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SYSTEMATIC REVIEW AND META-ANALYSIS

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BIM Gene Polymorphism Lowers the Efficacy of EGFR-TKIs in Advanced Nonsmall Cell Lung Cancer With Sensitive EGFR Mutations

A Systematic Review and Meta-Analysis

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Abstract: The strong association between bcl-2-like 11 (BIM) triggered apoptosis and the presence of epidermal growth factor receptor (EGFR) mutations has been proven in nonsmall cell lung cancer (NSCLC). However, the relationship between EGFR-tyrosine kinase inhibitor's (TKI's) efficacy and BIM polymorphism in NSCLC EGFR is still unclear.

Electronic databases were searched for eligible literatures. Data on objective response rates (ORRs), disease control rates (DCRs), and progression-free survival (PFS) stratified by BIM polymorphism status were extracted and synthesized based on random-effect model. Subgroup and sensitivity analyses were conducted.

A total of 6 studies that involved a total of 773 EGFR mutant advanced NSCLC patients after EGFR-TKI treatment were included. In overall, non-BIM polymorphism patients were associated with significant prolonged PFS (hazard ratio 0.63, 0.47–0.83, $P = 0.001$) compared to patients with BIM polymorphism. However, only marginal improvements without statistical significance in ORR (odds ratio [OR] 1.71, 0.91–3.24, $P = 0.097$) and DCR (OR 1.56, 0.85–2.89, $P = 0.153$) were observed. Subgroup analyses showed that the benefits of PFS in non-BIM polymorphism group were predominantly presented in pooled results of studies involving chemotherapy-naive and the others, and retrospective studies. Additionally, we failed to observe any significant benefit from patients without BIM polymorphism in every subgroup for ORR and DCR.

For advanced NSCLC EGFR mutant patients, non-BIM polymorphism ones are associated with longer PFS than those with BIM polymorphism after EGFR-TKIs treatment. BIM polymorphism status should be considered an essential factor in studies regarding EGFR-targeted agents toward EGFR mutant patients.

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Abbreviations: BIM = bcl-2-like 11, CI = confidence interval, DCR = disease control rate, EGFR = epidermal growth factor receptor, ERK = extracellular signal-regulated kinase, HRs = hazard ratios, MET = mesenchymal-epithelial transition, NSCLC = non-small-cell lung cancer, ORR = objective response rate, ORs = odds ratios, OS = overall survival, PFS = progression-free survival, TKIs = tyrosine kinase inhibitors.

INTRODUCTION

Nonsmall-cell lung cancer (NSCLC) is the primary cause of cancer-related death all over the world.[1] Unfortunately, most of NSCLC patients have few therapeutic methods because they are diagnosed at advanced stages.[2] However, the treatment of advanced NSCLC has surprisingly changed after the coming out of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs).[3–5] NSCLC patients with EGFR positive mutations who were treated with EGFR-TKI, such as gefitinib and erlotinib, as first-line therapy had longer progression-free survival (PFS) than did those who received platinum-based chemotherapy.[3,4,6,7]

Nevertheless, 10% of NSCLC patients, even if they have EGFR mutations, will get primary drug-resistance to EGFR-TKIs. Moreover, acquired drug-resistance occurs in those who respond to EGFR-TKIs at first after approximately 1-year treatment.[8–11] Various mechanisms of resistance to EGFR-TKIs have been revealed including the acquisition of the T790 M gatekeeper mutation,[11] kinase switching due to mesenchymal-epithelial transition amplification,[9,12] and transformation into small-cell lung cancer.[13] However, the mechanisms responsible for acquired EGFR-TKI resistance are not known in approximately 30% to 40% of patients.[14]

Bcl-2-like 11 (BIM) is a proapoptotic member of the B-cell CLL/lymphoma 2 (Bcl-2) family of proteins[15] and has emerged as a key modulator of apoptosis triggered by EGFR-TKI.[16,17] BIM mediated apoptosis through the intrinsic caspase pathway using EGFR-TKI treatment has been demonstrated in EGFR-TKI-sensitive cell lines.[17] Besides, another previous study showed that BIM deletion polymorphism was correlated with primary drug-resistance to EGFR-TKI.[18] In addition, scientists

