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Keywords: Idiopathic Pulmonary Fibrosis; Lung Neoplasms; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Database

Article

The Preventive Effects of Statin on Lung Cancer Development in Patients with Idiopathic Pulmonary Fibrosis Using the National Health Insurance Service Database in Korea

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Abstract: Little is known about the effect of statin use in lung cancer development in idiopathic pulmonary fibrosis (IPF). We analyzed the database of the National Health Insurance Service to further investigate the clinical impacts of statin on lung cancer development and overall survival (OS) in IPF patients. The analysis included 9,182 individuals diagnosed with IPF, of which 3,372 (36.7%) were statin users. Compared to statin non-users, the time from diagnosis of IPF to lung cancer development and OS were longer in statin users in IPF patients. In Cox proportional hazard regression models, higher statin compliance, statin use, and being female had an inverse association with lung cancer risk, while older age at diagnosis of IPF and smoking history were associated with higher risk of lung cancer in IPF patients. For OS, statin use, female sex, higher exercise frequency, and diabetes were associated with longer survival. In contrast, older age at diagnosis of IPF and smoking history were associated with shorter OS in IPF patients. These data from a large population indicate that statin had an independent protective association with lung cancer development and mortality in IPF patients.

Keywords: idiopathic pulmonary fibrosis; lung neoplasms; hydroxymethylglutaryl-CoA reductase inhibitors; database

1. Introduction

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that competitively block the active sites of lipid-lowering enzymes [1]. The main therapeutic effect is inhibition of cholesterol biosynthesis. However, other diverse actions called "pleiotropy" were reported, including improvement of cardiovascular function [2], anti-inflammatory effects [3], and anti-fibrotic effects [4,5].

Some studies have indicated that statins exert anticancer effects by inducing apoptosis and inhibiting tumor cell growth and angiogenesis [6–8]. Recent research suggests antitumor effects of statin [9–12] and its synergistic potency in chemo-resistant lung cancer populations [13–16].

Clinically, statin is associated with reduced all-cause mortality in interstitial lung disease and idiopathic pulmonary fibrosis (IPF) [17,18]. Also, statin attenuates decline in lung function in the elderly [19]. Lung cancer is a common complication of IPF [20,21], with an incidence of approximately 22.9 per 10,000 person-years, which is approximately five times that in the general population. Kim et al. published a study showing that IPF patients with lung cancer had poor 5-year survival rates compared to non-IPF patients (14.5% vs. 30.1%; $p < 0.001$) [22]. Moreover, there was higher tendency of treatment-related adverse events [23] such as postoperative clinical deterioration, acute exacerbation (AE), and radiation pneumonitis [24–26] among IPF patients with lung cancer. Therefore, the importance of lung cancer prevention in IPF patients is very high.

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To date, few studies have examined the role of statins in the risk of lung cancer development among IPF patients in large-scale cohorts. We analyzed the database of the National Health Insurance Service (NHIS) in Republic of Korea to further investigate the clinical impacts of consecutive statin use on lung cancer development and OS in IPF patients.

2. Materials and Methods

2.1. Study database

This study collected data from NHIS, which is based on a nationwide social security system with more than 50 years of history in Korea. Nearly all Korean citizens (97.2%, ~ 50 million) are enrolled in the NHIS, and data of the study population include demographics, medical treatment, and disease diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10) [27]. The NHIS dataset includes all inpatient and outpatient medical claims and the corresponding codes for diagnoses and treatment procedures [28].

We collected and retrospectively reviewed IPF patients among adults older than 40 years during the study period between 2002 and 2018 with a two-year washout period; the patients diagnosed with IPF from 2002 to 2004 were excluded. Among IPF patients older than 40, we grouped them based on more than two visits to an outpatient clinic per year.

IPF was defined as J841 or J848, and patients with possible interstitial lung diseases or other systemic involvement with lung disease codes were excluded as follows: M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.8, M06.9, M30.1, M31.3, M31.7, M32, M33, M34, M35.0, M35.1, D86, J84.0, J60~J70.9. Code J84 was classified as a rare intractable disease category in Korea. The government supports these patients with medical cost reduction of up to 10% of the total cost; therefore, the ICD for this disease indicates IPF patients retained in the database [29]. Lung cancer was defined as C33 or C34. To validate latent factors that would affect lung cancer development, we excluded those who had a history of cancer or were newly diagnosed before diagnosis of IPF. We also excluded those who were diagnosed with lung cancer less than one year before clinically proven IPF diagnosis during the washout period.

