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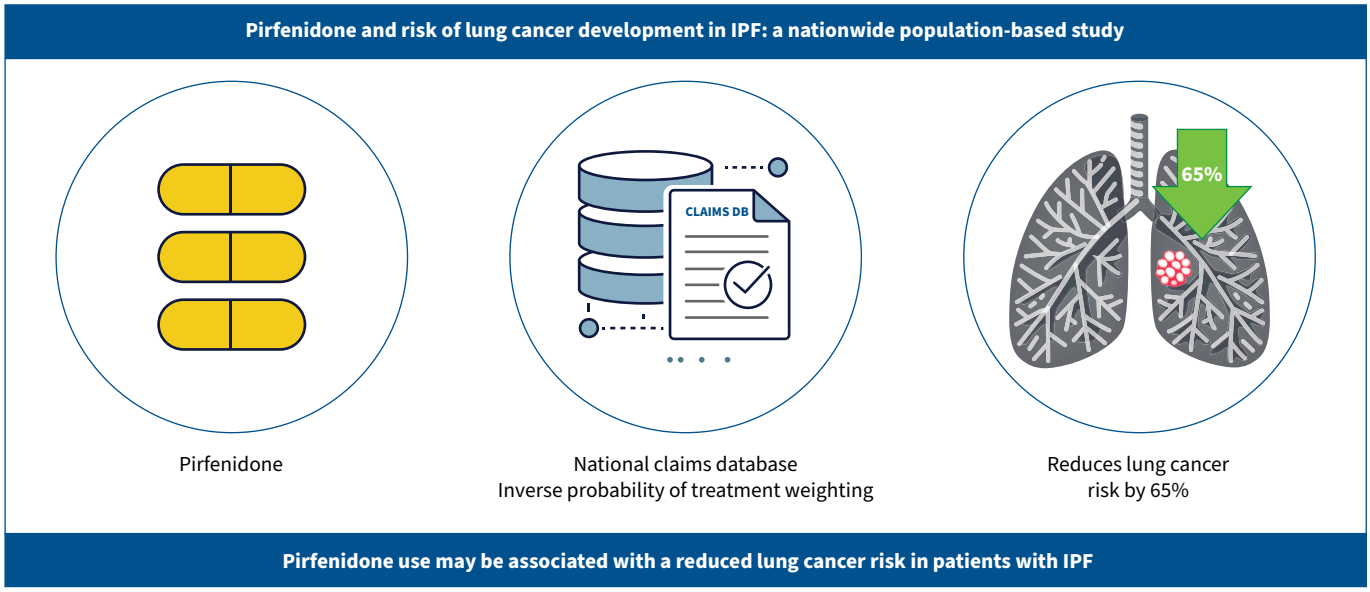

GRAPHICAL ABSTRACT Overview of the study. IPF: idiopathic pulmonary fibrosis.

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Pirfenidone and risk of lung cancer development in idiopathic pulmonary fibrosis: a nationwide population-based study

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Pirfenidone use may be associated with a reduced lung cancer risk in patients with idiopathic pulmonary fibrosis https://bit.ly/40Fymy6

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) carries a high risk of lung cancer, but the effect of pirfenidone on lung cancer development remains uncertain. We investigated the association between pirfenidone use and lung cancer development in patients with IPF.

Methods We included 9938 patients with IPF from the Korean national claims database. Propensity score analysis with inverse probability of treatment weighting (IPTW) and landmark analyses were employed to evaluate lung cancer occurrence according to pirfenidone use. The association was evaluated using Cox regression models adjusted for clinical and socioeconomic variables. A single-centre IPF clinical cohort (n=941) was used for validating the findings.

Results The mean patient age was 69.4 years, 73.7% were men and 32.1% received pirfenidone. Lung cancer developed in 766 patients with IPF (7.7%; 21.9 cases per 1000 person-years) during a median follow-up of 3.0 years. After IPTW, the pirfenidone group showed lower incidence (10.4 *versus* 27.9 cases per 1000 person-years) than the no pirfenidone group. Landmark analysis at 6 months after IPF diagnosis also showed lower incidence of lung cancer in the pirfenidone group than in the no pirfenidone group. Pirfenidone use was independently associated with a reduced lung cancer risk (weighted adjusted hazard ratio (HR) 0.347, 95% CI 0.258–0.466). A clinical cohort showed similar association (weighted adjusted HR 0.716, 95% CI 0.517–0.991). The association persisted across subgroups defined by age or sex.