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Author contributions: WFH and SXC conceived and designed the experiments. WFH and AHL carried out the search. HJZ and HMD extracted the data. AHL, HJZ, and HMD assessed the quality of included studies. HMD and LYL conducted the statistical analyses. WFH and SXC wrote the manuscript. All of the authors conducted a primary revision.
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also reported that BIM deletion polymorphism was not predictive of PFS for EGFR-TKIs.[19]

It is still unclear whether the efficacy of EGFR-TKIs for NSCLC was associated with BIM polymorphism status in EGFR mutant patients. A comprehensive analysis of all the subgroup data from previous studies is warranted. Thus, we sought to perform a meta-analysis incorporating all available evidences to evaluate the clinical outcome according to the BIM polymorphism status in advanced NSCLC patients with EGFR mutations after the treatment of EGFR-TKIs.

MATERIALS AND METHODS

Literature Search

We searched through PubMed, Embase, Cochrane Central Register of Controlled Trials, and Chinese Biomedical Literature database to find relevant articles using a combination of the terms ''Bcl-2-like 11 (BIM),'' ''epidermal growth factor receptor (EGFR),'' ''mutation,'' ''lung,'' ''nonsmall-cell lung cancer (NSCLC),'' and ''tyrosine kinase inhibitor (TKI).'' Besides, we also searched through the reference lists of pertinent reviews as additional search. The literature retrieval was carried out by 2 reviewers independently. There were no language or date restrictions in the retrieval.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: prospective or retrospective studies which investigate or report advanced NSCLC EGFR mutant patients after EGFR-TKIs treatment which were not used as combined therapy or maintenance therapy; clinical outcomes were stratified by BIM polymorphism status; the primary outcome was available. Studies failing to meet the above inclusion criteria will be excluded from this meta-analysis.

Outcomes Measures, Data Extraction, and Quality Assessment

PFS was the primary outcome for this meta-analysis. PFS data were extracted as hazard ratios (HRs) of patients without BIM polymorphism compared to those with BIM polymorphism in advanced EGFR-TKI-treated NSCLC and corresponding 95% confidence interval (CI) from subgroup analysis. If the HRs and its 95% CIs were not showed directly in our eligible studies, we would use median PFS and the *P* value to calculate them. Other outcomes were objective response rate (ORR) and disease control rate (DCR). The data on lead author, drug, patient status, study category, pathological type, EGFR mutation status, BIM polymorphism status, ORR, DCR, and PFS were extracted by 2 investigators independently. Three reviewers used the Newcastle–Ottawa scale specific to cohort study to assess all included studies. The Newcastle–Ottawa Scale assigns a maximum score of 4 for selection, 2 for comparability, and 3 for outcome. The quality score was ranked as low ($\leq$5 points) or high ($\geq$6 points). Studies of low methodological quality in which the estimate of quality is incorporated into the meta-analyses can alter the interpretation of the overall results. As a result, studies ranked as low quality level will be excluded for meta-analyses. Discrepancies were discussed by all investigators to reach a consensus. All eligible studies were of high quality after the assessment (more details in Table 1). Because our study is a systematic review and meta-analysis, each eligible study has been approved by local institutional review board. And each local institution has obtained matching informed consent from their patients, respectively. As a result, ethical approval and patient consent was not necessary for our study.