2.2. Endpoints and study outcomes

The primary endpoint of this study was the development of lung cancer in IPF patients according to statin use during the study period. This was calculated by subtracting the date of first IPF diagnosis from first lung cancer diagnosis. The secondary endpoint was the OS of IPF patients according to statin use. OS was the duration from the day of first IPF diagnosis to death or the study end date.

2.3. Statin use

We defined a regular statin user as a patient who had been prescribed statin consecutively at least four weeks (28 days) after the diagnosis of IPF. If the interval between prescriptions was less than two weeks, the patient was included in the regular statin group. The study did not include any patients prescribed statin before diagnosis of IPF to exclude conditional bias of statin use. Drug compliance was estimated as the ratio of total dates of prescription to the study period.

2.4. Statistical analysis

The paired t-test was used for continuous data, and the chi-square test was used for categorical data to generate descriptive tables. Survival was analyzed using a Kaplan–Meier plot and the log-rank test. Kaplan-Meier analysis was used to visualize the duration between lung cancer diagnosis and death according to statin use. Log rank test was used to validate the significant difference of time-to-event between statin and non-statin user groups. Cox proportional hazard regression analysis was used to adjust for multiple variables affecting the hazard of lung cancer development

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with a 95% confidence interval (CI). All P-values were two-tailed, with statistical significance set to $p < 0.05$. All statistical analyses were performed using SAS Version 7.1 (SAS Institute, Inc., Cary, NC, USA) and R Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The final analysis included 9,182 individuals diagnosed with IPF, of which 3,372 (36.7%) were statin users. The baseline characteristics of study patients are listed in Table 1. The age at first diagnosis of IPF was younger in the statin user group (67.2 ± 11.2 vs. 64.0 ± 10.2, $p < 0.001$). The proportion of males was higher in the statin non-user group (67.1% vs. 59.4%, $p < 0.001$). Mean body mass index (BMI) (23.0 ± 3.2 vs. 24.0 ± 3.1, $p < 0.001$), total cholesterol (184.2 ± 34.8 vs. 199.7 ± 42.6, $p < 0.0001$), and systolic (125.2 ± 17.1 vs. 126.6 ± 16.8, $p < 0.0001$) and diastolic blood pressure (76.3 ± 10.6 vs. 77.3 ± 10.8, $p < 0.0001$) were higher in the statin user group. Smoking history as never, ex-, or current was not statistically different between statin users and statin non-users. However, the statin non-user group showed a higher smoking amount than the statin user group (38.1% vs. 25.7% for less than a half pack, 14.3% vs. 23.3% for a pack to less than two packs, $p < 0.001$). In terms of drinking habits, the proportion of daily drinking (6.2% vs. 4.6%, $p = 0.004$) was higher in the statin non-user group, but the amount consumed at a time (50.1% vs. 43% for one to two drinks; 7.2% vs. 12.7% for five to six drinks; 5.7% vs. 7.3% for seven to nine drinks; $p = 0.001$) was lower. Interestingly, the frequency of no physical activity was higher (63.9% vs. 57.5%, $p < 0.0001$) and the mean frequency of vigorous (0.8 ± 1.7 vs. 0.9 ± 1.8, $p = 0.022$) and moderate (1.0 ± 1.9 vs. 1.2 ± 2.0, $p = 0.036$) physical activity per week were lower in the statin non-user group. The proportion of comorbidities of hypertension (14.7% vs. 18.7, $p < 0.0001$) and heart disease (3.0% vs. 4.2%, $p = 0.026$) was higher in the statin user group, but that of cerebrovascular diseases (1.9% vs. 1.0%, $p = 0.013$) was higher in the statin non-user group.

Table 1. Demographic characteristics of study groups by statin use.

