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Original Article

Low BMI patients with advanced *EGFR* mutation-positive NSCLC can get a better outcome from metformin plus EGFR-TKI as first-line therapy: A secondary analysis of a phase 2 randomized clinical trial

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ABSTRACT

Background: The synergistic association between metformin and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) has been confirmed in *in vitro* studies. It is still controversial which patients can benefit from metformin plus EGFR-TKIs treatment. Body mass index (BMI) was proved to be independently associated with prolonged progression-free survival (PFS) and overall survival (OS). This study aimed to investigate whether BMI is associated with the synergistic effect of metformin and EGFR-TKIs in advanced *EGFR* mutation (*EGFR*m)-positive non-small cell lung cancer (NSCLC) among nondiabetic Asian population.

Methods: We performed a *post hoc* analysis of a prospective, double-blind phase II randomized clinical trial (COAST, NCT01864681), which enrolled 224 patients without diabetes with treatment-naïve stage IIIB-IV *EGFR*m NSCLC. We stratified patients into those with a high BMI (≥24 kg/m^2) and those with a low BMI (<24 kg/m^2) to allow an analysis of the difference in PFS and OS between the two groups. The PFS and OS were analyzed using Kaplan–Meier curves, and the differences between groups were compared using log-rank test.

Results: In the univariate analysis, patients who had a high BMI (n = 56) in the gefitinib + metformin group (n = 28) did not have a better PFS (8.84 months *vs.* 11.67 months; P = 0.351) or OS (15.58 months *vs.* 24.36 months; P = 0.095) than those in the gefitinib + placebo group (n = 28). Similar results were also observed in the low-BMI groups. Strikingly, in the metformin plus gefitinib group, patients who had low BMI (n = 69) showed significantly better OS than those with high BMI (24.89 months [95% CI, 20.68 months–not reached] *vs.* 15.58 months [95% CI, 13.78–31.53 months]; P = 0.007), but this difference was not observed in PFS (10.78 months *vs*. 8.84 months; P = 0.285).

Conclusions: Our study showed that nondiabetic Asian advanced NSCLC patients with *EGFR* mutations who have low BMI seem to get better OS from metformin plus EGFR-TKI treatment.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] In recent years, non-small cell lung cancer (NSCLC) patients harboring sensitizing epidermal growth factor receptor (*EGFR*) mutations have shown significant responses to EGFR tyrosine kinase inhibitors (TKIs).[2] Despite impressive initial responses, almost all patients eventually relapsed due to the occurrence of acquired resistance.[3] Various studies have pursued approaches to delay or overcome resistance to EGFR-TKIs, including developing next-generation TKIs and exploring novel drug combinational strategies. However, the third-generation EGFR-TKI osimertinib is still inevitably challenged by the issue of drug resistance as well.[4] Thus, novel combinational strategies are urgently required to overcome acquired resistance to EGFR-TKIs in NSCLC patients.

Metformin is a kind of oral hypoglycemic drug, which has been proven to influence tumorigenesis of several cancer types in both cell lines and animal models.[5–7] Meanwhile, previous studies also demonstrated that the combination of metformin and EGFR-TKIs could overcome acquired resistance to EGFR-TKIs through decreasing proliferation, promoting apoptosis, and enhancing autophagy of cancer cells.[8–12] Especially, in NSCLC cells harboring wild-type *LKB1* genes, combined use of metformin and gefitinib induced a strong antiproliferative and proapoptotic effect.[11] Other studies also reported combinatorial therapy including metformin effectively inhibited TKI-resistant cancer cells, due to reduced interleukin-6 (IL-6) secretion and expression.[9] Based on these findings, current research is focusing on therapeutic combination with metformin that might increase long-term efficacy of EGFR-TKIs,

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Table 1
Baseline characteristics of advanced *EGFR* mutation-positive NSCLC patients with high BMI (≥24 kg/m^2).

