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Statins use and its impact in EGFR-TKIs resistance to prolong the survival of lung cancer patients: A Cancer registry cohort study in Taiwan

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Abstract

Statins have been shown to be a beneficial treatment as chemotherapy and target therapy for lung cancer. This study aimed to investigate the effectiveness of statins in combination with epidermal growth factor receptor-tyrosine kinase inhibitor therapy for the resistance and mortality of lung cancer patients. A population-based cohort study was conducted using the Taiwan Cancer Registry database. From January 1, 2007, to December 31, 2012, in total 792 non-statins and 41 statins users who had undergone EGFR-TKIs treatment were included in this study. All patients were monitored until the event of death or when changed to another therapy. Kaplan-Meier estimators and Cox proportional hazards regression models were used to calculate overall survival. We found that the mortality was significantly lower in patients in the statins group compared with patients in the non-statins group (4-y cumulative mortality, 77.3%; 95% confidence interval (CI), 36.6%-81.4% vs. 85.5%; 95% CI, 78.5%-98%; P = .004). Statin use was associated with a reduced risk of death in patients the group who had tumor sizes <3 cm (hazard ratio [HR], 0.51, 95% CI, 0.29-0.89) and for

Abbreviations: ARR, absolute risk reduction; ATC, anatomical therapeutic chemical; BNHI, Bureau of National Health Insurance; CCI, Charlson Comorbidities Index; EGFR, epidermal growth factor receptor; HWDS, Health and Welfare Data Science; ICD-9, International Classification of Disease, Ninth Revision; MOHW, Ministry of Health and Welfare; NNT, number needed to treat; NSCLC, non–small-cell lung carcinoma; PFS, progression-free survival; TCR, Taiwan Cancer Registry; TDR, Taiwan Death Registry; TKIs, tyrosine kinase inhibitors; YAP, YES-associated protein.

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patients in the group who had CCI scores <3 (HR, 0.6; 95% CI, 0.41-0.88; P = .009). In our study, statins were found to be associated with prolonged survival time in patients with lung cancer who were treated with EGFR-TKIs and played a synergistic anticancer role.

KEYWORDS

EGFR-TKIs resistance, lung cancer, statins related mortality, synergistic anticancer, Taiwan cancer registry

1 | 1 INTRODUCTION

Lung cancer is the most common cause of death worldwide, including in Taiwan.[1,2] Mutation in the *EGFR* gene is a driver in lung adenocarcinoma[3,4] as this gene is overexpressed in more than 50% of NSCLC in Asia.[5,6] Previous studies had shown that treatment with EGFR-TKIs offered a better response rate and produced less adverse events than platinum-based chemotherapy.[7-11] Most patients benefited from TKI therapies, but *c*. 5%-10% of patients did not achieve disease control when administered EGFR-TKIs and therefore acquired drug resistance within 10-12 mo.[8,10-12]

Various mechanisms for overcoming EGFT-TKI resistance have been explored. Although various changes have been reported as second EGFR mutations, the mutation T790M is the most common cause of resistance.[10,13] Activation of other pathways or oncogene shifts could lead to activation of downstream survival signaling, such as the amplification or activation of *HER2* in breast cancer,[14] *MET* in lung cancer,[15] or *KRAS* in colorectal cancer.[16] The Hippo tumor-suppressor pathway, YAP, is involved in chemo-resistance in different cancer cells by acting in parallel with other pathways of tumor progression.[17] YAP functions as a transcriptional coactivator and is essential for the regulation of cell growth, tissue homeostasis, and increased cell sensitivity to anti-tumor drugs in various cancers.[17,18] Recently, a study reported that when reducing YAP expression using YAP inhibitors, TKI-resistant cells become TKI sensitive.[19] Thus, the combination of EGFR-TKIs and YAP inhibitors, statins, might prolong survival among lung cancer patients. Evidence from this population-based study, however, is still unclear.

In this study, we aimed to investigate the effectiveness of statin use to increase the survival of lung cancer patients who are also receiving EGFR-TKI therapy. We examined the association of statin drugs in different subgroups and also calculated the NNT for 1 less mortality related.

