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Metformin Prolongs Survival in Type 2 Diabetes Lung Cancer Patients With EGFR-TKIs

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Abstract

Background: Metformin use reportedly reduces cancer risk and improves survival in lung cancer patients. This study aimed to investigate the effect of metformin use in patients with diabetes mellitus (DM) and lung cancer receiving epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy. **Methods:** A nationwide, population-based cohort study was conducted using the Taiwan National Health Insurance Research Database. From January 1, 2004, to December 31, 2012, a total of 373 metformin and 1260 non-metformin lung cancer cohorts with type 2 DM and EGFR-TKI treatment were studied. **Results:** Metformin use was significantly associated with a reduced risk of death (hazard ratio: 0.73, 95% confidence interval [CI]: 0.62-0.85, $P < .001$), as well as a significantly longer median progression-free survival (9.2 months, 95% CI: 8.6-11.7, vs 6.4 months, 95% CI: 5.9-7.2 months, $P < .001$) and median overall survival (33.4 months, 95% CI: 29.4-40.2, vs 25.4 months, 95% CI: 23.7-27.2 months, $P < 0.001$). **Conclusions:** In conclusion, metformin may potentially enhance the therapeutic effect and increase survival in type 2 DM patients with lung cancer receiving EGFR-TKI therapy.

Keywords

lung cancer, metformin, DM, EGFR, TKI

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Introduction

Lung cancer is the most common cause of cancer death worldwide,[1] and most patients have advanced-stage disease at diagnosis. Despite treatment-related advances, the prognosis of lung cancer remains poor with a 5-year survival rate of 4% in distant-stage disease.[2,3] Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy is a promising treatment for non–small cell lung cancer (NSCLC). Specific

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mutations in the tyrosine kinase domain of the *EGFR* gene are associated with favorable EGFR-TKI therapy-related clinical outcomes[4] in patients with NSCLC. Most mutations are present in exons 18 to 21 of the *EGFR* gene,[5] and are frequently observed in lung adenocarcinoma.[6] *EGFR* mutations are found in <10% of non-Asian NSCLC patients[7] and in 30% to 50% of East Asian patients.[8] Missense mutations in exon 21 (L858R) and in-frame deletions within exon 19 are the most frequently occurring EGFR-TKI-sensitive mutations (80%) in patients with NSCLC.[9] *EGFR* mutations in patients with lung cancer are associated with a favorable response to the administration of EGFR-TKIs,[10] such as gefitinib,[11] erlotinib,[12] and afatinib,[13] versus standard chemotherapy (CT).

Metfromin (N′,N′-dimethylbiguanide) has been a standard drug for the treatment of type 2 diabetes mellitus (T2DM) for more than 50 years. A lower cancer-related mortality has been noted in T2DM cancer patients with metformin use compared with those with sulfonylurea and insulin use.[14] Recently, metformin was observed to decrease the incidence of lung cancer in T2DM patients[15] and was associated with a decreased mortality in T2DM lung cancer patients receiving CT.[16,17] The synergistic effect of metformin and EGFR-TKI was reported recently in a retrospective clinical study.[18]

In this study, we proposed that metformin use may enhance the effect of EGFR-TKI and prolong survival in T2DM patients with lung cancer receiving this therapy. A nationwide population-based study was conducted to determine the effect of metformin use in patients with T2DM and lung cancer receiving EGFR-TKI therapy.

Material and Methods

Data Source

The National Health Insurance (NHI) is a compulsory program for all Taiwan residents. The Taiwan National Health Insurance Research Database (NHIRD)—a comprehensive health care database that covers nearly the entire 23.7-million-strong population of this country—was used in our study. Data on patients' characteristics, such as sex and date of birth, and information regarding admissions and outpatient visits, including date of admission, date of discharge, dates of visits, and up to 5 discharge diagnoses or 3 outpatient visit diagnoses, were collected. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used for diagnosis. All patients with "catastrophic illnesses" were also included in this database. The Ethics Review Board of Chang Gung Memorial Hospital, Chiayi Branch, Taiwan, approved this study (201600067B1). The data used in this study were analyzed anonymously in accordance with strict confidentially guidelines and regulations regarding personal electronic data protection. The requirement for informed consent was waived by the institutional review board.