Characteristics	Statin use		*p*-value
	No (n = 5810)	Yes (n = 3372)	
Age at diagnosis of IPF	67.2 ± 11.2	64.0 ± 10.2	< 0.001
Sex			< 0.001
Male	3896 (67.1%)	2002 (59.4%)	
Female	1914 (32.9%)	1370 (40.6%)	
BMI	23.0 ± 3.2	24.0 ± 3.1	< 0.001
Total cholesterol	184.2 ± 34.8	199.7 ± 42.6	< 0.0001
Blood pressure			
Systolic	125.2 ± 17.1	126.6 ± 16.8	< 0.0001
Diastolic	76.3 ± 10.6	77.3 ± 10.8	< 0.0001
Smoking history			0.076
Never	3409 (61.1%)	2016 (62.3%)	
Ex-smoker	1100 (19.7%)	574 (17.7%)	
Current smoker	1073 (19.2%)	644 (19.9%)	
Smoking amount			< 0.001
Less than a half pack	258 (38.1%)	95 (25.7%)	
Half pack to less than one pack	312 (46.1%)	180 (48.8%)	
One pack to less than two packs	97 (14.3%)	86 (23.3%)	
More than two packs	10 (1.5%)	8 (2.2%)	
Smoking duration			0.217
Less than five years	43 (4.1%)	16 (2.9%)	
Five to nine years	41 (3.9%)	23 (4.2%)	

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10 to 19 years	146 (13.9%)	66 (12.1%)	
20 to 29 years	187 (17.8%)	120 (22.1%)	
30 years or more	634 (60.3%)	319 (58.6%)	
Drinking frequency			0.004
None	2363 (70.0%)	1285 (69.3%)	
Less than once per month	311 (9.2%)	155 (8.4%)	
Once per month	347 (10.3%)	214 (11.5%)	
Once per week	147 (4.4%)	113 (6.1%)	
Daily	210 (6.2%)	86 (4.6%)	
Drinking amount at a time			0.001
One to two drinks	499 (50.1%)	241 (43%)	
Three to four drinks	369 (37.0%)	208 (37.1%)	
Five to six drinks	72 (7.2%)	71 (12.7%)	
Seven to nine drinks	57 (5.7%)	41 (7.3%)	
Physical activity frequency			< 0.0001
None	2143 (63.9%)	1060 (57.5%)	
One to two days per week	582 (17.3%)	391 (21.2%)	
Three to four days per week	274 (8.2%)	171 (9.3%)	
Five to six days per week	72 (2.1%)	41 (2.2%)	
Seven days per week	284 (8.5%)	179 (9.7%)	
Physical activity intensity (per week)			
Vigorous	0.8 ± 1.7	0.9 ± 1.8	0.022
Moderate	1.0 ± 1.9	1.2 ± 2.0	0.036
Walk	2.5 ± 2.6	2.6 ± 2.6	0.156
Comorbidities			
Liver disease	65 (1.9%)	45 (2.4%)	0.258
Hypertension	508 (14.7%)	353 (18.7%)	< 0.0001
Cerebrovascular diseases	67 (1.9%)	19 (1.0%)	0.013
Heart disease	103 (3.0%)	79 (4.2%)	0.026
Diabetes	241 (7.0%)	158 (8.4%)	0.073
Other cancers	58 (1.7%)	19 (1.0%)	0.064

Data are presented as n (%) or mean ± SD. IPF; Idiopathic pulmonary fibrosis, BMI; Body mass index.

The clinical outcomes of this study are shown in Table 2. Among 9,182 IPF patients analyzed during the study period, 850 were diagnosed as lung cancer. The incidence of lung cancer was similar in the statin user group and statin non-user group (9.2% vs. 9.4%, $p = 0.803$) during the study period. However, the duration from the date diagnosed with IPF to the development of lung cancer was significantly longer in the statin group (2,194.6 ± 1601.4 vs. 3,361.0 ± 1331.2, $p < 0.001$). Comparing the mortality rate between the statin user and non-user groups, OS was longer in the statin users (2413.9 ± 1778.7 vs. 3,741.8 ± 1443.1 days, Log rank $p < 0.0001$) and total number of deaths was significantly lower in (66.9% vs, 41.6%, hazard ratio [HR] 0.41, 95% CI 0.39–0.44, Log rank $p < 0.0001$). We obtained cumulative lung cancer incidence curves of stain users and statin non-users based on Kaplan-Meier plot analysis (Figure 1).

