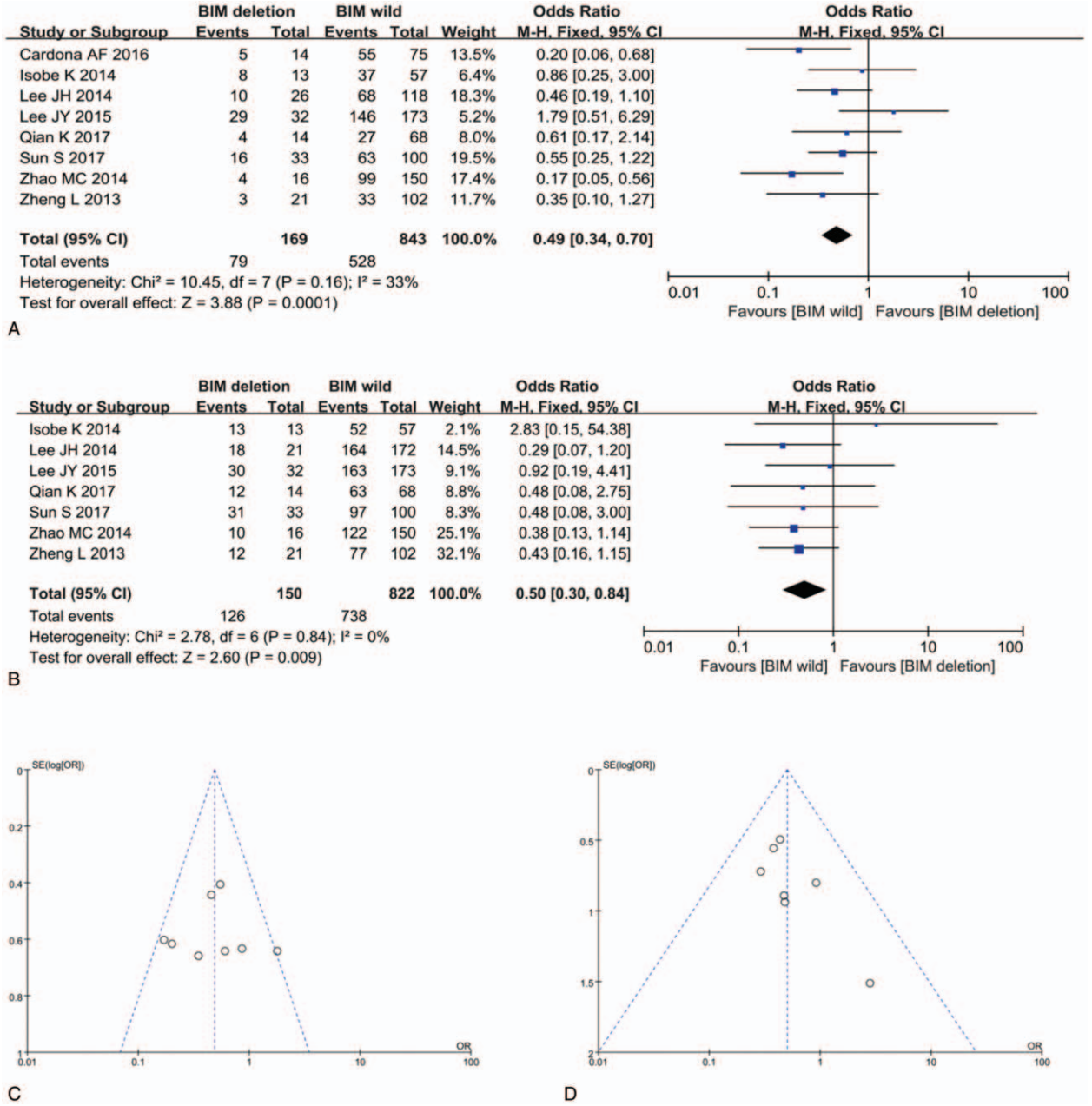

Figure 2. Impact of BIM deletion polymorphism on response to EGFR-TKIs. (A) Odds ratio (OR) for objective response rate (ORR) to EGFR-TKIs in NSCLC patients with BIM deletion polymorphism versus those with BIM wild. (B) OR for disease control rate (DCR) to EGFR-TKI in NSCLC patients with BIM deletion polymorphism versus those with BIM wild. (C) Funnel plot of ORR analysis. (D) Funnel plot of DCR analysis. BIM = B cell lymphoma-2-like 11, EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors, NSCLC = nonsmall cell lung cancer.