1.1 | 1.1 EGFR-TKIs therapy regulation in Taiwan

EGFR-TKIs are covered by the Taiwan BNHI, and since 2004 patients have had to co-pay less than 18% of the cost of medications.[20,21] Before June 2011, molecular testing for the EGFR mutation was not performed or approved by the Taiwan BNHI for EGFR-TKIs as first-line therapy for lung cancer. Gefitinib, trade name Iressa, was the first EGFR-TKI to be used and was approved in November 2004; the next TKI was erlotinib, trade name Tarceva, which was approved in June 2007 as a second-line therapy for lung adenocarcinoma. Afatinib, brand name Gilotrif, was not approved during the study time and was used in late 2012. However, these TKI drugs also required pre-audit approval by the National Health Insurance (NHI) administration. First-line systemic therapy for NSCLC was platinum-based doublet chemotherapy and second-line therapy was a single-agent chemotherapy, such as erlotinib or gefitinib, and used from 2004 to 2011. These drugs were then approved as first-line therapy for lung cancer by the BNHI program after 2013.

2 | 2 MATERIALS AND METHODS

2.1 | 2.1 Study design and data source

We performed a retrospective cohort study of a randomly sampled 2 million population with data retrieved from Taiwan HWDS from January 1, 2005, to December 31, 2013, as described in Supporting Information Figure S1. The HWDS claim data, which are managed by the Taiwan MOHW, consist of all medical records of more than 99% Taiwanese residents.[22] The diagnostic accuracy of the major diseases such as stroke, cardiovascular, and cancers was confirmed in other studies.[22-24] The database is linked to the cancer patient data from the TCR and patient mortality from the TDR.[25] This study was approved by the institutional review board committee at Taipei Medical University, and the data were anonymized before analysis.

2.2 | 2.2 Study population

We identified patients who were diagnosed with primary lung cancer (International Classification of Disease, Ninth Revision [ICD-9] code 162) for the first time between January 1, 2007, and December 31, 2012. The diagnosis accuracy of lung cancer was confirmed by both specific ICD-9 codes and inclusion in the cancer registration database.[25] We excluded patients if they were younger than 20 y of age at the date of diagnosis of lung cancer.

By following the Taiwan NSCLC guidelines, only cancer patients who were undergoing second-line chemotherapy (ie patients using EGFR-TKIs, ATC codes L01XE, as treatment after failure of first-line

chemotherapy; see Table S1), were included in our study cohorts. Patients were excluded if they received TKI medications for less than 1 mo, that is 30 d during treatment for lung cancer.[26]

2.3 | 2.3 Statin use exposure

HWDS has recorded information on all prescribed drugs dispensed from Taiwan pharmacies since 1995 and has links to the cancer registry database. Statins were classified as ATC code C10AA; codes for other cholesterol-lowering medications are C10BA, C10AX, and C10BX (see Table S2). For each prescription for each study participant, we recorded drug codes, the date of dispensing, and the total amount of the daily dose.

Statin use was measured both before and after the date of a cancer diagnosis. In an analysis we considered if patients had ever used statins, and which cancer patients had received statins for more than 1 mo after cancer diagnosis, that is for 30 d, compared with those who did not use statins. In addition, those who took statins not during the treatment with EGFR-TKIs were excluded from statin users.

For those patients had received statins for more than 1 mo, that is 30 d and within 1 y, that is 360 d before the date of cancer diagnosis, were classified as regular statin users. This information was then used in further analysis for outcome adjustment.

2.4 | 2.4 Outcome measurement

All patients were monitored from the date of starting EGFR-TKI chemotherapy, that is gefitinib or erlotinib; data were censored at the date of death or at the time the subject changed to other EGFR-TKI medications, loss to follow-up, or termination of insurance, or the end of the study, ie December 31, 2013. We ascertained the study outcomes using HWDS claims and vital status data from the TDR.

2.5 | 2.5 Measurement of covariates

We identified comorbidities that might be associated with mortality based on diagnostic codes from both outpatient and inpatient datasets. All diseases from CCI except for human immunodeficiency virus (HIV), or a metastatic solid tumor, were included in the analysis. Patients with the following conditions were excluded from the study: comorbidities, listed by ICD-9 codes, included myocardial infarction (410-414), heart failure (428), cerebrovascular disease (430-438), chronic obstructive pulmonary disease (490-496), peptic ulcer disease (531-534), diabetes (250), liver disease (570, 571, 572.2-572.8), renal disease (584-586), hypertension (401-405), anxiety (300), and depression (296.2-296.3, 311). These conditions were considered if they were diagnosed in at least 2 outpatient claims or 1 hospitalization over the 2 y before cancer diagnosis date.

The TCR records information for cancer patients at initial cancer diagnosis, such as patient demographics, tumor stage, tumor size, comorbid diseases, and so forth.[22] This information was reported once by the hospital in which cancer patients were diagnosed. For this study, we obtained data for cancer patients including their initial tumor stage and tumor size.

Furthermore, other confounding factors might influence outcome measurements, such as location (ie regions) and socioeconomic status (SES) (ie based on total amount of payment to NHI), were included in this study.