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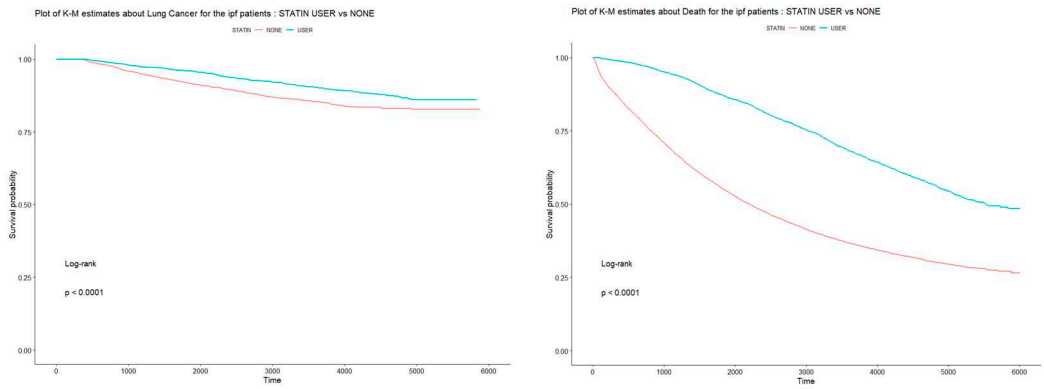
Table 2. Comparison of clinical outcomes in IPF patients with and without statin use.

	Statin non-user (n=5810)	Stain user (n=3372)	*p*-value
Lung cancer development in IPF patients			
(n = 850)	534 (9.2%)	316 (9.4%)	0.803
Duration (days)			
Lung cancer development	2194.6 ± 1601.4	3361.0 ± 1331.2	< 0.0001
IPF diagnosis to death	2413.9 ±1778.7	3741.8 ± 1443.1	< 0.0001
No. of deaths	3887 (66.9%)	1404 (41.6%)	< 0.0001

Data are presented as n (%) or mean ± SD. IPF; Idiopathic pulmonary fibrosis.



(**a**) (**b**)

Figure 1. Kaplan-Meier plot displaying cumulative incidence of lung cancer development (A) and overall survival (B) in IPF patients with and without statin use. IPF; Idiopathic pulmonary fibrosis, K-M; Kaplan-Meier

In multivariate analysis using a Cox regression model for lung cancer development in IPF patients, higher statin compliance (adjusted HR [aHR] 0.66, 95% CI 0.48–0.90, $p < 0.001$), statin use (aHR 0.63, 95% CI 0.53–0.76, $p < 0.001$), and female sex (aHR 0.43, 95% CI 0.33–0.56, $p < 0.001$) were independently associated with reduced lung cancer development in IPF patients. In contrast, the risk of cancer development increased in the group of patients diagnosed with IPF at an older age (aHR 1.05, 95% CI 1.04–1.06, $p < 0.001$) and with smoking (aHR 1.55, 95% CI 1.39–1.72, $p < 0.001$).

Table 3. Cox proportional hazard regression analysis of the clinical variables affecting lung cancer development in IPF patients.

	aHR	Lower .95	Upper .95	*p*-value
Statin compliance	0.6561	0.4807	0.8954	< 0.001
Statin use	0.6329	0.5260	0.7614	< 0.001
Sex – female	0.4311	0.3332	0.5576	< 0.001
Age at first diagnosis of IPF	1.0455	1.0357	1.0554	< 0.001
BMI	1.0057	0.9762	1.0362	0.707
Blood pressure				
Systolic	0.9995	0.9922	1.0069	0.366
Diastolic	0.9995	0.9880	1.0111	0.934
Smoking history (ex + current)	1.5460	1.3911	1.7183	< 0.001
Alcohol frequency	0.9982	0.9315	1.0696	0.959
Exercise frequency	0.9537	0.8886	1.0235	0.188
Comorbidities				

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Liver diseases	1.2332	0.6567	2.3158	0.514
Hypertension	1.0478	0.8229	1.3342	0.705
Stroke	1.7280	0.7670	3.8930	0.187
Heart diseases	1.0514	0.6454	1.7129	0.84
Diabetes	1.0218	0.7330	1.4246	0.899
Cancers	0.7224	0.3960	1.3180	0.289

aHR; Adjusted hazard ratio, IPF; Idiopathic pulmonary fibrosis, BMI; Body mass index.