Statistical Analysis and Publication Bias

HRs for PFS and odds ratios (ORs) for dichotomous data (ORR and DCR) with 95% CI were pooled. Forest plots and the inconsistency statistic (I^2) were used to assess the heterogeneity across studies. In case of potential heterogeneity and avoiding underestimation of standard errors of pooled estimates, we used random-effects model in our meta-analyses. Calculations of our manuscript were performed by STATA 11.0 software. Subgroup analysis was conducted according to study type and treatment line, respectively. An OR value >1 reflected a better ORR or DCR in patients without BIM polymorphism, while a HR value <1 stood for more benefit from EGFR-TKIs in terms of PFS for

TABLE 1. Quality Assessment of Eligible Studies Using the Newcastle–Ottawa Quality Assessment Scale

Lead Author, yr	Selection*	Comparability†	Outcome‡	Total Scores§
Ng (2012)	3	1	2	6
Zhang (2013)	3	2	3	8
Isobe (2014)	3	2	2	7
Lee (2012)	3	2	2	7
Zhao (2014)	3	2	2	7
Lee (2014)	3	2	3	8

* Selection (0–4 points): (1) Representativeness of the exposed cohort (1 point, truly or somewhat representative of the average level in the community; 0 point, selected group of users or no description of the derivation of the cohort). (2) Selection of the nonexposed cohort (1 point, drawn from the same community as the exposed cohort; 0 point, drawn from a different source or no description of the derivation of the nonexposed cohort); (3) Ascertainment of exposure (1 point, secure record or structured interview; 0 point, written self-report or no description); (4) Demonstration that outcome of interest was not present at start of study (1 point, yes; 0 point, no).

† Comparability (0–2 points) (2 points, study controls for the most important factor and any additional factor; 1 point, study controls for the most important factor or any additional factor; 0 point, study controls without the most important factor or any additional factor).

‡ Outcome (0–3 points): (1) Assessment of outcome (1 point, independent blind assessment or record linkage; 0 point, self-report or no description); (2) Was follow-up long enough for outcomes to occur (1 point, yes; 0 point, no); (3) Adequacy of follow up of cohorts (1 point, complete follow up or subjects lost to follow up unlikely to introduce bias; 0 point, follow up rate $<$80% and no description of those lost, or no statement).

§ The quality score was ranked as low ($\leq$5 points) or high ($\geq$6 points).

those without BIM polymorphism. We considered a 2-sided *P* value <0.05 as statistically significant. Publication bias was evaluated using funnel plots, Begg's and Egger's tests.[20,21]

RESULTS

Eligible Studies

Six hundred eighty one records were identified according to the search strategy and finally 6 studies were enrolled,[18,19,22–25] which involved 773 chemo-naive or previously treated advanced NSCLC patients with EGFR mutations that referred to the efficacy of EGFR-TKIs (gefitinib or erlotinib or afatinib) stratified by BIM polymorphism status. Figure 1 summarizes the flow chart. Patients with a deletion polymorphism of Bcl-2-like protein 11 were categorized as BIM polymorphism cohort (n = 113), while the rest of patients were no BIM polymorphism patients (n = 660). Data of ORR and DCR were not available in 3 studies,[18,19,23] so that they were excluded in related subgroup analysis. Table 2 summarizes the characteristics of involved studies for meta-analysis.

Meta-Analyses of the BIM Polymorphism Group and Non-BIM Polymorphism Group in Terms of ORR, DCR, and PFS

In overall, when we compared to the BIM polymorphism group, the non-BIM polymorphism group was associated with significantly longer PFS (HR 0.63, 95% CI 0.47–0.83, $P = 0.001$; Figure 2C). However, although some improvement in ORR (OR 1.71, 95% CI 0.91–3.24, $P = 0.097$; Figure 2A) was observed, the benefits did not reach statistical significance. Additionally, there was no significant difference in DCR (OR 1.56, 95% CI 0.85–2.89, $P = 0.153$; Figure 2B) between groups with BIM polymorphism and without BIM polymorphism.