2.6 | 2.6 Statistical analysis

A comparison of cumulative probabilities in competing for the risk of death was estimated using modified Kaplan-Meier and Gray methods.[27] We tested differences in the full time to event between patients in the statin-use and non–statin-use groups using a log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CI) associated with statin use were computed using Cox proportional hazards regression in the competing risk of death after adjusting for age, sex, CCI scores, liver disease, diabetes, tumor stage, tumor size, location, and SES.

NNT represented the number of patients who needed to be treated for 1 less mortality and was calculated by the inverse of the ARR.

All data management was performed using SAS v.9.3 software (SAS Institute Inc). Statistical tests were 2-sided, and a P-value <.05 was considered to indicate statistical significance.

3 | 3 RESULTS

3.1 | 3.1 Baseline characteristics of patients

We identified 4265 potentially eligible lung cancer patients diagnosed for the first time and registered at the TCR. We excluded 1852 patients diagnosed with lung cancer before January 1, 2007, and 21 patients who were younger than 20 y of age at the date of the cancer diagnosis. Those (1548) patients who did not receive EGFR-TKIs chemotherapy or used it for less than 1 mo (ie 30 d) were also not included. Another 11 patients who took statins before treatment by EGFR-TKI therapy were excluded. Therefore, 833 patients (ie non-statin users, 792 patients; statin users, 41 patients) were included in this study (Figure 1).

Demographic characteristics, comorbidities, CCI score, tumor stage, tumor size, and the follow-up duration of the study groups are presented in Table 1. The mean (SD) ages of patients in the statin and the non-statin groups were 67.9 (9.41) y and 64.8 (12.61) y, respectively. Patients in the statin group had a significantly higher prevalence of liver disease (19.5%) and diabetes (41.5%) when compared with patients in the non-statin group (8.1% and 11.7%) (P = .014 for liver disease and P < .0001 for diabetes). Patients with statin use had higher CCI scores compared with those with no statin use (CCI > 0,

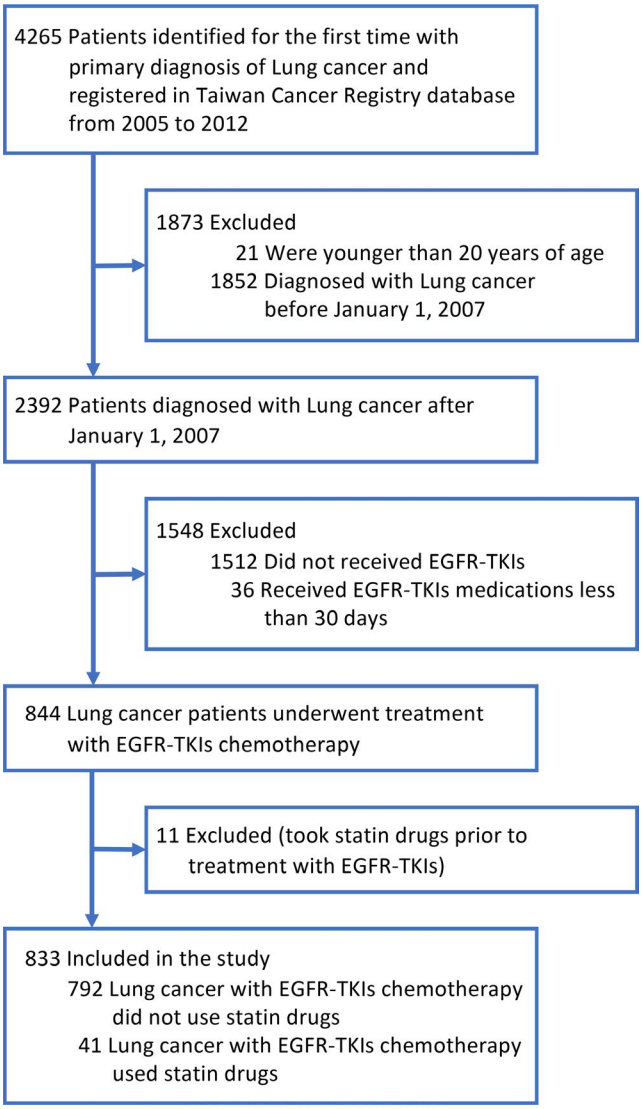

FIGURE 1 Enrollment process of the study population

73.2% for statin vs. 49.3% for the non-statin group, P = .003). For both groups, cancer patients were at stage IV (53.7% for statin vs. 72% for non-statin) at the initial cancer diagnosis. The follow-up durations for the statin group were a mean (SD) of 1.65 (1.23) y and a median (interquartile range [IQR]) of 1.15 [0.56-1.86] y, and for the non-statin group, a mean (SD) of 1.04 (0.83) y and a median [IQR] of 0.84 [0.44-1.37] y.