Study Cohorts

We identified all patients with DM (ICD-9-CM 249-250) and an initial and primary diagnosis of lung cancer (ICD-9-CM 162) between January 1, 2004, and December 31, 2012, from the NHIRD. Patients who underwent EGFR-TKI therapy (gefitinib or erlotinib) were included, while those diagnosed with other types of cancer, aged <40 years, or with insulin use were excluded. Since insulin is used in the treatment of type 1 DM, all the patients in our study were T2DM patients. The metformin cohort comprised patients who had taken metformin for more than 28 cumulative defined daily doses after a diagnosis of lung cancer and with the use of EGFR-TKI (Figure 1). All participants were followed-up till the end of 2013.

Demographic Variables and Comorbidities

Demographic variables, including age, sex, income for the estimation of insurance payment, and urbanization of the participants' residential areas, were included. Monthly income was categorized as follows: ≤NT$15 840, NT$15 841 to $25 000, and ≥NT$25 000. The urbanization level was categorized as "very high," "high," "moderate," or "low," based on the population density.[19] Hypertension (ICD-9-CM 401-405), coronary artery disease (ICD-9-CM 414-419), stroke (ICD-9-CM 430-438), renal insufficiency (ICD-9-CM 585, 586), chronic obstructive pulmonary disease (COPD; ICD9-CM 491, 492, 496), and smoking-related disorders (ICD9-CM 305.1, 491.2, 492.8, 496, 523.6, and V15.82) were included as comorbidities. Radiotherapy (RT), CT, or both (concurrent chemoradiotherapy [CCRT]) were also included in our study. EGFR-TKI responders were defined as patients who received EGFR-TKI therapy for more than 90 days; the remaining patients were defined as nonresponders.[20] The CT regimens before EGFR-TKI therapy were also included in this study.

The EGFR-TKIs used were approved by the NHI in November 2007 (gefitinib) and June 2008 (erlotinib) for the treatment of stage IIIB or IV lung cancer as the second-line therapy for lung adenocarcinoma and the third-line therapy for NSCLC (erlotinib), and in June 2011 and November 2013, as the first-line therapy for lung adenocarcinoma with *EGFR* mutations (gefitinib and erlotinib, respectively), in Taiwan. The performance of imaging studies and the application of EGFR-TKI therapy every 3 months were requested in patients who received EGFR-TKI therapy. EGFR-TKI therapy was declined by the NHI once progressive disease was observed. Since the results of imaging studies were not available in the NHIRD, we alternatively defined progression-free survival (PFS) in our study as the interval from the beginning to the end of EGFR-TKI therapy. All patients receiving second-line