We also analyzed the risk factors for mortality in IPF patients after adjusting for demographic variables using multivariate Cox regression (Table 4). Statin use (aHR 0.43, 95% CI 0.39–0.46, $p < 0.001$), female sex (aHR 0.67, 95% CI 0.61–0.73, $p < 0.001$), higher exercise frequency (aHR 0.93, 95% CI 0.90–0.96, $p < 0.001$), and diabetes (aHR 0.78, 95% CI 0.69–0.88, $p < 0.001$) were associated with reduced risk of mortality in IPF patients. In contrast, older age at IPF diagnosis (aHR 1.07, 95% CI 1.07–1.08, $p < 0.001$) and smoking history (aHR 1.06, 95% CI 1.01–1.11, $p = 0.0182$) were associated significantly with shorter OS in IPF patients.

Table 4. Cox proportional hazard regression analysis of the clinical variables affecting mortality in IPF patients.

	aHR	**Lower .95**	**Upper .95**	***p*-value**
Statin use	0.4254	0.3919	0.4617	< 0.001
Sex – female	0.6668	0.6121	0.7264	< 0.001
Ages at first diagnosis of IPF	1.0714	1.0673	1.0756	< 0.001
BMI	1.0020	0.9902	1.0139	0.7414
Total cholesterol	1.0005	0.9996	1.0014	0.2637
Blood pressure				
Systolic	0.9996	0.9968	1.0024	0.7931
Diastolic	0.9999	0.9954	1.0044	0.959
Smoking history (ex + current)	1.0580	1.0096	1.1087	0.0182
Drinking experiences	0.9884	0.9586	1.0190	0.453
Exercise frequency	0.9291	0.9028	0.9563	< 0.001
Comorbidities				
Liver diseases	0.9104	0.7143	1.1604	0.4482
Hypertension	1.0847	0.9868	1.1924	0.0921
Stroke	0.9767	0.7646	1.2477	0.8504
Heart diseases	0.9949	0.8323	1.1891	0.9548
Diabetes	0.7783	0.6885	0.8798	< 0.001
Cancers	1.0853	0.8276	1.4233	0.5539

aHR; Adjusted hazard ratio, IPF; Idiopathic pulmonary fibrosis, BMI; Body mass index

4. Discussion

We identified clinical impacts of regular consecutive statin use in IPF patients who had both delayed lung cancer and prolonged OS. In Cox proportional hazard regression models, higher statin compliance, statin use, and female sex were independently associated with reduced risk of lung cancer, and older age at diagnosis of IPF and smoking history were associated with higher risk of lung cancer in IPF patients. For OS, statin use, female sex, higher exercise frequency, and diabetes were associated with longer survival. In contrast, older age at diagnosis of IPF and smoking history were associated with shorter OS in IPF patients.

Aside from the well-known lipid-lowering effect, statins were reported to have anti-cancer effects through various pathways including inhibition of inflammation, immunomodulation, and

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angiogenesis [7]. Recently, the long-term use of statins was reported to reduce the risk of mortality in patients with lung cancer [30]. In a meta-analysis, statin use after diagnosis of lung cancer had a survival benefit for OS (HR 0.68, 95% CI 0.51–0.92) compared to those using statins before diagnosis.[31] Statins were also associated with prolonged survival in non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)s.[32] Furthermore, statins can overcome EGFR-TKI resistance in patients with lung cancer harboring KRAS mutation, and they provided an increased response rate in lung cancer patients previously treated with nivolumab [33,34]. In contrast, there was no significant difference in efficacy between a group with addition of simvastatin to afatinib and a group with afatinib alone in patients with non-adenocarcinomatous NSCLC.[35]