3.2 | 3.2 The 4 y of cumulative incidence of mortality

Cumulative incidences of mortality in both groups are shown in Figure 2. The risk of death was significantly lower in patients with statin use (4-y cumulative mortality, 77.3%; 95% CI, 36.6%-81.4%) than in patients without statin use (85.5%; 95% CI, 78.5%-98%) (P = .004). The difference in 4-y mortality was 8.2%. The unadjusted incidence rate ratio (IRR) of patients with statin use was 0.67 (95%CI, 0.48-0.95)

TABLE 1 Demographic characteristics of study population

	Statin group[a] (n = 41)	Non-statin group[a] (n = 792)	*P*-value[b]
Age, N (%)			.724
Mean (SD)	67.9 (9.41)	64.8 (12.61)	.052
Median (IQR)	68.5 (58-73)	65 (55-74)	.532
Less than 65 y	17 (41.5)	409 (51.6)	
65-75 y	17 (41.5)	227 (28.7)	
More than 75 y	7 (17.0)	156 (19.7)	
Gender, N (%)			
Female	20 (48.8)	415 (52.4)	.927
Male	21 (51.2)	377 (47.6)	
Comorbid conditions, N (%)			
Myocardial infarction	1 (2.4)	9 (1.1)	.315
Congestive heart failure	3 (7.3)	33 (4.2)	.164
Cerebrovascular disease	5 (12.2)	55 (6.9)	.099
COPD	8 (19.5)	142 (17.9)	.155
Rheumatic disease	2 (4.9)	7 (0.9)	.279
Peptic ulcer disease	9 (22.0)	108 (13.6)	.058
Liver disease	8 (19.5)	64 (8.1)	**.014**
Diabetes	17 (41.5)	93 (11.7)	**<.0001**
Renal disease	2 (4.9)	15 (1.9)	.378
Hypertension	18 (43.9)	261 (33.0)	.123
Anxiety	5 (12.2)	97 (12.2)	.968
Depression	2 (4.9)	16 (2.0)	.222
CCI, N (%)[c]			**.003**
Mean (SD)	3.95 (2.59)	3.91 (2.55)	.911
Median (IQR)	1 (0-2)	0 (0-1)	**<.0001**
CCI = 0	11 (26.8)	401 (50.6)	
CCI < 3	22 (53.7)	352 (44.4)	
CCI ≥ 3	8 (19.5)	39 (4.9)	
Tumor stage, N (%)[d]			
Missing	3 (7.3)	74 (9.3)	.181
III	16 (39.0)	148 (18.7)	
IV	22 (53.7)	570 (72.0)	
Tumor size (T), N (%)[e]			
Missing	10 (24.4)	191 (24.1)	**.023**
T ≤ 3 cm	6 (14.6)	163 (20.6)	
3 < T ≤ 7 cm	21 (51.2)	368 (46.5)	
T > 7 cm	4 (9.8)	70 (8.8)	
Follow-up, N (%			
Mean (SD) y	1.65 (1.23)	1.04 (0.83)	**<.0001**
Median [IQR] y	1.15 [0.56-1.86]	0.84 [0.44-1.37]	**.022**

(Continues)

TABLE 1 (Continued)

	Statin group[a] (n = 41)	Non-statin group[a] (n = 792)	*P*-value[b]
Region, N (%)			
Taipei	18 (43.9)	259 (32.7)	**.003**
Northern	4 (9.8)	93 (11.7)	
Central	4 (9.8)	122 (15.4)	
Southern	8 (19.5)	163 (20.6)	
Pingtung	6 (14.6)	140 (17.7)	
Eastern	1 (2.4)	15 (1.9)	
SES, N (%)			
Low income	7 (17.0)	161 (20.3)	**.032**
Mid income	17 (41.5)	416 (52.5)	
High income	17 (41.5)	215 (27.2)	

Those bold numbers are statistical significances.

Abbreviations: CCI, Charlson Comorbidities Index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation; SES, social economic status; y, years.

[a]Statin and non-statin groups indicate patients who are received stain drugs and those who are not, respectively.

[b]*P*-value was calculated using Student *t* test with continuous variables and chi-square or Fisher exact test with category variables.

[c]Charlson score represents degree of health; a high score indicates a worse health condition.

[d]Tumor stage, represents the stage at the initial registry of a cancer patient.

[e]Tumor size, represents how much size of the tumor at the initial registry of a cancer patient; the unit is centimeters.