Characteristics	Gefitinib + metformin (n = 28)	Gefitinib + placebo (n = 28)	Statistics	P values
Age (years)	58 (54, 62)	58 (50, 62)	−0.591*	0.555
Sex			0.072†	1.000
Male	14 (50.0)	15 (53.6)		
Female	14 (50.0)	13 (46.4)		
BMI (kg/m^2)	26.05 (25.60, 26.70)	25.95 (24.70, 26.88)	−0.525*	0.600
Disease stage			–	0.252
IIIB	2 (7.1)	6 (21.4)		
IV	26 (92.9)	22 (78.6)		
Smoking status			–	0.550
Former smoker	9 (32.1)	6 (21.4)		
Current smoker	0 (0)	0 (0)		
Never smoker	19 (67.9)	22 (78.6)		
Histologic type			–	0.611
Adenocarcinoma	27 (96.4)	25 (89.3)		
Squamous	0 (0)	1 (3.6)		
NOS	1 (3.6)	2 (7.1)		
WHO performance status			–	0.718
0	8 (28.6)	10 (35.7)		
1	18 (64.3)	15 (53.6)		
2	2 (7.1)	3 (10.7)		

Data are presented as median (Q_1, Q_3) or n (%).
BMI: Body mass index; CI: Confidence interval; *EGFR*: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; NOS: Not a specific histologic type; OS: Overall survival; PFS: Progression-free survival; WHO: World Health Organization; –: Not available.
* Z value.
† χ^2 value.

due to the low risk of toxic effects. However, these effects require further investigation by clinical trials.

At present, it is still controversial whether the addition of metformin to standard EGFR-TKIs improves progression-free survival (PFS) or overall survival (OS) in nondiabetic patients with advanced NSCLC and *EGFR* mutations.[13,14] Determining which patients can really benefit from metformin combination therapy is still a research hotspot. Recently, Arrieta et al.[15] published a secondary analysis of NCT03071705 and concluded that the addition of metformin to regimens given to patients with a body mass index (BMI) of 24 kg/m^2 or higher was independently associated with longer PFS and OS. We are very interested in whether similar results can be observed in Asian populations, so we performed a secondary analysis in our previously published clinical research data on whether BMI is associated with the synergistic effect of metformin and EGFR-TKIs.[13]

Material and methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and approved by the Ethics Committee of Daping Hospital (ethical review of medical research [2013-017]) for studies involving humans. Written informed consent was obtained from all subjects involved in the study.

Patients and study design

Patients were recruited to this *post hoc* secondary analysis from a previously published, prospective, double-blind, placebo-controlled phase II randomized clinical trial (RCT) (NCT01864681).[13] Patients were recruited at nine hospitals in China between August 12, 2013, and December 14, 2015. The trial was undertaken in accordance with the Good Clinical Practice (GCP) and consolidated standards of reporting trials (CONSORT) guidelines. Eligible patients were Chinese individuals aged 18–75 years who had histocytologically confirmed metastatic or unresectable locally advanced NSCLC with *EGFR*-activating mutations. They were randomly assigned to receive gefitinib plus metformin or gefitinib plus placebo in a ratio of 1:1. Investigators retrieved anthropometric variables of BMI from the clinical trial database. Referring to Arrieta's research, we stratified patients into those with a high BMI (≥24 kg/m^2) and those with a low BMI (<24 kg/m^2) to analyze the differences in PFS and OS.[15] The efficacy of the improved intention to treat (ITT) population was statistically analyzed as described previously.[13]

Statistical analyses

Continuous data with non-normal distribution were presented as median (Q_1, Q_3) and categorical data were expressed as n (%). PFS and OS were analyzed using Kaplan–Meier curves, and differences between groups were compared using log-rank test. Comparisons between medians were performed with the Mann–Whitney U test, and prognostic factors for survival and hazard ratios (HRs) were determined via Cox regression models. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with R software version 4.0.3 (R foundation of statistical computing, available online: http://www.r-project.org). Forest plots were performed with R software version 4.0.3 using "forestplot" package.

Results

Comparison of survival between gefitinib plus metformin or gefitinib plus placebo group stratified by BMI

A total of 202 patients were included in the analysis. There were 97 patients in the gefitinib + metformin group and 105 patients in the gefitinib + placebo group. The clinical characteristics of these patients with high and low BMI are shown in Tables 1 and 2. In the univariate analysis, patients who had a high BMI (n = 56 [27.7%]) in the gefitinib + metformin group (n = 28) did not have a better PFS or OS than those in the gefitinib + placebo group (n = 28). The median PFS (mPFS) was 8.84 (95% CI, 5.82–15.42) months in the gefitinib + metformin group *vs.* 11.67 (95% CI, 8.45–17.19) months in the gefitinib + placebo group (HR: 1.34; 95% CI, 0.75–2.51; P = 0.354; Fig. 1A). Similarly, there was no significant difference in median OS (mOS) between gefitinib + metformin group and gefitinib + placebo group in patients who

Table 2
Baseline characteristics of advanced *EGFR* mutation-positive NSCLC patients with low BMI (<24 kg/m^2).