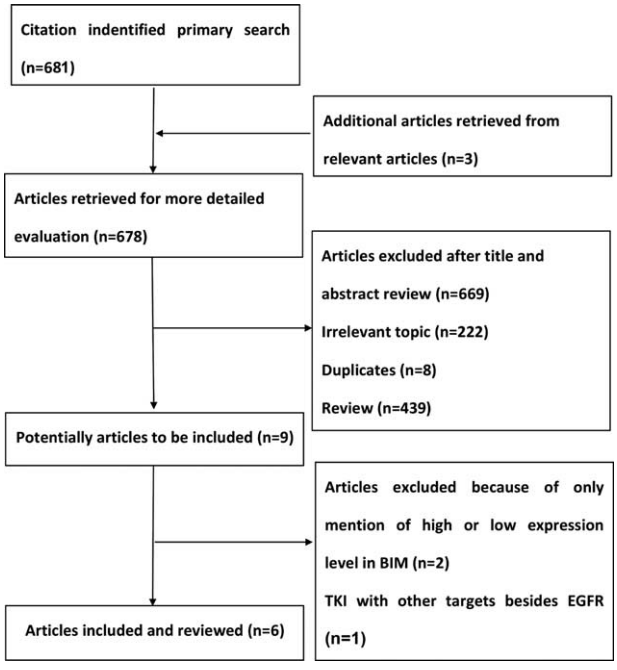

FIGURE 1. Profile summarizing the trial flow. BIM = bcl-2-like 11; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

TABLE 2. Characteristics of Included Studies for Meta-Analyses

Lead Author, yr	EGFR-TKIs	Patients Status	Study Type	Pathological Type	BIM Polymorphism Status (Sample Size)	ORR, %	DCR, %	Median PFS, m	*P* Value of PFS	HR* for PFS (95% CI)
Ng (2012)	Gefitinib or erlotinib	CT-naïve or previously treated	Retro	AC (n = 128); BAC (n = 4); SCC (n = 7); others (n = 9)	NBP (n = 115)	NA	NA	11.3	0.0027	0.555 (0.378–0.815)
					BP (n = 26)	NA	NA	11.9		
Zhang (2013)	Gefitinib or erlotinib	Previously treated	Pro	AC (n = 97); others (n = 26)	NBP (n = 102)	33/102 (32.4%)	77/102 (75.5%)	6	0.008	0.583 (0.391–0.869)
					BP (n = 21)	3/21 (14.3%)	11/21 (57.1%)	3.5		
Isobe (2014)	Gefitinib or erlotinib	NA	Retro	AC (n = 63); SCC (n = 7)	NBP (n = 57)	37/57 (64.9%)	52/57 (91.2%)	17.8	<0.001	0.427 (0.257–0.709)
					BP (n = 13)	8/13 (61.5%)	13/13 (100%)	7.6		
Lee (2012)	Gefitinib or erlotinib	CT-naïve or previously treated	Retro	AC (n = 191); NSCLC (n = 5); ASC (n = 1)	NBP (n = 172)	NA	NA	11.3	0.791	1.053 (0.718–1.543)
					BP (n = 21)	NA	NA	11.9		
Zhao (2014)	Gefitinib or erlotinib	CT-naïve or previously treated	Retro	AC (n = 140); SCC (n = 8); ASC (n = 9); others (n = 9)	NBP (n = 150)	99/150 (66.0%)	122/150 (81.3%)	11	0.003	0.427 (0.243–0.749)
					BP (n = 16)	4/16 (25.0%)	10/16 (62.5%)	4.7		
Lee (2014)	Gefitinib or erlotinib or afatinib	CT-naïve	Pro	AC (n = 189); NAC (n = 12); nonspecified (n = 3)	NBP (n = 64)	NA	NA	9.4	0.18	0.787 (0.555–1.117)
					BP (n = 16)	NA	NA	7.4		

AC = adenocarcinoma; ASC = adenosquamous carcinoma; BAC = bronchioalveolar carcinoma; BIM = bcl-2-like 11; BP = BIM polymorphism; CI = confidence interval; CT = chemotherapy (not specific); DCR = disease control rate; EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors; HR = hazard ratio; NA = not available; NAC = nonadenocarcinoma; NBP = no BIM polymorphism; NSCLC = nonsmall-cell lung cancer; ORR = objective response rate; PFS = progression-free survival; Pro = prospective; Retro = retrospective; SCC = squamous cell carcinoma.
*HR represents $HR_{\text{no BIM polymorphism/BIM polymorphism}}$ in patients using EGFR-TKIs.