these studies. The pooled estimate of the ORs in NSCLC patients harboring BIM deletion, compared with those harboring BIM wild was 0.49, 95% CI: 0.34 to 0.70, $P < .001$ (Fig. 2A). Sensitivity analysis ensured the consistent result and Begg test showed that there was no publication bias (Fig. 2C).

3.4. DCR analysis

Seven studies including 972 patients were pooled for DCR analysis. $P_H = 2.78$, $I^2 = 0\%$, indicating low heterogeneity of these studies. NSCLC patients harboring BIM deletion polymorphism showed worse DCR (OR, 0.50; 95% CI: 0.30–0.84; $P = .009$) than those harboring BIM wild (Fig. 2B). Sensitivity analysis ensured the consistent result and Begg test showed that there was no publication bias (Fig. 2D).

3.5. OS analysis

Six studies including 655 patients were pooled for OS analysis. $P_H < .001$, $I^2 = 82\%$, indicating high heterogeneity of these studies. Meta-regression revealed that the exp(b) for South Korea and Taiwan versus other countries was 1.80, 95% CI: 1.31 to 2.47, $P = .007$ (Fig. 3B); therefore, countries may be the source of heterogeneity. In the subgroup of South Korea and Taiwan,

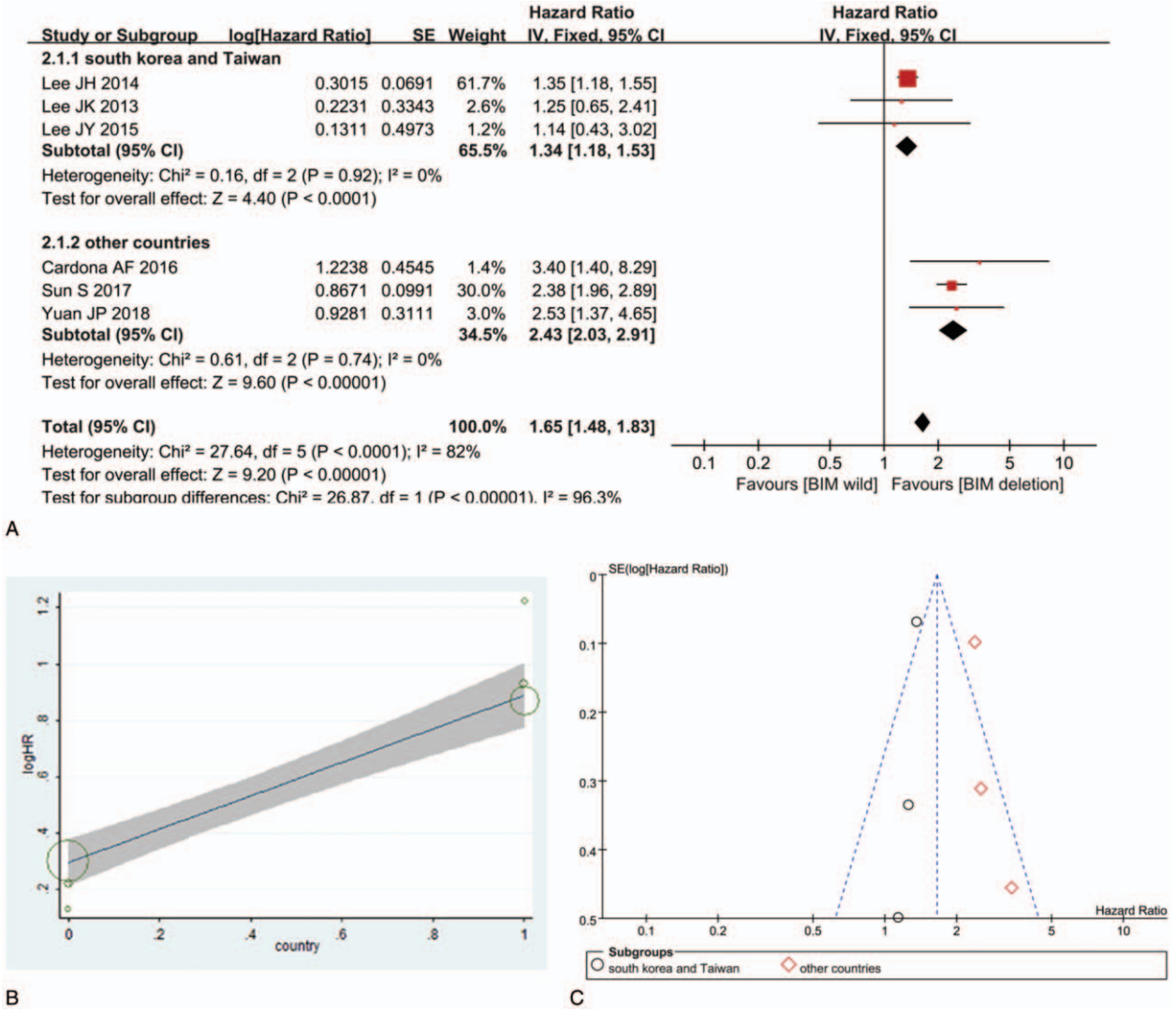

Figure 3. Impact of BIM deletion polymorphism on overall survival (OS) to EGFR-TKI. (A) Hazard ratio (HR) for overall survival (OS) to EGFR-TKI in NSCLC patients with BIM deletion polymorphism versus those with BIM wild. (B) Effect of country (South Korea and Taiwan vs. other countries) on heterogeneity across studies. (C) Funnel plot of OS analysis. BIM = B cell lymphoma-2-like 11, EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors, NSCLC = nonsmall cell lung cancer.