Characteristics	Gefitinib + metformin (n = 69)	Gefitinib + placebo (n = 77)	Statistics	P values
Age (years)	59 (52, 68)	60 (55, 64)	−0.445*	0.656
Sex			0.250†	0.733
Male	44 (63.8)	46 (59.7)		
Female	25 (36.2)	31 (40.3)		
BMI (kg/m^2)	20.80 (19.50, 22.40)	21.50 (20.20, 22.50)	−1.486*	0.137
Disease stage			–	0.517
IIIB	6 (8.7)	4 (5.2)		
IV	63 (91.3)	73 (94.8)		
Smoking status			–	0.918
Former smoker	13 (18.8)	16 (20.8)		
Current smoker	1 (1.4)	1 (1.3)		
Never smoker	55 (79.7)	60 (77.9)		
Histologic type			–	0.022
Adenocarcinoma	64 (92.8)	77 (100.0)		
Squamous	1 (1.4)	0 (0)		
NOS	4 (5.8)	0 (0)		
WHO performance status			1.046†	0.625
0	14 (20.3)	16 (20.8)		
1	45 (65.2)	54 (70.1)		
2	10 (14.5)	7 (9.1)		

Data are presented as median (Q_1, Q_3) or n (%).
BMI: Body mass index; CI: Confidence interval; *EGFR*: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; NOS: Not a specific histologic type; OS: Overall survival; PFS: Progression-free survival; WHO: World Health Organization; –; Not available.
* Z value.
† χ^2 value.