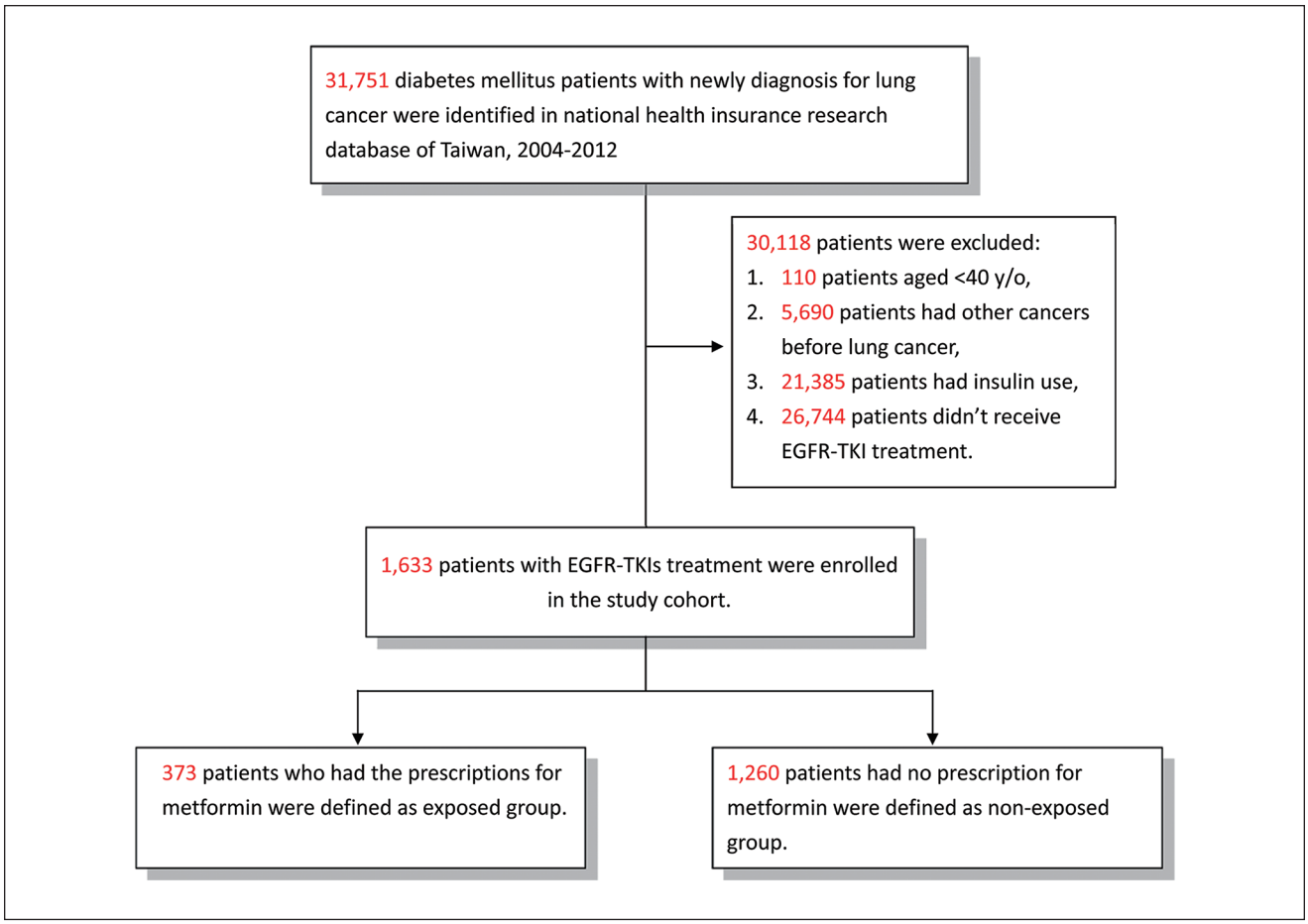

Figure 1. Flowchart of the patient enrollment process of the metformin cohort and matched non-metformin cohort.

gefitinib and erlotinib therapy in our study had adenocarcinoma, and those receiving third-line erlotinib therapy had NSCLC. Since data on the *EGFR* mutation status are not available in the NHIRD, EGFR-TKI responders were used as surrogates of *EGFR* mutations in our study. Overall survival (OS) was defined as the time from diagnosis to any cause of death or the time of censoring at the last follow-up.

Statistical Analysis

The differences in the demographic characteristics and comorbidities between the metformin and non-metformin cohorts were examined by the χ^2 test. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of death for metformin users compared with the comparison cohort were examined by Cox proportional hazard regression analysis. Survival analysis was performed using Kaplan-Meier analysis and a log-rank test. A multivariate Cox proportional hazards model was used to determine the risk factors of mortality in patients with lung cancer and their adjusted HR within the metformin cohort. All analyses were conducted using SAS statistical software (Version 9.4; SAS Institute, Cary, NC).