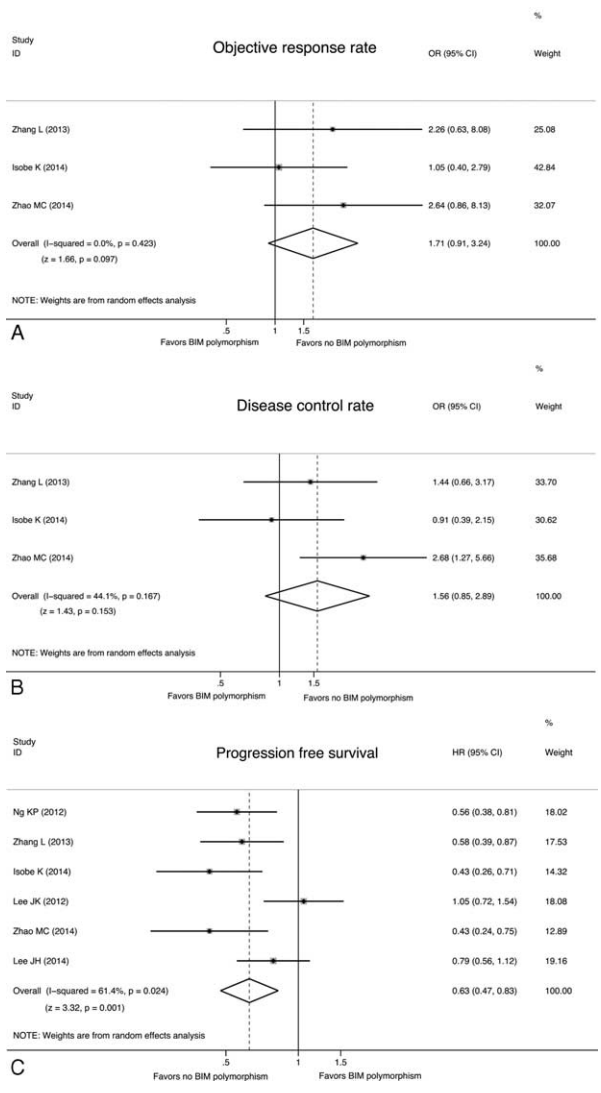

FIGURE 2. Meta-analyses of non-BIM polymorphism group versus BIM polymorphism group in EGFR mutant nonsmall cell lung cancer patients receiving EGFR-TKIs: A: ORR; B: DCR; C: PFS. BIM = bcl-2-like 11; CI = confidence interval; DCR = disease control rate; EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors; HR = hazard ratio; OR = odds ratio; ORR = objective response rate; PFS = progression-free survival.

Subgroup Analyses, Sensitivity Analyses, and Publication Bias

When stratifying patients according to study type and treatment line, we observed results that significant benefits of PFS in non-BIM polymorphism group were found in subgroup involving chemotherapy-naive patients (chemotherapy-naive vs chemotherapy-naive and the others: HR, 95% CI, *P* value 0.79, 0.55–1.12, 0.179 vs 0.59, 0.42–0.82, 0.002) and there is no significant difference in retrospective studies (retrospective studies vs prospective studies: HR, 95% CI, *P* value 0.59, 0.38–0.91, 0.017 vs 0.69, 0.51–0.92, 0.012) (Table 3). In terms of ORR and DCR, we failed to obtain enough data to get the results. As a result, the conclusions regarding all outcomes did not alter. There was no publication bias for outcome measures, with symmetrical appearance on funnel plot analysis (Figure 3) and all *P* values >0.05 in Begg's test and Egger's test.

DISCUSSION

For advanced NSCLC patients with EGFR mutations, the association of BIM polymorphism status and efficacy of EGFR-TKIs therapy remains unclear. A meta-analysis incorporating all available data from correlative studies is a good way to address this question. We conducted this study and found that non-BIM polymorphism patients had significant reduced disease progression risk than the patients with BIM polymorphism after EGFR-TKIs. Additionally, favorable outcomes of ORR and DCR in non-BIM polymorphism patients were presented in our work, but the statistical significance was not approached.