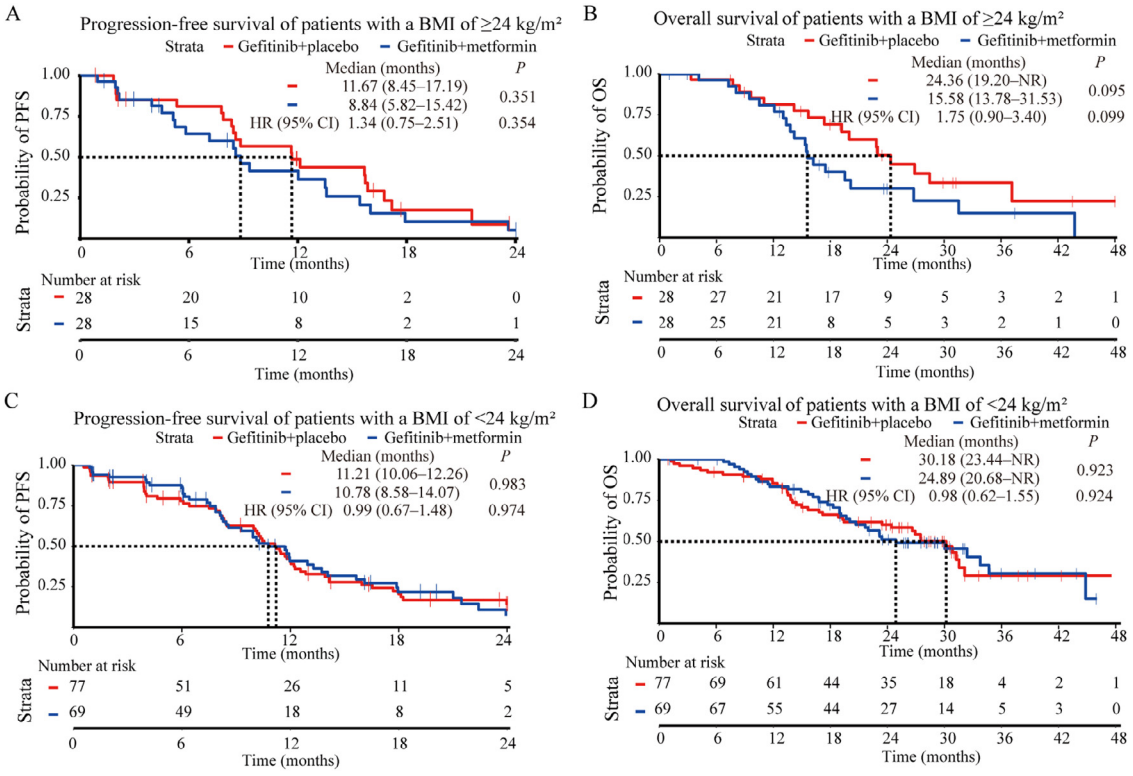

Fig. 1. (A) Kaplan–Meier estimates of PFS in advanced *EGFR* mutation-positive NSCLC patients with high BMI (≥24 kg/m^2). (B) Kaplan–Meier estimates of OS in advanced *EGFR* mutation-positive NSCLC patients with high BMI (≥24 kg/m^2). (C) Kaplan–Meier estimates of PFS in advanced *EGFR* mutation-positive NSCLC patients with low BMI (<24 kg/m^2). (D) Kaplan–Meier estimates of OS in advanced *EGFR* mutation-positive NSCLC patients with low BMI (<24 kg/m^2). BMI: Body mass index; CI: Confidence interval; *EGFR*: Epidermal growth factor receptor; HR: Hazard ratio; NA: Not reached; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

had a high BMI (15.58 months [95% CI, 13.78–31.53 months] *vs.* 24.36 [95% CI, 19.20 months–not reached]; HR: 1.75; 95% CI, 0.90–3.40; P = 0.099; Fig. 1B). Similar results were observed in patients with BMI below 24 kg/m^2, which did not show improved PFS (10.78 [95% CI, 8.58–14.07] months *vs.* 11.21 [95% CI, 10.06–12.26] months; HR: 0.99; 95% CI, 0.67–1.48; P = 0.974; Fig. 1C) and OS (24.89 months [95% CI, 20.68 months–not reached] *vs.* 30.18 months [95% CI, 23.44 months–not reached]; HR: 0.98; 95% CI, 0.62–1.55; P = 0.924; Fig. 1D) from the addition of metformin to gefitinib over those patients who received gefitinib alone. After adjustment for age, sex, disease stage, smoking status,