Results

Differences in Demographic Characteristics and Comorbidities Between the Metformin and Non-Metformin Diabetes EGFR-TKI Lung Cancer Cohorts

A total of 1633 patients with T2DM and lung cancer, undergoing EGFR-TKI therapy from 2004 to 2012, were included in our study. Of these patients, 373 patients were enrolled in the metformin cohort and 1260 patients in the non-metformin cohort. The metformin cohort had a significantly higher presence of hypertension, less COPD, renal insufficiency, and smoking-related disorders than the non-user cohort (Table 1). The metformin cohort also had a significantly higher proportion of patients without CT or/and RT, and with gefitinib use. In the non-metformin cohort, 103 of the 1260 patients received oral antidiabetic agents (Table S1, available online) after the diagnosis of lung cancer. The

Table 1. Characteristics of NSCLC Patients Undergoing EGFR-TKI Therapy.

	Metformin Use			
Variables	User	Nonuser	*P*	Total
Patients, n (%)	373 (100.0%)	1260 (100.0%)		1633 (100.0%)
Sex, n (%)			.8065	
Female	196 (52.5%)	653 (51.8%)		849 (52.0%)
Male	177 (47.5%)	607 (48.2%)		784 (48.0%)
Age (years), n (%)				
40-64	129 (34.6%)	428 (34.0%)		557 (34.1%)
≥65	244 (65.4%)	832 (66.0%)		1076 (65.9%)
Median (IQR)	69.0 (62.0-76.0)	70.0 (61.0-76.0)		70.0 (62.0-76.0)
Urbanization, n (%)			.1460	
Very high	118 (31.6%)	372 (29.5%)		490 (30.0%)
High	168 (45.0%)	517 (41.0%)		685 (41.9%)
Moderate	54 (14.5%)	232 (18.4%)		286 (17.5%)
Low	33 (8.8%)	139 (11.0%)		172 (10.5%)
Income (NT$), n (%)			.7835	
0	143 (38.3%)	448 (35.6%)		591 (36.2%)
1-15 840	70 (18.8%)	238 (18.9%)		308 (18.9%)
15 841-25 000	111 (29.8%)	397 (31.5%)		508 (31.1%)
≥25 000	49 (13.1%)	177 (14.0%)		226 (13.8%)
Comorbidities, n (%)				
Hypertension	292 (78.3%)	900 (71.4%)	.0088*	1192 (73.0%)
Stroke	89 (23.9%)	363 (28.8%)	.0606	452 (27.7%)
CAD	142 (38.1%)	514 (40.8%)	.3459	656 (40.2%)
COPD	111 (29.8%)	501 (39.8%)	.0005*	612 (37.5%)
Renal insufficiency	8 (2.1%)	66 (5.2%)	.0116*	74 (4.5%)
Smoking-related disorder	64 (17.2%)	331 (26.3%)	.0003*	395 (24.2%)
CT/RT, n (%)			.0091*	
CCRT	135 (36.2%)	566 (44.9%)		701 (42.9%)
CT	129 (34.6%)	409 (32.5%)		538 (32.9%)
RT	34 (9.1%)	102 (8.1%)		136 (8.3%)
Without CT or RT	75 (20.1%)	183 (14.5%)		258 (15.8%)
EGFR-TKI, n (%)			.0248*	
Gefitinib	215 (57.6%)	633 (50.2%)		848 (51.9%)
Erlotinib	129 (34.6%)	487 (38.7%)		616 (37.7%)
Both	29 (7.8%)	140 (11.1%)		169 (10.3%)
EGFR-TKI response, n (%)			.0534	
Responder	239 (64.1%)	737 (58.5%)		976 (59.8%)
Nonresponder	134 (35.9%)	523 (41.5%)		657 (40.2%)
CT regimens before EGFR-TKI, n (%)			.3316	
≤1	261 (70.0%)	848 (67.3%)		1109 (67.9%)
≥2	112 (30.0%)	412 (32.7%)		524 (32.1%)
Follow-up duration (months)				
Median (IQR)	22.9 (14.9-36.1)	21.2 (13.5-33.5)		21.5 (13.9-34.3)

Abbreviations: NSCLC, non–small cell lung cancer; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; IQR, interquartile range; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.
*$P < .05$.

Table 2. Comparison of Hazard Ratios.