The basis for the above association derived the following interpretations. It was reported that BIM is a BH3-only proapoptotic member of the Bcl-2 protein family, and gene products with BH3 domains are required to induce apoptosis. In EGFR mutant lung cancer, BIM plays a central role in the induction of apoptosis in response to EGFR-TKIs.[16,26] On the one hand, Li et al[27] found that the apoptosis of cancer cell could be induced by gefitinib via up-regulation of BIM level in drug-sensitive cell lines. Gong et al[17] reported that both transcriptional and post-transcriptional regulations could influence the expression of BIM. Furthermore, the downstream signaling of EGFR, extracellular signal-regulated kinase, could also mediate the regulation of BIM.[17] On the other hand, if the polymorphism leads to expression of the BIM protein BIMγ in which 2903 bases are deleted in intron 2 of the BIM gene leading to loss of the BH3 domain, it cannot induce apoptosis.[18] And Li et al[27] found that silencing of BIM by small interfering RNA could alleviate

TABLE 3. Summary of Subgroup Analyses Results in Terms of PFS

			Effect Size		Heterogeneity	
Subgroup/Total	**No. of Studies**	**HR* (95% CI)**	**Z**	***P* Value**	***P* Value**	**I^2, %**
Prospective	2	0.69 (0.51–0.92)	2.50	0.012	0.268	18.5
Retrospective	4	0.59 (0.38–0.91)	2.38	0.017	0.010	73.8
Chemotherapy-naive	1	0.79 (0.55–1.12)	1.34	0.179	NA	NA
Chemotherapy-naive or others	5	0.59 (0.42–0.82)	3.10	0.002	0.021	65.3
Total	6	0.63 (0.47–0.83)	3.32	0.001	0.024	61.4

CI = confidence interval; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitors; HR = hazard ratio; NA = not available; PFS = progression-free survival.

* HR represents $HR_{\text{no BIM polymorphism/BIM polymorphism}}$ in patients using EGFR-TKIs.