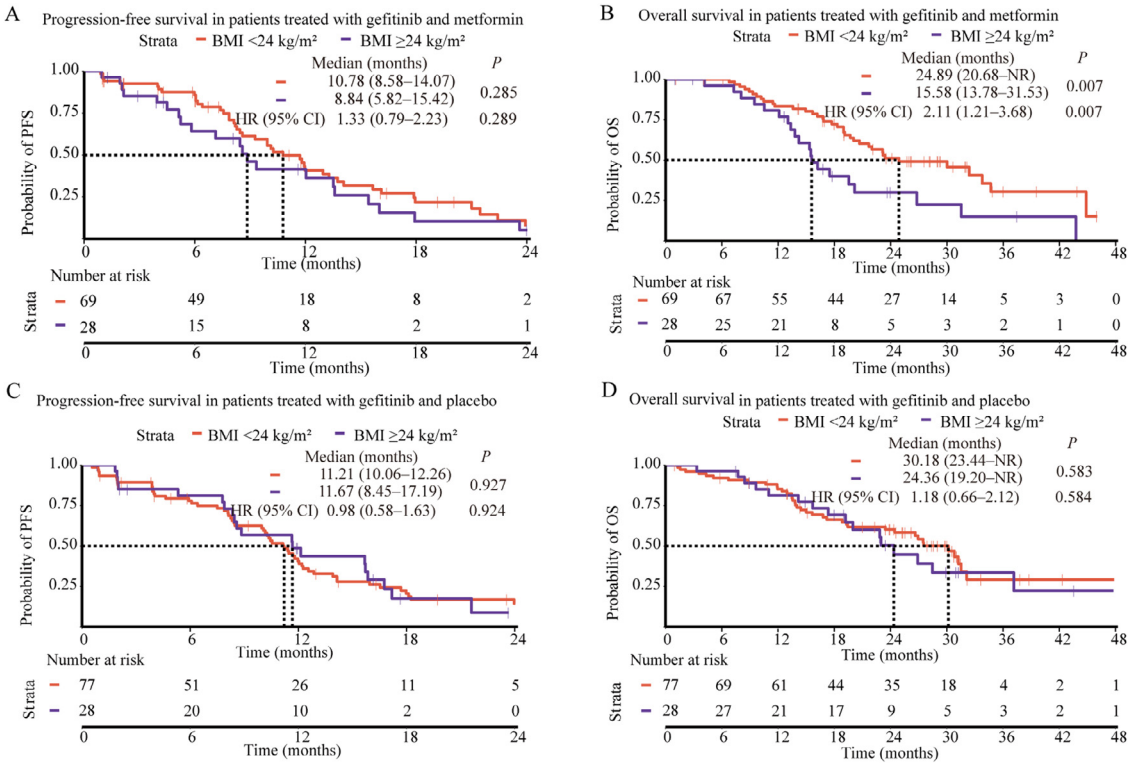

Fig. 2. (A) Kaplan–Meier estimates of PFS in advanced *EGFR* mutation-positive NSCLC patients with high or low BMI treated with gefitinib + metformin. (B) Kaplan–Meier estimates of OS in advanced *EGFR* mutation-positive NSCLC patients with high or low BMI treated with gefitinib + metformin. (C) Kaplan–Meier estimates of PFS in advanced *EGFR* mutation-positive NSCLC patients with high or low BMI treated with gefitinib + placebo. (D) Kaplan–Meier estimates of OS in advanced *EGFR* mutation-positive NSCLC patients with high or low BMI treated with gefitinib + placebo. BMI: Body mass index; CI: Confidence interval; *EGFR*: Epidermal growth factor receptor; HR: Hazard ratio; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

histologic type, and WHO performance status, the HRs for PFS and OS were 0.87 (95% CI: 0.56–1.33, $P = 0.506$) and 0.97 (95% CI: 0.60–1.56, $P = 0.901$) by a Cox regression model.

Comparison of survival between patients with high and low BMI in the gefitinib + metformin and gefitinib + placebo group

We further stratified patients treated with metformin and gefitinib into those with a high BMI ($n = 28$) and those with a low BMI ($n = 69$) to analyze the differences in PFS and OS. The baseline characteristics of the two groups (high BMI *vs*. low BMI) were identical (all $P > 0.05$). It is noteworthy that patients who had a low BMI had significantly better OS than those who had a high BMI (24.89 months [95% CI, 20.68 months–not reached] *vs.* 15.58 months [95% CI, 13.78–31.53 months]; HR: 2.11; 95% CI, 1.21–3.68; $P = 0.007$), but this difference was not observed in PFS (10.78 [95% CI, 8.58–14.07] months *vs.* 8.84 [95% CI, 5.82–15.42] months; HR: 1.33; 95% CI, 0.79–2.23; $P = 0.289$; Fig. 2A, B). Forest plots of patients in metformin plus gefitinib group showed that patients with lower BMI benefited more from OS (HR: 2.16; 95% CI, 1.24–3.76; $P = 0.007$) than those with higher BMI, but they did not show better PFS (HR: 1.32; 95% CI, 0.78–2.23; $P = 0.302$) after adjustment for age and sex [Fig. 3A, B]. After adjustment for age, sex, disease stage, smoking status, histologic type, and WHO performance status, the HR for OS was 2.47 (95% CI, 1.38–4.39, $P = 0.002$). However, patients with a high BMI did not show improved PFS (11.67 [95% CI, 8.45–17.19] months *vs.* 11.21 [95% CI, 10.06–12.26] months; HR: 0.98; 95% CI, 0.58–1.63; $P = 0.924$; Fig. 2C) and OS (24.36 months [95% CI, 19.20 months–not reached] *vs.* 30.18 months [95% CI, 23.44 months–not reached]; HR: 1.18; 95% CI, 0.66–2.12; $P = 0.584$; Fig. 2D) than patients with low BMI ($n = 77$) in the gefitinib+ placebo group.

Discussion

Previous studies have confirmed that metformin is the cornerstone of the treatment of type II diabetes. Meanwhile, preclinical reports have shown the antitumor activity of metformin across several types of cancer both *in vitro* and *in vivo*. Metformin has been shown to impair the transforming growth factor-β (TGF-β)-induced mesenchymal state in a variety of pathological processes[16] and inhibit the IL-6/signal transducer and activator of transcription 3 (STAT3) pathway, thus making drug-resistant cells more susceptible to EGFR-TKIs.[9] Metformin may sensitize EGFR-TKIs based on the molecular mechanism mentioned above. Epidemiological and clinical studies have confirmed these findings. Metformin seems to be related to the reduction of cancer risk and improvement of prognosis in nondiabetic patients with breast cancer, prostate cancer, gastric cancer, endometrial cancer, lung cancer, and other malignant tumors.[17–22] Because of its low cost and safety, metformin was expected to be used in combination with other anticancer drugs in clinic.[23–26]