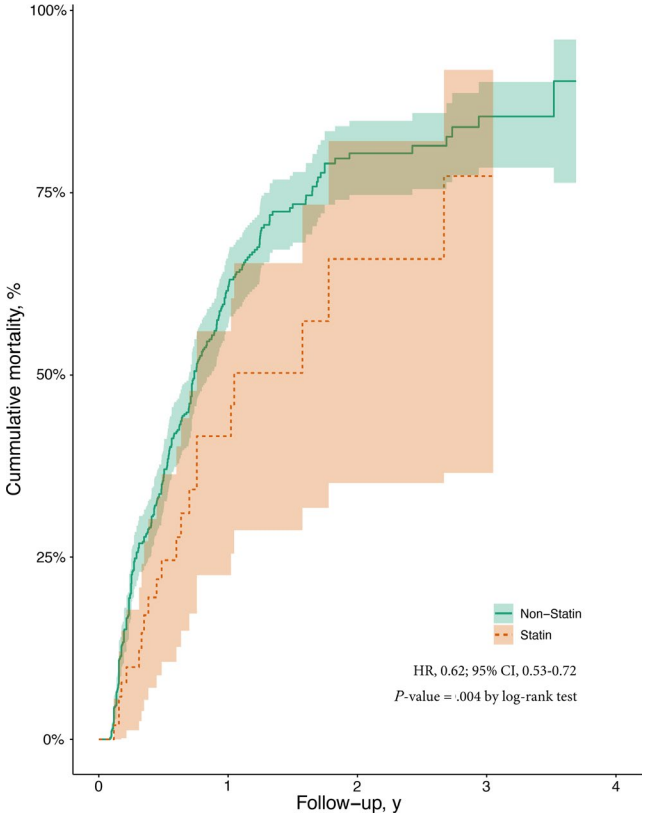

FIGURE 2 Cumulative mortality incidences of both statins and non-statins groups

compared with those without statin use. In other computations, the NNT (ie using statin drugs) that associated with 1 less death within 4 y was 3 (95% CI, 2.2-5.0) (S3). This implies that the use of statin in 3 lung cancer patients during the treatment of EGFR-TKIs chemotherapy was associated with 1 less death within 4 y.

3.3 | 3.3 Multivariable stratified analysis

Multivariable stratified analyses, including patient demographics, tumor stage, tumor size, location, SES, and patients' comorbidities are shown in Figures 3 and 4. Statin use was found to be associated with a reduced risk of death for both male (HR, 0.6; 95% CI, 0.36-1.00; *P* = .049) and female (HR, 0.6; 95% CI, 0.37-0.97; *P* = .038) groups. For those patients younger than 65 y, the statin group had a significantly decreased risk of death compared with the non-statin group (HR, 0.55; 95% CI, 0.33-0.93). Patients who had a tumor size less than 3 cm (T ≤ 3 cm) were significantly associated with a lower risk of mortality when receiving statins compared with those who did not (HR, 0.51, 95% CI, 0.29-0.89).

Similarly, statin use was associated with a significantly lower risk of mortality in patients with a CCI score less than 3 (CCI < 3) (HR, 0.6; 95% CI, 0.41-0.88; *P* = .009) and in patients with related comorbidities, including for diabetic patients (HR, 0.51; 95% CI, 0.28-0.92), patients without hypertension (HR, 0.57; 95% CI, 0.37-0.89), without COPD (HR, 0.66; 95% CI, 0.45-0.96), without liver disease (HR, 0.61; 95% CI, 0.42-0.9), and patients without depression (HR, 0.59; 95% CI, 0.42-0.84). These observations further confirmed the association between statin use and the reduced risk of mortality in comorbidities related to lung cancer patients with EGFR-TKIs treatment. The detail information related to NNT is shown in Tables S3 and S4.

4 | 4 DISCUSSION

We report a retrospective, longitudinal cohort study, in which statin use was associated with prolonged survival among lung cancer patients who were receiving EGFR-TKI therapy. In this study, statin was also found to reduce the risk of death in different patient subgroups.