	Crude			Adjusted		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Metformin use (ref: nonuser)						
User	0.69	0.59-0.81	<.001*	0.73	0.62-0.85	<.001*
Sex (ref: female)						
Male	1.60	1.42-1.81	<.001*	1.41	1.24-1.61	<.001*
Age (ref: 40-64 years)						
≥65	1.11	0.97-1.26	.120	1.00	0.86-1.16	.993
Urbanization (ref: low)						
Very high	0.74	0.60-0.92	.0056*	0.78	0.62-0.98	.0321*
High	0.84	0.68-1.02	.078	0.94	0.76-1.16	.549
Moderate	0.91	0.73-1.14	.408	0.97	0.77-1.21	.777
Income (NT$) (ref: 0)						
1-15 840	1.02	0.86-1.20	.866	0.88	0.74-1.05	.157
15 841-25 000	1.20	1.04-1.39	.0134*	1.12	0.95-1.32	.172
≥25000	0.83	0.68-1.01	.058	0.84	0.68-1.04	.109
Comorbidities (ref: without)						
Hypertension	1.00	0.88-1.15	.955	1.09	0.94-1.26	.235
Stroke	1.21	1.06-1.38	.0042*	1.16	1.01-1.33	.0409*
CAD	0.92	0.82-1.04	.205	0.88	0.77-1.00	.046
COPD	1.11	0.98-1.26	.089	0.81	0.69-0.96	.0124*
Renal insufficiency	0.98	0.73-1.33	.916	1.01	0.75-1.37	.945
Smoking-related disorder	1.37	1.19-1.57	<.001*	1.36	1.14-1.63	.0009*
CT/RT (ref: without CT or RT)						
CCRT	1.23	1.01-1.51	.0444*	1.06	0.85-1.31	.627
CT	1.08	0.88-1.34	.458	0.93	0.74-1.16	.505
RT	1.65	1.26-2.17	<.001*	1.46	1.11-1.93	.0075*
EGFR-TKI response (ref: nonresponder)						
Responder	0.34	0.30-0.39	<.001*	0.34	0.30-0.39	<.001*
CT regimens before EGFR-TKI (ref: ≤1)						
≥2	1.09	0.96-1.23	.184	0.89	0.78-1.01	.072

Abbreviations: HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.
*$P < .05$.

average years from the diagnosis of T2DM to the diagnosis of lung cancer in the metformin (6.7 ± 4.7 years) and non-metformin (6.9 ± 4.3 years) cohorts were not significantly different ($P = .419$).

Clinical Variables and HRs of Death in Diabetes Patients With Lung Cancer Undergoing EGFR-TKI Therapy

The risks of death in the metformin user and nonuser cohorts were then compared with the different clinical variables. In the univariate analysis, a reduced risk of death was observed in the metformin users (HR: 0.69, 95% CI: 0.59-0.81, $P < .001$), those from very high urbanization areas (HR: 0.74, 95% CI: 0.60-0.92, $P = .0056$), and the EGFR-TKI responder group (HR: 0.34, 95% CI: 0.30-0.39, $P < .001$). An increased risk of death was observed in patients with male sex (HR: 1.60, 95% CI: 1.42-1.81, $P < .001$), a monthly income of 15 841 to 25 000 NT$ (HR: 1.20, 95% CI: 1.04-1.39, $P = .0134$), stroke (HR: 1.21, 95% CI: 1.06-1.38, $P = .0042$), smoking-related disorders (HR: 1.37, 95% CI: 1.19-1.57, $P < .001$), CCRT (HR: 1.23, 95% CI: 1.01-1.51, $P = .044$), and RT (HR: 1.65, 95% CI: 1.26-2.17, $P < 0.001$; Table 2).

After adjustment for metformin use, age, sex, urbanization, income, hypertension, stroke, CAD, COPD, smoking-related disorders, CT/RT, EGFR-TKI response, and the regimens used before EGFR-TKI therapy, a reduced risk of death was still observed in the metformin users (HR: 0.73, 95% CI: 0.62-0.85, $P < .001$), those from very high urbanization areas (HR: 0.78, 95% CI: 0.62-0.98, $P = .0321$), COPD (HR: 0.81, 95% CI: 0.69-0.96, $P = .0124$), and the EGFR-TKI responders (HR: 0.34, 95% CI: 0.30-0.39, $P < .001$). An increased risk of death

Table 3. Adjusted Hazard Ratios of Mortality in Subpopulations Treated With Metformin.