Although the synergistic association between metformin and EGFR-TKI has been confirmed in *in vitro* studies, the clinical trials about the synergistic association between EGFR-TKIs and metformin have not produced consistent results.[9,11,13,14] Nevertheless, we still observe that many advanced NSCLC patients with *EGFR* mutations are treated with metformin combined with EGFR-TKI in clinical settings.[27] Recognizing which patients can benefit from combination therapy may have profound clinical significance. Arrieta et al.[15] reported that the addition of metformin to a standard EGFR-TKIs treatment regimen for patients with *EGFR*-mutated lung adenocarcinoma and BMI of 24 kg/m^2 or higher significantly prolonged PFS and OS. However, we found that patients with lower BMI enjoyed significantly longer OS when given a metformin

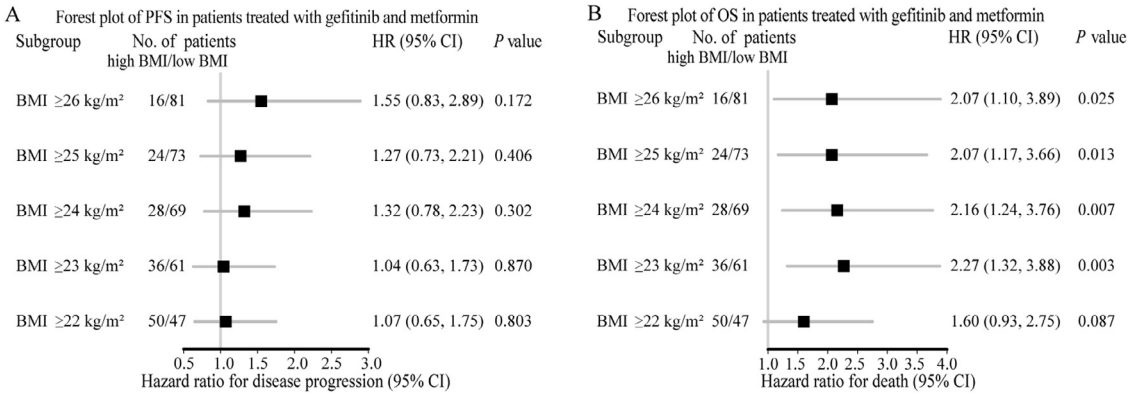

Fig. 3. Forest plots of PFS (A) and OS (B) according to different BMIs in advanced *EGFR* mutation-positive NSCLC patients treated with metformin + gefitinib. Cox regression models were used, and HRs were obtained by adjusting for age and sex. BMI: Body mass index; CI: Confidence interval; *EGFR*: Epidermal growth factor receptor; HR: Hazard ratio; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

plus gefitinib regimen than patients with higher BMI did. These results showed that low BMI could be used to predict the efficacy of metformin plus gefitinib, at least in Asian patients without diabetes with *EGFR* mutations and advanced NSCLC.

Our previous research shows that metformin cannot render patients more sensitive to gefitinib if those patients are nondiabetic and have advanced NSCLC.[13] This is not entirely unexpected, because a cohort study conducted by the US military health system on patients with type II diabetes with NSCLC has shown that improved results were observed only in early stage patients and patients who started using metformin before the diagnosis of NSCLC.[28] Our retrospective clinical study has also shown a synergistic effect of metformin and EGFR-TKIs on the prognosis of NSCLC patients with type 2 diabetes mellitus. These patients had been taking metformin for a long time.[27] This study found that nondiabetic patients with low BMI who received metformin plus gefitinib treatment benefited in OS rather than PFS, which also shows that long-term application of metformin is necessary.

According to the clinical data of patients with pancreatic cancer, the conventional dose of metformin may not be enough to make it effective, because the antiproliferative effect of metformin is dose-dependent. This suggests that only patients with high plasma concentrations (>1 mg/L) of metformin can gain survival benefits.[29,30] That may explain why laboratory models show antineoplastic activity by metformin, but clinical trials do not. This could be because the metformin concentrations used in many experiments exceed those achieved with conventional doses used for diabetes treatment.[30] Because the regimen of metformin combined with EGFR-TKIs is still a research hotspot of NSCLC, some advanced NSCLC patients decided to adopt this regimen by themselves due to the influence of relevant clinical research. Our data suggested that nondiabetic Asian advanced NSCLC patients with low BMI may benefit more from metformin plus EGFR-TKI treatment.

This study does have some limitations, including its *post hoc* design, small sample size and lack of therapeutic monitoring of metformin levels. It is important that dynamic therapeutic monitoring of metformin be performed during treatment in any future trials.

Taken together, when nondiabetic Asian patients with *EGFR* mutations and advanced NSCLC underwent co-treatment with metformin and gefitinib, lower BMI might be associated with better OS.

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Conflicts of interest

None.

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