Previous studies on YAP have helped to elucidate EGFR-TKI resistance in lung adenocarcinomas, showing that sustained YAP expression is essential for survival of TKI-resistant cells.[19,28] Hippo pathway transcriptional coactivator YAP/TAZ and microRNA regulation have either a pro-oncogenic or an elicit-oncogenic role in different systems.[28-30] The underlying mechanism of how statins increase the effectiveness of EGFR-TKI for lung cancer cells inside the human body remains unclear. Oxidative stress has shown to be an important factor in lung cancer pathogenesis. Protection from

Variables	Statin			non-Statin				
	Events	PY	Rate	Events	PY	Rate	IRR (95% CI)	HR (95% CI)[b]
Overall	34	50.517	0.67	711	710.989	1.00	0.67 (0.48-0.95)*	0.62 (0.53-0.72)***
Gender								
Female	17	22.967	0.74	372	341.847	1.09	0.73 (0.45-1.19)	0.60 (0.37-0.97)*
Male	17	27.55	0.62	339	369.142	0.92	0.67 (0.41-1.09)	0.60 (0.36-0.99)*
Age								
<65 y	15	25.231	0.59	357	371.744	0.96	0.62 (0.37-1.04)	0.55 (0.33-0.93)*
65-75 y	14	20.544	0.68	209	197.325	1.06	0.64 (0.37-1.11)	0.61 (0.34-1.07)
>75 y	5	4.742	1.05	145	141.919	1.02	1.03 (0.42-2.52)	0.85 (0.38-1.93)
Comorbidity[c]								
Yes	9	14.44	0.62	236	237.14	1.00	0.63 (0.28-1.21)	0.59 (0.39-0.88)**
No	25	36.08	0.69	475	473.85	1.00	0.69 (0.46-1.03)	0.65 (0.33-1.28)
CCI								
CCI = 0	10	15.26	0.66	354	364.48	0.97	0.67 (0.36-1.27)	0.71 (0.38-1.33)
CCI < 3	18	28.38	0.63	320	309.94	1.03	0.61 (0.38-0.99)*	0.60 (0.41-0.88)**
CCI ≥ 3	6	6.88	0.87	37	36.57	1.01	0.86 (0.33-1.94)	0.60 (0.25-1.43)
Tumor Stage								
III	13	19.631	0.66	133	136.458	0.97	0.68 (0.37-1.17)	0.58 (0.33-1.03)
IV	18	23.256	0.77	516	506.469	1.02	0.76 (0.47-1.22)	0.72 (0.45-1.16)
Tumor size								
T ≤ 3 cm	6	8.897	0.67	144	168.247	0.86	0.79 (0.28-1.76)	0.51 (0.29-0.89)*
3 < T ≤ 7 cm	17	17.711	0.96	328	322.922	1.02	0.95 (0.58-1.54)	0.79 (0.49-1.29)
T > 7 cm	4	8.239	0.49	67	59.275	1.13	0.43 (0.11-1.15)	0.42 (0.13-1.34)
Region								
Taipei	12	18.728	0.64	231	224.958	1.03	0.62 (0.32-1.11)	0.66 (0.39-1.12)
Northern	3	3.694	0.81	81	96.111	0.84	0.96 (0.19-2.92)	0.77 (0.24-2.44)
Central	4	7.014	0.57	112	103.453	1.08	0.53 (0.14-1.39)	0.54 (0.20-1.48)
Southern	6	14.822	0.4	143	151.969	0.94	0.43 (0.16-0.96)*	0.30 (0.12-0.75)*
Pingtung	5	5.883	0.85	130	119.503	1.09	0.78 (0.25-1.87)	0.75 (0.31-1.84)
Eastern	4	7.014	0.57	14	15.197	0.92	0.61 (0.15-1.97)	0.60 (0.36-1.93)
Social Economic Status - SES								
Low-income	6	6.194	0.97	152	138.553	1.10	0.88 (0.32-1.98)	0.81 (0.36-1.84)
Mid-income	16	32.658	0.49	367	377.061	0.97	0.50 (0.31-0.83)**	0.48 (0.29-0.79)**
High-income	12	11.664	1.03	192	193.897	0.99	1.04 (0.53-1.86)	0.93 (0.52-1.67)