IPF has a progressive clinical course including a decline in pulmonary function, decrease in vital capacity, and diffusing capacity for carbon monoxide (DLCO).[36] Further, lung cancer is a common morbidity of IPF with a prevalence of 4.4% to 13%.[37] If lung cancer develops in IPF patients, treatment modalities are limited regardless of lung cancer stage. The treatment goal for early-stage resectable lung cancer is complete remission. Standard curative treatment for patients with NSCLC is lobectomy.[38] Lung resection including lobectomy can cause a reduction in lung function, acute exacerbation (AE) of IPF, and acute respiratory distress syndrome (ARDS).[39] For patients who are not surgical candidates due to medical reasons (e.g., cardiac or pulmonary failure), stereotactic ablative radiotherapy is a potential treatment option with comparable efficacy to surgery.[40] However, severe pulmonary toxicity such as radiation pneumonitis or ARDS was reported in 1.5–20% of patients who received stereotactic ablative radiotherapy in lung cancer patients with IPF.[41] Drug pneumonitis and IPF AE often recur in the advanced stages of lung cancer in IPF patients.[42,43] In a retrospective study, the incidence of lung cancer was reduced in IPF patients treated with pirfenidone.[44] However, no definite conclusion can be drawn from that retrospective study. For these reasons, strategies for early diagnosis and prevention of lung cancer are needed in IPF patients.

In our study, stain use was associated with delayed time from IPF diagnosis to lung cancer development. In a randomized controlled trial, there was a lower forced vital capacity (FVC) decline in IPF patients who received statins at baseline versus those who did not.[45] Also, statin use attenuated the decline in lung function in the elderly, and the effect of statins was estimated to be beneficial regardless of smoking status even though the size of the improvement varied among smoking groups.[19] In IPF patients, risk factors for lung cancer included being male, current smoking at IPF diagnosis, and rapid annual decline of 10% or more in FVC.[36] Decreased lung function is linked to increased inflammation and oxidative stress, and anti-inflammatory properties of statins were investigated in respiratory disease. In an animal study, statins reduced neutrophil levels in lung tissue damaged by lipopolysaccharides.[46] Also, statins protected against smoking-induced lung damage and showed anti-inflammatory effects on the lung.[47] In lung transplant recipients, the levels of neutrophils and lymphocytes in the bronchoalveolar lavage of statin users were reduced compared with nonusers.[48] The inhibitory effect of statin on Ras farnesylation was well investigated. Kras alleles are activated in human lung adenocarcinomas, and inhibition of this is important in lung cancer prevention.[49] Also, lovastatin inhibits cell proliferation, cell cycle progression, and apoptosis in NSCLC cells through minichromosome maintenance (MCM) 2, involved in G1/S cell cycle inhibition.[50] Inflammation affects many aspects of malignancy including the proliferation and survival of cancer cells, angiogenesis, tumor metastasis, and tumor response to chemotherapeutic drugs.[51] The exact mechanism of the preventive effect of statin on lung cancer development in IPF patients is not fully understood, but it is believed that anti-inflammation actions on fibrotic lungs and the resulting lower decline in lung function may delay the occurrence of lung cancer. However, in meta-analysis, non-significant decrease of total lung cancer risk was observed among all statin users (RR = 0.89, 95% CI 0.78–1.02).[52] Further randomized controlled trials and high quality cohort studies are needed to confirm this association.

In our study, statin users had lower risk of death among IPF patients. This finding is consistent with a previous study. Kreuter et al. reported that statins might have a beneficial effect on the clinical outcomes of IPF patients including lower risks of death, six-minute walk distance decline, all-cause

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hospitalization, and IPF-related mortality.[18] Repetitive alveolar epithelial injury triggered the early development of IPF. The exact etiology of IPF is unknown, and all stages of fibrosis are accompanied by innate and adaptive immune responses.[53] Modulatory effects of statins on pathways of fibrosis were investigated by in vitro studies. Exposure to statins resulted in a reversible and time-dependent change in cell morphology in human renal fibroblasts.[54] Fluvastatin inhibits TGF-ß1-induced thrombospondin-1 expression in coronary artery smooth muscle cells.[55] However, statin use and all-cause mortality in IPF patients showed controversial results based on a statistical analysis.[56] A prospective cohort study with dosage of statin, statin adherence, and use of concurrent antifibrotics is needed to confirm beneficial effects of statin therapy in IPF patients.