$P_H = .92$, $I^2 = 0\%$, in the subgroup of other countries, $P_H = 0.74$, $I^2 = 0\%$, suggesting the consistency of the studies in the 2 subgroups. In both subgroups, NSCLC patients with TKI therapy who harbored BIM deletion polymorphism had statistically significant shorter OS than those with BIM wild (in subgroup of South Korea and Taiwan, HR = 1.34, 95% CI: 1.18–1.53, $P < .001$; in subgroup of other countries, HR = 2.43, 95% CI: 2.03–2.91, $P < .001$) (Fig. 3A). Sensitivity analysis ensured the consistent result and Begg test showed that there was no publication bias (Fig. 3C).

3.6. PFS analysis

Fourteen studies including 2114 patients were pooled for PFS analysis (Table 2). $P_H < .001$, $I^2 = 79\%$, indicating high heterogeneity of these studies. To find out the sources of heterogeneity, meta-regression was performed using STATA 11.0 software. The exp(b) for male versus female was 0.88, 95% CI: 0.48 to 1.62, $P = .65$. The exp(b) for no smoking history versus smoking history was 0.79, 95% CI: 0.56 to 1.04, $P = .09$. The exp (b) for ECOG 0 to 1 versus ECOG 2 to 4 was 1.02, 95% CI: 0.99 to 1.04, $P = .13$. The exp(b) for adenocarcinoma versus non-adenocarcinoma was 0.11, 95% CI: 0.004 to 2.76, $P = .16$. The exp(b) for clinical stage III versus clinical stage IV and relapse was 1.76, 95% CI: 0.30 to 10.40, $P = .50$. The exp(b) for exon19 versus L858R was 1.36, 95% CI: 0.62 to 3.05, $P = .41$. The exp (b) for gefitinib versus erlotinib and afatinib was 1.01, 95% CI: 0.96 to 1.07, $P = .49$. The exp(b) for first-line therapy versus second-line or more line therapy was 0.93, 95% CI: 0.46 to 0.90, $P = .82$. Therefore, the reported clinical characteristics (i.e., sex, smoking history, ECOG, pathology, clinical stage, EGFR mutation, TKI type, and line of TKI treatment) in the original articles did not account for the heterogeneity.