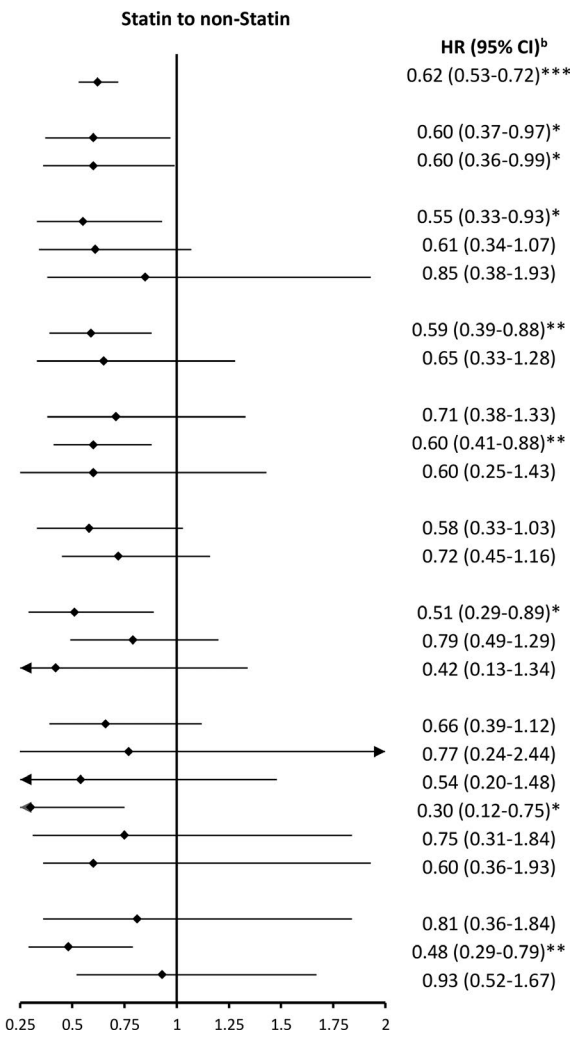

FIGURE 3 Statins use and their association with overall mortality by different covariates[a]. Note: CI, confidence intervals; IRR, incidence rate ratio; PY, 1000 person-year; Rate, incidence rate; yrs., years; *P < .05; **P < .01; ***P < .001; [a]Multivariable analysis is by Cox proportional hazards model. [b]Adjusted for covariate factors, including age, gender, comorbidities, Charlson Comorbidities Index (CCI), tumor stage, tumor size, region, and social economic status. [c]Comorbidity is determined if the patient has any comorbid conditions listed in Table 1

reactive oxygen species, therefore, appears to be crucial strategy for lung cancer prevention, particularly in the presence of tobacco smoke and air pollution.[31-33] The antioxidant system is disturbed during carcinogenesis. Lipid products such as low density lipoprotein (LDL) and its oxidative product induce adhesion molecule expression and macrophage adhesion to endothelial cells, causing endothelial dysfunction. Intercellular adhesion molecule-1 (ICAM-1) and E-selection are both common adhesion molecules that play important roles in inflammation. The LDL inflammation mechanism may interact with the environment as a carcinogen in lung cancer formation.[34] Other reports have shown that lipid accumulation and expression of CXCL16 and Nephrin are induced by oxidized LDL.[35] Statin use might reduce the inflammatory cytokine concentration by decreasing LDL and other lipid productions, which may provide additional anticancer effects.

Statin use in combination cancer therapies have historically seen mixed results. Lin and colleagues found that the combination of TKIs and statins did not show a statistically significant benefit in the overall survival of patients (HR, 0.87; 95% CI, 0.75-1.03).[36] In contrast, another study reported that lung cancer patients who received statins and TKI therapies had a longer PFS and better overall survival than patients who received only TKIs.[37] Some in vitro studies showing that statins overcome gefitinib resistance support the findings of this study. Park and colleagues[38] and Chen and colleagues[39] found that use lovastatin and atorvastatin overcame gefitinib resistance in human NSCLC cells with the *KRAS* mutation through downregulation of RAS protein. Another study reported that simvastatin might overcome gefitinib resistance in T790M mutant NSCLCs via the AKT/β-catenin signaling-dependent pathway.[40] However, to clarify the underlying interaction mechanism of various EGFR-TKIs and statins, further molecular studies must be undertaken to test our hypotheses. Some clinical studies have shown the advantages of combining statins and EGFR-TKIs to treat lung cancer. Han and colleagues[41] demonstrated that simvastatin improved the efficacy of gefitinib and prolonged PFS in patients with wild-type EGFR-TKI non-adenocarcinomas. Fiala and colleagues[42] also showed the significant impacts of prolonged PFS for