	Metformin								
	User			Nonuser			Reference: nonuser		
Stratified Variables	Patients	Death	%	Patients	Death	%	HR[a]	95% CI	*P*
Sex									
Female	196	85	43.4%	653	414	63.4%	0.66	0.52-0.84	.0006*
Male	177	111	62.7%	607	467	76.9%	0.80	0.65-0.99	.0442*
Age (years)									
40-64	129	66	51.2%	428	288	67.3%	0.79	0.60-1.05	.102
≥65	244	130	53.3%	832	593	71.3%	0.71	0.59-0.86	.0006*
Hypertension									
Without	81	45	55.6%	360	258	71.7%	0.70	0.50-0.97	.0311*
With	292	151	51.7%	900	623	69.2%	0.75	0.63-0.90	.002*
Stroke									
Without	284	150	52.8%	897	615	68.6%	0.75	0.63-0.90	.0023*
With	89	46	51.7%	363	266	73.3%	0.63	0.45-0.87	.0047*
CAD									
Without	231	128	55.4%	746	519	69.6%	0.76	0.62-0.92	.0055*
With	142	68	47.9%	514	362	70.4%	0.70	0.53-0.91	.0083*
COPD									
Without	262	137	52.3%	759	520	68.5%	0.74	0.61-0.89	.0016*
With	111	59	53.2%	501	361	72.1%	0.71	0.54-0.95	.0195*
Renal insufficiency									
Without	365	194	53.2%	1194	838	70.2%	0.74	0.63-0.87	.0002*
With	8	2	25.0%	66	43	65.2%	0.10	0.02-0.55	.0085*
Smoking-related disorder									
Without	309	156	50.5%	929	634	68.2%	0.72	0.60-0.86	.0002*
With	64	40	62.5%	331	247	74.6%	0.79	0.55-1.13	.190
CT/RT									
CCRT	135	88	65.2%	566	445	78.6%	0.79	0.62-1.00	.0457*
CT	129	67	51.9%	409	269	65.8%	0.75	0.57-0.98	.0383*
RT	34	15	44.1%	102	79	77.5%	0.46	0.25-0.84	.0118*
Without CT or RT	75	26	34.7%	183	88	48.1%	0.79	0.50-1.25	.308
EGFR-TKI									
Gefitinib	215	103	47.9%	633	422	66.7%	0.64	0.51-0.79	<.001*
Erlotinib	129	84	65.1%	487	380	78.0%	0.82	0.64-1.04	.100
Both	29	9	31.0%	140	79	56.4%	0.44	0.21-0.94	.0343*
EGFR-TKI response									
Responder	239	91	38.1%	737	434	58.9%	0.62	0.49-0.78	<.001*
Nonresponder	134	105	78.4%	523	447	85.5%	0.85	0.69-1.06	.143
CT regimens before EGFR-TKI									
≤1	261	116	44.4%	848	542	63.9%	0.67	0.54-0.82	<.001*
Gefitinib (adenocarcinoma)	194	72	37.1%	574	340	59.2%	0.59	0.46-0.77	<.001*
Erlotinib (adenocarcinoma)	67	44	65.7%	274	202	73.7%	0.81	0.57-1.14	.223
≥2	112	80	71.4%	412	339	82.3%	0.87	0.68-1.12	.290
Gefitinib (adenocarcinoma)	48	40	83.3%	178	154	86.5%	0.98	0.68-1.41	.894
Erlotinib (NSCLC)	64	40	62.5%	234	185	79.1%	0.82	0.57-1.17	.265

Abbreviations: HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC, non-small-cell lung cancer.

[a] HRs were adjusted for sex, age, urbanization, income, hypertension, stroke, CAD, COPD, renal insufficiency, smoking-related disorders, CT/RT, CT regimens used before EGFR-TKI therapy.

*$P < .05$.