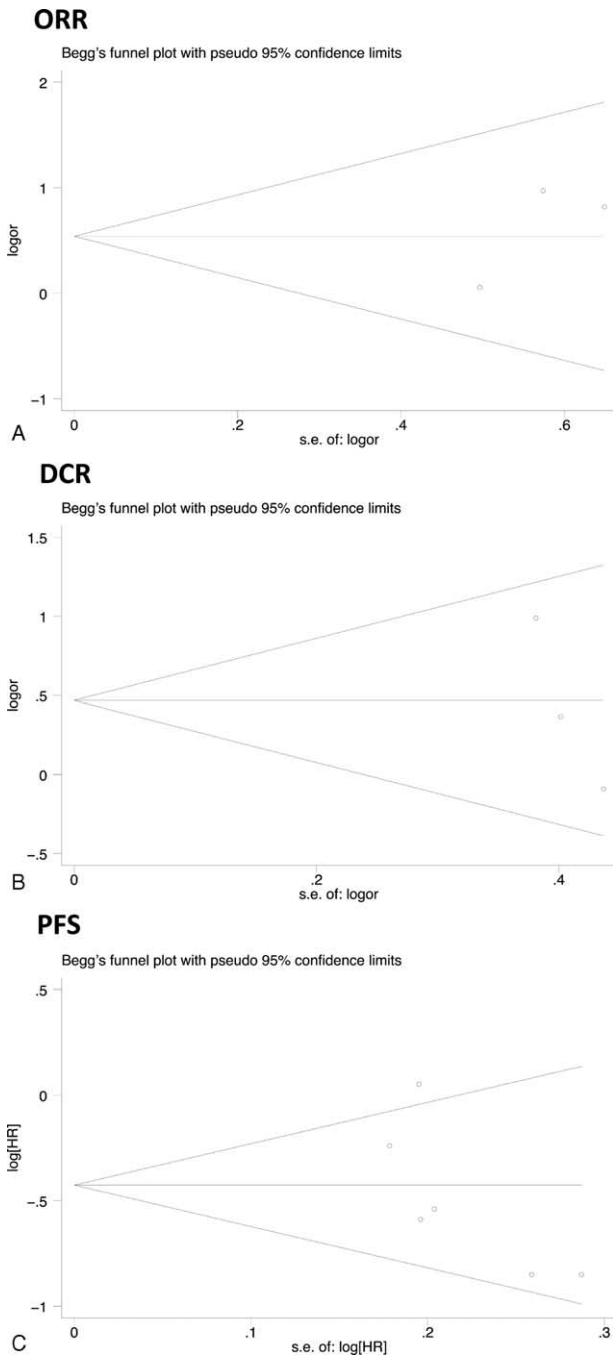

FIGURE 3. Funnel plots of SE by log OR/HR (A: ORR; B: DCR; C: PFS). DCR = disease control rate; HR = hazard ratio; OR = odds ratio; ORR = objective response rate; PFS = progression-free survival; SE = standard error.

apoptosis induced by gefitinib. Nevertheless further in vitro and in vivo research will be conducted to explore epigenetic factors and signal crosstalk that may have an impact on the expression or function of BIM.

Additionally, exon 19 deletion has been associated with better outcomes than L858R in several previous studies.[28–30] And as a key modulator of apoptosis triggered by EGFR-TKI,[16] BIM could motivate the better outcomes in NSCLC. So we had to doubt that whether the different TKI-sensitive EGFR mutation subtype resulted in BIM deletion polymorphism status and signaling that were resistant to TKIs in patients with NSCLC. However, until now the association of EGFR subtype and BIM polymorphism was still unclear, more work is needed to understand it better.

Notably, this is the first study to comprehensively answer the impact of BIM polymorphism status on response to EGFR-TKIs in advanced NSCLC patients with EGFR mutations. Nevertheless, there exist several limitations. First, our meta-analysis was mostly based on subgroup data extracted from prospective and retrospective studies, which somehow compromised the evidence level. However, considering the strict eligible criteria, only 2 prospective and 4 retrospective studies were all that we could enroll to extract relevant data. Second, data of ORR and DCR were not available in all the included studies which might influence statistically significances in pooled analyses of ORR and DCR, as well as subgroup analyses. Third, almost all the eligible articles failed to provide data regarding overall survival (OS) of BIM polymorphism group and non-BIM polymorphism group, so we have to compromise to conduct our study without analysis referred to OS. Besides, we could not evaluate the respective effect of different EGFR-TKIs due to lack of enough data. To be sure, further studies were warranted to complete the information.

Nonetheless, regardless of above limitations, this comprehensive analysis statistically has confirmed that non-BIM polymorphism patients with EGFR mutations are associated with longer PFS for EGFR-TKIs treatment compared to those with BIM polymorphism. The result leads to some important hints. First, we suggest that investigators should consider the BIM polymorphism status as a stratification factor in designing or reviewing clinical studies involving TKIs therapy in EGFR mutants. In addition, Kuroda et al[31] showed that small changes of BIM protein concentrations influenced the apoptosis ability and the degree of TKI (imatinib) resistance of Bcr/Abl positive leukemic cells. It implied that BIM-associated resistance to EGFR-TKIs might be overcome by BH3-mimetic drugs[18] and we could achieve the treatment of BIM-associated resistance to EGFR-TKI by regulation of the concentration of EGFR-TKIs according to the expression of BIM. Furthermore, more efforts should be made to investigate mechanisms of EGFR-TKIs' resistance induced by BIM polymorphism in different genotypes of EGFR mutants thereby finding-related solutions.

In conclusion, for advanced NSCLC EGFR mutant patients, non-BIM polymorphism ones are associated with longer PFS than those with BIM polymorphism after EGFR-TKIs treatment. BIM polymorphism status should be considered an essential factor in studies regarding EGFR-targeted agents toward EGFR mutant patients.

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