Variables	Statin			non-Statin			Statin to non-Statin	
	Events	PY	Rate	Events	PY	Rate	IRR (95% CI)	HR (95% CI)[b]
Hypertension								
Yes	13	17.478	0.74	220	222.728	0.99	0.75 (0.39-1.32)	0.66 (0.38-1.15)
No	21	33.039	0.64	491	488.261	1.01	0.63 (0.41-0.98)*	0.57 (0.37-0.89)*
Diabetes								
Yes	14	20.939	0.67	83	75.167	1.10	0.61 (0.32-1.07)	0.51 (0.28-0.92)*
No	20	29.578	0.68	628	635.822	0.99	0.68 (0.44-1.07)	0.61 (0.39-0.96)*
COPD								
Yes	6	8.769	0.68	135	114.367	1.18	0.58 (0.21-1.30)	0.45 (0.20-1.03)
No	28	41.747	0.67	576	596.622	0.97	0.69 (0.48-1.02)	0.66 (0.45-0.96)*
Liver disease								
Yes	7	10.508	0.67	57	58.319	0.98	0.68 (0.26-1.50)	0.58 (0.25-1.37)
No	27	40.008	0.67	654	652.669	1.00	0.67 (0.46-0.99)*	0.61 (0.42-0.90)*
Depression								
Yes	2	0.181	11.08	16	15.672	1.02	10.85 (1.21-46.15)*	15.50 (0.97-247.9)
No	32	50.336	0.64	695	695.317	1.00	0.64 (0.45-0.91)*	0.59 (0.42-0.84)**
Rheumatic disease								
Yes	2	2.308	0.87	7	7.767	0.90	0.96 (0.10-5.05)	0.49 (0.06-4.32)
No	32	48.208	0.66	704	703.222	1.00	0.66 (0.47-0.94)*	0.61 (0.43-0.87)**

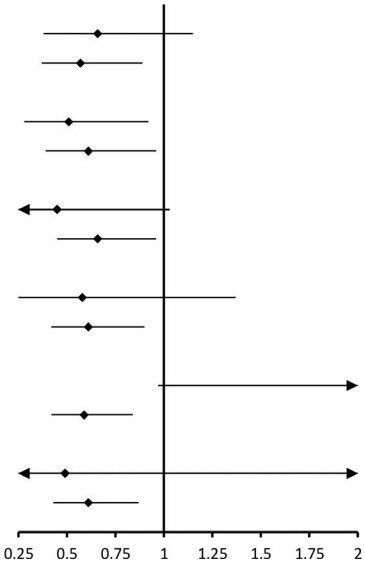

FIGURE 4 Statins use and their association with overall mortality by different comorbidities[a]. Note: Rate, incidence rate; PY, 1000 person-years; IRR, incidence rate ratio; CI, confidence intervals; yrs., years; *P < .05; **P < .01; [a]Multivariable analysis is by Cox proportional hazards model. [b]Adjusted for covariate factors, including age, gender, comorbidities, Charlson Comorbidities Index, tumor stage, tumor size, region, and social economic status

patients in advanced-stage NSCLC harboring the *KRAS* mutation and when treated with a combination of statins and EGFR-TKIs.

Parameters investigated in this study showed similar responses to those of statin combination therapies in previous studies. For instance, men and women had a similar outcome when treated with statins plus EGFR-TKI therapy.[43] Younger patients (<65 y) may be more responsive to treatment compared with older patients after EGFR-TKI failure.[44] In contrast, our study showed that diabetes mellitus was not associated with inferior prognosis of lung cancer patients, as described in the report by Zhu and colleagues.[45] The prognosis of patients treated with statins showed a better median survival compared with patients not treated with statins (1.15 vs. 0.84 y).[46] There were no statistically significant differences noted between SES and the survival of lung cancer patients, except in the middle-income group when compared with previous studies.[47-49]

These are several limitations to the present study. First, the direct causality of the association between stain use and death among lung cancer patients cannot be inferred based on an observational study. Although the significant impact of combining statins with EGFR-TKIs is still being debated, confounding factors may exist and should be considered for further outcomes. In addition, we did not have information for patients on aspects such as lifestyle, including smoking, drinking, and diet. This study did not include family history of malignant diseases, BMI, environmental, or genetic factors, which can all contribute to risk of death. We considered cancer-related diseases such as COPD, heart problems, diabetes, anxiety, depression, location, Charlson comorbidity scores, and SES to introduce bias in the study. Moreover, multivariable analysis was performed to adjust for any potential factors. Another limitation is that patients had self-paid for EGFR-TKI therapies, mostly before the study period of 2004 when the BNHI did not cover the cost of drugs; data for lung cancer patients undergoing TKI therapies, therefore, were not include in the study.

In patients diagnosed with lung cancer who were undergoing EGFR-TKI therapies, we observed an association between statin use and reduced risk of cancer-related mortality, with a reduction of up to 8.2%. Further prospective studies, however, are needed to evaluate the benefit of the combination of statins and EGFR-TKIs in lung cancer treatment.

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CONFLICT OF INTEREST

All authors declare none.

AUTHORS' CONTRIBUTION

PAN, CCC, MHH, and YCL led the study and wrote most of the first draft. PAN, CJG completed and edited the final manuscript. PAN, HCY, and YSW collected and assimilated necessary data. All authors participated in design, execution, and oversight of the study. All authors had access to the data, commented on subsequent drafts,

and approved the final submitted version. YCL acts as guarantor and made the final decision to submit for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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