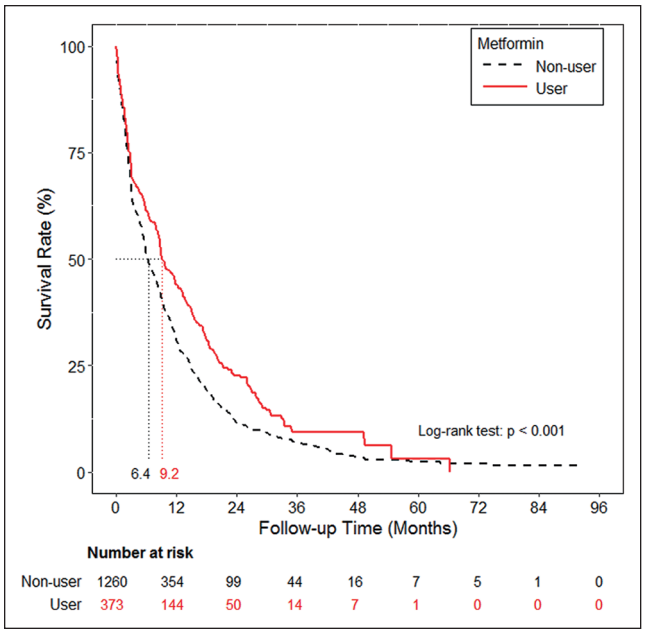

Figure 2. Progression-free survival curve of the metformin and non-metformin cohorts.

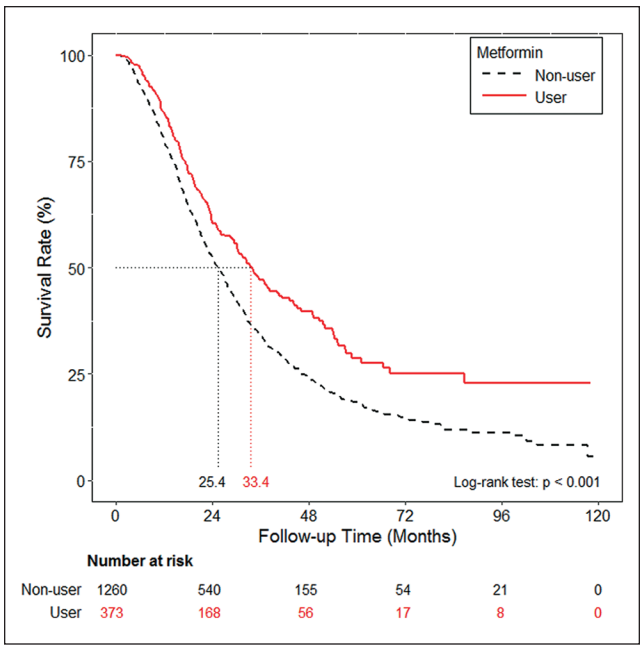

Figure 3. Overall survival curve of the metformin and non-metformin cohorts.

was observed in patients with male sex (HR: 1.41, 95% CI: 1.24-1.61, $P < .001$), stroke (HR: 1.16, 95% CI: 1.01-1.33, $P = .0409$), smoking-related disorders (HR: 1.36, 95% CI: 1.14-1.63, $P = .0009$), and RT (HR: 1.46, 95% CI: 1.11-1.93, P = *0*.0075; Table 2).

HRs of Death in Subpopulations Treated With Metformin

The risk of death after metformin use was then evaluated in subpopulations of diabetic lung cancer patients with EGFR-TKI therapy. All subpopulations of metformin users stratified by sex, age, hypertension, stroke, CAD, COPD, and renal insufficiency before EGFR-TKI treatment had a significantly reduced risk of death (Table 3). A significantly reduced risk of death was also observed in patients without smoking-related disorders, and patients with CCRT, CT, RT, gefitinib, or ≤1 CT regimen before EGFR-TKI therapy (Table 3).