Although the overall HR of the 14 studies is 1.66, 95% CI: 1.27 to 2.17, $P < .001$, this cannot be interpreted because the high heterogeneity. However, 2 subgroups could be obtained through sensitivity analysis. In subgroup A, $P_H = .36$, $I^2 = 9\%$, NSCLC patients with TKI therapy who harbored BIM deletion

Table 2

Characteristics of studies included for PFS analysis.

Study ID	Cases with PFS	EGFR mutation, %	Median PFS (BIM wild vs. BIM deletion, mo)	*P* value of median PFS	HR for PFS (95% CI)
Ng KP 2012[1]	141	100	11.9 vs. 6.6	.0027	2.08 (1.29–3.38)
Lee JK 2013[21]	193	100	11.9 vs. 11.3	.791	0.94 (0.64–1.40)
Zheng L 2013[12]	123	NA	6.0 vs. 3.5	.008	1.82 (1.03–3.22)
Isobe K 2014[13]	70	100	17.77 vs. 7.56	<.001	3.99 (1.86–8.55)
Lee JH 2014[14]	153	49.51	8.6 vs. 4.6	.004	2.15 (1.32–3.51)
Zhao MC 2014[15]	352	100	11 vs. 4.7	.016	2.09 (1.15–3.82)
Zhong J 2014[16]	135	100	9.53 vs. 7.30	.034	1.59 (1.23–2.04)
Lee JY 2015[22]	173	100	11.9 vs. 10.9	.16	0.74 (0.49–1.13)
Atsumi J 2016[17]	29	100	38.1 vs. 23.2	.007	6.7 (1.34–33.5)
Cardona AF 2016[18]	82	100	21.7 vs. 10.8	.029	3.0 (1.2–7.6)
Wu SG 2016[23]	327	100	10.5 vs. 8.5	.34	0.95 (0.79–1.14)
Qian K 2017[19]	85	100	12.8 vs. 7.1	.013	2.11 (1.38–3.21)
Sun S 2017[24]	140	100	17 vs. 21	.27	0.80 (0.33–1.96)
Yuan JP 2018[20]	111	65.77	11.3 vs. 7.5	.005	2.38 (1.30–4.34)

BIM = B cell lymphoma-2-like 11, CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, NA = not available, PFS = progression-free survival.

polymorphism had statistically significant shorter PFS than those with BIM wild (HR = 2.03, 95% CI: 1.71–2.40, $P < .001$). In subgroup B, $P_H = .740$, $I^2 = 0\%$, NSCLC patients with BIM deletion and with BIM wild had similar PFS (HR = 0.92, 95% CI: 0.79–1.07, $P = .26$) (Fig. 4). Begg test showed that there was publication bias (Fig. 5).

4. Discussion

Meta-analyses of the correlation of BIM deletion polymorphism and response to EGFR-TKIs in NSCLC patients have been conducted before the year 2016,[29–33] which were performed based on small number of studies and high heterogeneity. Therefore, the conclusions made by these meta-analyses should be interpreted cautiously. Since more original studies in this area have been published in recent 3 years,[17–20,23,24] we conducted this updated meta-analysis to obtain an objective and consistent conclusion. To the best of our knowledge, this updated meta-analysis collected the comprehensive literature and was more accurate as the heterogeneity in the analysis was low.

In 2012, using paired-end DNA sequencing, Ng et al[11] discovered a 2903-bp germline deletion polymorphism in intron