In our study, higher exercise frequency decreased all-cause mortality by 8% in IPF patients. It is well known that cardiopulmonary exercise tests and six-min walk tests provide prognostic value of mortality in patients with IPF. [57] Decreased physical activity was associated with lower progression-free survival (HR 12.1, 95% CI, 1.9–78.8, P = 0.009) in IPF patients. Lower quadriceps strength and higher depression scores contribute to lower physical activity. [58] Pulmonary rehabilitation using exercise training is effective for improving exercise capacity, dyspnea, and quality of life in IPF patients. [59] Also, pulmonary rehabilitation noncompletion and nonresponse were associated independently with increased one-year all-cause mortality in IPF patients. [60] Even without active intervention such as respiratory rehabilitation, life style behaviors such as shorter daily sitting and longer weekly walking were associated with reduced hospitalization and mortality risks in patients with IPF. [61] Although the exercise frequency of our study was collected using a subjective self-report, it supports the previous study findings that exercise can lower the mortality of IPF patients based on large-scale cohort data.

Interestingly, not only did the exercise frequency reduce all-cause mortality, but comorbid diabetes showed a 22% risk reduction of death in IPF patients. The biology of aging may influence the susceptibility to lung fibrosis in the elderly, increasing the incidence of IPF in patients over 60 years of age [62]. Relatively older populations with IPF have variable comorbidities such as hypertension, cardiovascular diseases, and diabetes. Type 2 diabetes mellitus (DM) is a common underlying disease in many IPF patients [63]. DM is a systemic metabolic disease characterized by persistent hyperglycemia, and the lungs are targeted by diabetic micro-vascular damage [64]. Epidemiological research reported that diabetes is a risk factor for IPF, with the prevalence of IPF accompanied by DM estimated to be 10–42% even when excluding cases treated with glucocorticoids [65,66]. Further, DM was reported to be a risk factor with higher mortality in an IPF population (HR 2.5, 95% CI 1.04–5.9) [67]. Contrary to the prior study, our study suggested that DM was associated with reduced risk of mortality in IPF patients. This may be partly due to diabetic medications. Metformin is the first-choice of treatment for glycemic control [68]. Aside from the glucose lowering effect, metformin was involved in anti-fibrotic physiology associated with AMPK activation and showed an inhibitory effect in myofibroblasts differentiation [69]. Also, GLP-1 receptor agonists were found to have anti-pulmonary fibrotic effects and alleviated bleomycin-induced lung damage and fibrosis through inactivation of nuclear factor kappa-B in animal studies. [70] In our study, we did not conduct an investigation of diabetic drugs, so it was not possible to confirm whether mortality was reduced by DM or diabetic drugs. Further investigations through a survey on individualized diabetic medication intake are necessary to determine the effect of DM on mortality in IPF patients.

The limitations of our study should be recognized. First, as the study design was retrospective and based on a large population-based cohort, there is the possibility of selection bias of confounding factors that might have influenced the study results. Second, we tried to include drug compliance, but the true medication adherence could not be estimated. Instead, we performed a mathematical assessment of drug compliance based on the total days of statin prescribed divided by the study period. Third, the dose and the different potency of statin were not included as confounding factors. Also, we did not consider antifibrotics (including pirfenidone and nintedanib) as confounding factors. Lastly, we did not include the severity and status of IPF based on pulmonary function (e.g., FVC, DLCO). To identify further effects of statin use on lung cancer development and mortality in IPF patients, a well-designed large scale prospective study is necessary.

5. Conclusions

The goal of this study was to assess the clinical impact of consecutive statin administration on the development of lung cancer and OS in patients with IPF using the NHIS database. The findings of this study showed that consecutive statin use delayed the onset of lung cancer in IPF patients and improved OS rates. Considering the higher prevalence of comorbidities such as diabetes and hypertension, in IPF patients, addition of statin would be beneficial for clinical outcomes. A well-designed large-scale cohort study is needed to confirm the beneficial effects of statin use on preventing lung cancer development and reduced risk of mortality in IPF patients.

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Data Availability Statement: Publicly available datasets were analyzed in this study. This data can be found here: NHIS sharing service websites (http://nhiss.nhis.or.kr, accessed on 15 April 2022).

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