PFS and OS in the Metformin and Non-Metformin Diabetes Patients With Lung Cancer Undergoing EGFR-TKI Therapy

PFS and OS were also evaluated among the metformin users and nonusers. Metformin use was associated with a significantly longer median PFS (9.2 months, 95% CI: 8.6-11.7 vs 6.4 months, 95% CI: 5.9-7.2, $P < .001$; Figure 2), and OS (33.4 months, 95% CI: 29.4-40.2 vs 25.4 months, 95% CI: 23.7-27.2, $P < .001$; Figure 3).

Discussion

In this retrospective, nationwide, longitudinal cohort study, we observed that metformin use was associated with a decreased risk of death, and prolonged PFS and OS in patients with T2DM and lung cancer receiving EGFR-TKI therapy.

The underlying mechanism of how metformin enhances the effect of EGFR-TKIs in lung cancer has been explored in several studies. Metformin increases the sensitivity of EGFR-TKI-resistant lung cancer cells to erlotinib or gefitinib through the inhibition of interleukin-6 signaling and reversal of epithelial-mesenchymal transition.[21] Metformin has antitumor effects via the inhibition of the mTORC1 through either AMP kinase-dependent or independent signaling pathways,[22] and also inhibits the PI3K/AKT/mTOR signaling pathway.[23] Since the aberrant activation of the PI3K/AKT/mTOR signaling pathway is one of the mechanisms behind the acquired resistance to EGFR-TKI therapy in patients with adenocarcinoma and *EGFR* mutations,[24] the use of metformin in combination with an EGFR-TKIs could produce a synergistic antitumor effect on lung cancer cells.

In our study, an increased risk of death was observed in patients with male sex, stroke, COPD, smoking-related disorders, and RT. These findings are similar to those of previous studies. Male sex has a negative impact on EGFR-TKI therapy outcomes compared with female sex.[25] An increased risk of stroke was reported in patients with lung cancer.[26] The administration of RT may imply a more advanced stage

of lung cancer, such as the presence of brain or bone metastasis, and the prognosis of such patients is poor.[27] Smoking is a risk factor of NSCLC and is associated with a lower response to EGFR-TKI therapy.[28]

As data on the *EGFR* mutation status is not available in the NHIRD, we alternatively used EGFR-TKI responders as surrogates for *EGFR* mutations.[20,29] In the subgroup analysis, EGFR-TKI responders had a reduced risk of death in the metformin cohort, implying that metformin may have protective effects mainly in lung patients with *EGFR* mutations. The protective effect of metformin was also more prominent in patients with first-line or second-line gefitinib use, owing perhaps to the smaller number of patients with erlotinib use, or the different effects of metformin on gefitinib or erlotinib. The protective effect of metformin was also more prominent in patients who received CT, RT, or both, which is consistent with the findings of previous studies in which metformin enhanced the effect of CT[30] and RT.[31]

DM is a poor prognostic factor in lung cancer patients.[29,32] In our study, metformin users had a prolonged OS of up to 33.4 months. The OS in our study is similar to that observed in previous studies focusing on the first-line treatment of patients with *EGFR* mutation-positive advanced NSCLC (23.6 to 30.5 months).[12,33] This implies that metformin use enhances the therapeutic effects of EGFR-TKI in patients with T2DM.

Our study has some limitations. Data on lung cancer stage, pathology, symptoms, physical status, smoking status, and genetic factors are not available in the NHIRD. The immortal bias could be a confounding factor in our study. In our study, patients in both the metformin and non-metformin cohorts received EGFR-TKI therapy after the diagnosis of lung cancer. We also reviewed our data and observed that no patients died in the non-metformin cohort within the 28 days immediately after the diagnosis of lung cancer. As a result, we assumed that the effects of immortal bias in our study could be minimal. Nevertheless, further prospective randomized controlled trials are needed to verify our findings.

Conclusions

In conclusion, our study showed that metformin use potentially enhances the therapeutic effect and decreases the mortality in T2DM patients with lung cancer receiving EGFR-TKI therapy. Our results suggest that in T2DM lung cancer patients with EGFR-TKI therapy, metformin could be the preferred oral hypoglycemic agent.

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Declaration of Conflicting Interests

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Supplemental Material

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