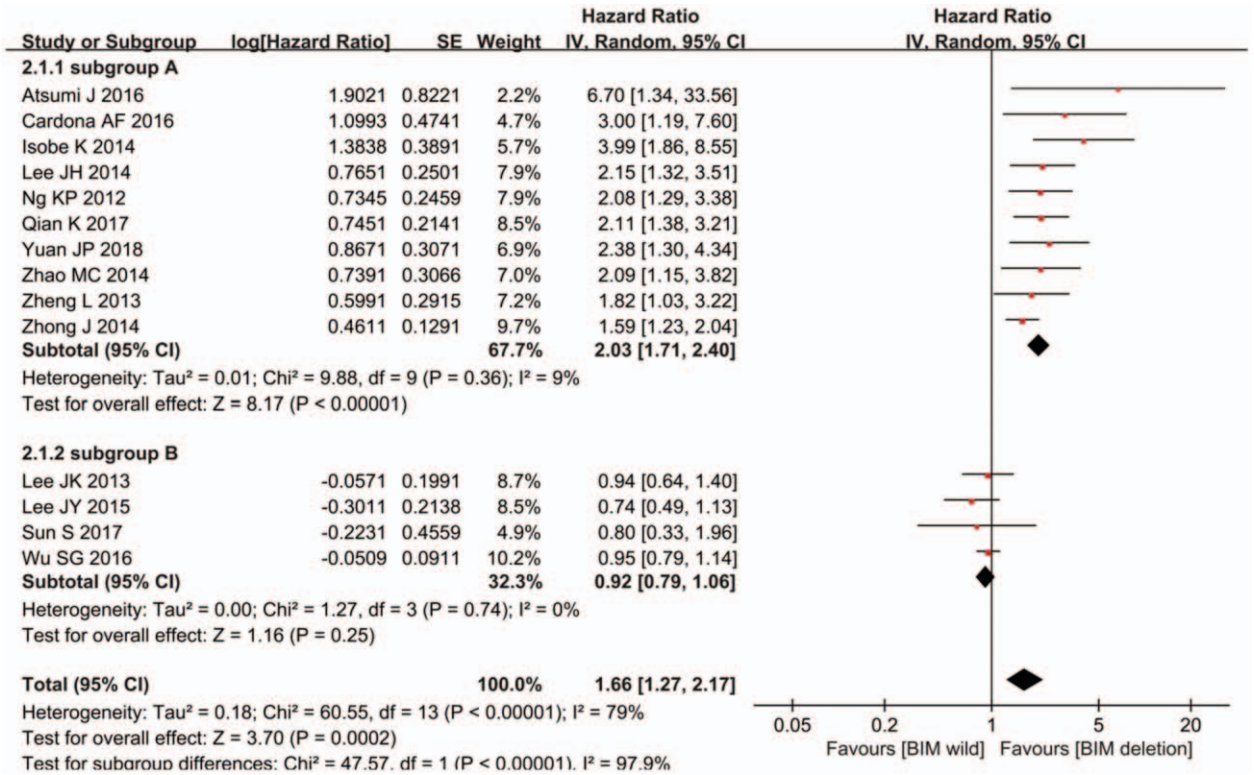

Figure 4. Impact of BIM deletion polymorphism on progression-free survival (PFS) to EGFR-TKIs. Hazard ratio (HR) for PFS to EGFR-TKIs in NSCLC patients with BIM deletion polymorphism versus those with BIM wild. BIM = B cell lymphoma-2-like 11, EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors, NSCLC = nonsmall cell lung cancer.

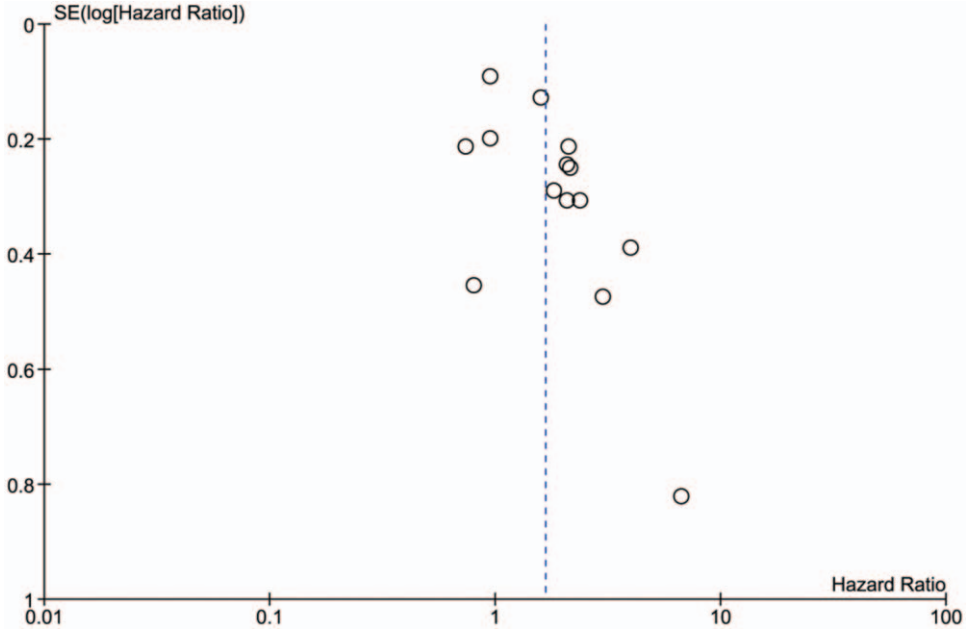

Figure 5. Funnel plot of progression-free survival analysis.

2 of BIM gene in East Asian populations. The polymorphism resulted in expression of BIM isoforms lacking the BH3 domain and lead to intrinsic TKI resistance in CML and EGFR-mutant NSCLC cell lines. In retrospective study in East Asian subjects from Singapore, Malaysia, and Japan, they found CML patients with BIM deletion polymorphism showed inferior DCR compared with controls after imatinib treatment and EGFR-mutant NSCLC patients with BIM deletion polymorphism showed shorter PFS compared with controls after gefitinib or erlotinib treatment. However, there was no influence of this polymorphism on response to imatinib in Chinese patients with CML.[34] Since BIM deletion polymorphism was found only in individuals of East Asian decent, the studies on the impact of BIM deletion polymorphism on the response of EGFR-TKIs in NSCLC were performed mainly in China, Japan, Korea, and South Korea. The results of these studies were contradictory.

By analysis of these studies, we found that NSCLC patients with BIM deletion polymorphism showed inferior ORR, DCR, and shorter OS than those without the polymorphism, which strongly suggested that BIM deletion polymorphism influenced the response to EGFR-TKIs and contributed to the resistance to EGFR-TKI in NSCLC patients. The EGFR-TKI-resistance due to BIM deletion can be circumvented by BH3 mimetics (ABT-737)[11] or histone deacetylase (HDAC) inhibitor (vorinostat).[35,36] Combined therapy of vorinostat and gefitinib to treat BIM deletion-associated resistance in EGFR-mutant NSCLC is under clinical trial in Japan.[37] If successful, EGFR-mutant NSCLC patients with BIM deletion polymorphism will benefit from the combined therapy.

Although this meta-analysis was performed with comprehensive literature and lower heterogeneity, the limitations cannot be neglected. First, PFS was taken as an important outcome in all the 14 original studies; it should be taken as the primary outcome in our analysis. However, the heterogeneity is high across studies, so it was taken as secondary outcome. Second, among the 14 studies, 10 studies were in favor of the correlation of BIM deletion polymorphism and poor response to EGFR-TKIs, while other 4 studies held that BIM deletion polymorphism had on influence on EGFR-TKIs response. Begg test showed that there was publication bias. Third, it was reported that smoking status and tumor histology are independent risk factors for the prediction of PFS to EGFR-TKIs therapy,[38,39] so we performed meta-regression with clinical characteristics to find out the source of heterogeneity across studies. However, the reported characteristics in original studies including sex, smoking history, ECOG performance status, pathology, clinical stage, EGFR mutation type, TKI type, line of TKI treatment, did not account for the heterogeneity. Song et al[40] reported that PFS of EGFR-TKI therapy in EGFR-mutant NSCLC could be stratified by the proposed 12-CT-phenotypic-feature-based signature, which may be the source of heterogeneity across studies.

5. Conclusions

In summary, this meta-analysis revealed that NSCLC patients with BIM deletion polymorphism showed poor response to EGFR-TKIs. BIM deletion polymorphism might be genetic cause of resistance to EGFR-TKIs therapy, and it could be used as a biomarker to predict the response to EGFR-TKIs in NSCLC patients, NSCLC patients without BIM deletion polymorphism will benefit from EGFR-TKIs therapy.

Author contributions

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Formal analysis: Wenxia Su.
Funding acquisition: Wenxia Su, Meiyu Peng.
Investigation: Wenxia Su.
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Validation: Yuliang Wang.
Writing – original draft: Wenxia Su.
Writing – review & editing: Fengbin Wang, Yuliang Wang.

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