Conclusion Pirfenidone use may be associated with a reduced lung cancer risk in patients with IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease [1–3], with various complications, including lung cancer [4]. The prevalence of lung cancer in patients with IPF ranges from 3.75% to 31.3%, with a risk up to six times higher than that in the general population after adjusting for age, sex and smoking [5]. The association between IPF and lung cancer may be due to several common risk factors, including older age, male sex, smoking and environmental exposures [6–8]. Additionally, certain genetic mutations may be involved in the pathogenesis of both IPF and lung cancer [9, 10]. Treatment of lung cancer in patients with IPF is challenging due to impaired lung function and the potential risk of acute exacerbations following treatment [11, 12]. Therefore, patients diagnosed with both IPF and lung cancer typically have a worse prognosis than those diagnosed with IPF alone [4]. In some studies, patients with both IPF and lung cancer had a median survival of 35.0–38.7 months in contrast to 55.0–63.9 months for patients with IPF alone [13, 14], with 5-year survival rates of 14.5% *versus* 30.1%, respectively [14].

Pirfenidone, an antifibrotic agent for the treatment of IPF, has been shown to reduce the decline in lung function and risk of mortality [15, 16]. Recently, there has been an increasing interest in its potential role

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in the prevention of lung cancer in IPF; two Japanese studies have suggested that pirfenidone may reduce the risk of lung cancer and lung cancer-related mortality in patients with IPF [17, 18]. Miura *et al*. [18], in a retrospective single-centre study including 261 patients with IPF, reported that those treated with pirfenidone had a significantly reduced lung cancer incidence compared to those in the no pirfenidone group (2.4% *versus* 22.0%) during a median follow-up period of ∼4 years. In another study that included 345 patients with IPF, those on antifibrotic therapy (pirfenidone or nintedanib) had a significantly lower lung cancer incidence (1.07 *versus* 4.53 per 100 person-years) and prevalence (2.7% *versus* 19.2%) than those without the therapy [17]. However, these studies are limited by small sample sizes (n=261–345) and low numbers of lung cancer events (n=35–41). Therefore, our study aimed to evaluate the association between pirfenidone and lung cancer development in a larger number of patients using national claims data and a clinical cohort.

Materials and methods

Data sources

We used data from the National Health Insurance Sharing Service database of the National Health Insurance Corporation, which stores all medical claims data in South Korea, including qualification, insurance premium, registration status for rare and incurable diseases, health check-up, clinic visits, and treatment details. Survival status was determined using data from the Cause of Death Statistics of the Korean Statistical Information Service.

This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (approval number S2021-1136) and informed consent was waived due to the retrospective study design.

Study population

IPF cases were defined using the Korean Standard Classification of Diseases, Revision 7 (KCD-7) diagnostic code (J84.1), which is adapted from the International Classification of Disease and Related Health Problems, 10th Revision, as well as the rare intractable diseases (RID) registration code (V236). The RID programme provides medical expense support to patients with rare and incurable diseases, and its registration criteria are rigorous, ensuring high reliability of associated diagnosis codes. Previous studies using the RID registration database have been reported [19–21]. The RID registration criteria for IPF require the usual interstitial pneumonia pattern on a surgical lung biopsy or chest computed tomography (CT), excluding other causes of interstitial lung disease.

Patients who visited secondary or tertiary medical institutions with both KCD-7 and RID registration codes and underwent chest CT within 3 months of the date of code assignment between January 2002 and December 2018, and received national health screening, were included as IPF cases. Among the 13 356 eligible patients with IPF screened, we excluded those who received an IPF diagnosis code for the first time in 2018 (n=2407) due to insufficient follow-up time, those aged <50 years (n=767) due to low probability of IPF diagnosis and those diagnosed with lung cancer before or at the time of the index date (n=244). Ultimately, a total of 9938 patients were included in this study (figure 1).

Definition

The primary outcome was development of lung cancer, identified by the KCD-7 code for malignant neoplasm of the bronchus and lung (C34). The observation period was defined as the time from the index date to the development of lung cancer or censoring (December 2018). The index date was identified as the first date with J84.1 and V236 codes for the no pirfenidone group, and the first pirfenidone prescription date for the pirfenidone group. The duration of pirfenidone treatment was determined cumulatively by considering all prescription dates from the first to the last prescription.

Ever-smokers (including current and former smokers) were those who had smoked over 5 packs (100 cigarettes) at the index date; current smokers were active smokers at the index date, whereas former smokers were smokers who had quit. Comorbidities were identified if patients had more than two visits to medical institutions with the same KCD-7 disease code within 1 year of the index date (supplementary table S1). We used Quan's code to calculate the Charlson Comorbidity Index (CCI) and applied weights originally proposed by Charlson and co-workers [22, 23]. Low-income referred to the bottom 30% of the National Health Insurance cost. Medical Aid was a government-administered programme in South Korea designed to assist low-income households with medical services, covering ∼3% of the population [24]. Based on patient's residential addresses, urban areas encompassed Seoul and metropolitan cities, while rural areas encompass other regions. Steroid use was defined as the use of oral or injectable steroids prescribed for ⩾1 month after the index date (supplementary table S2).

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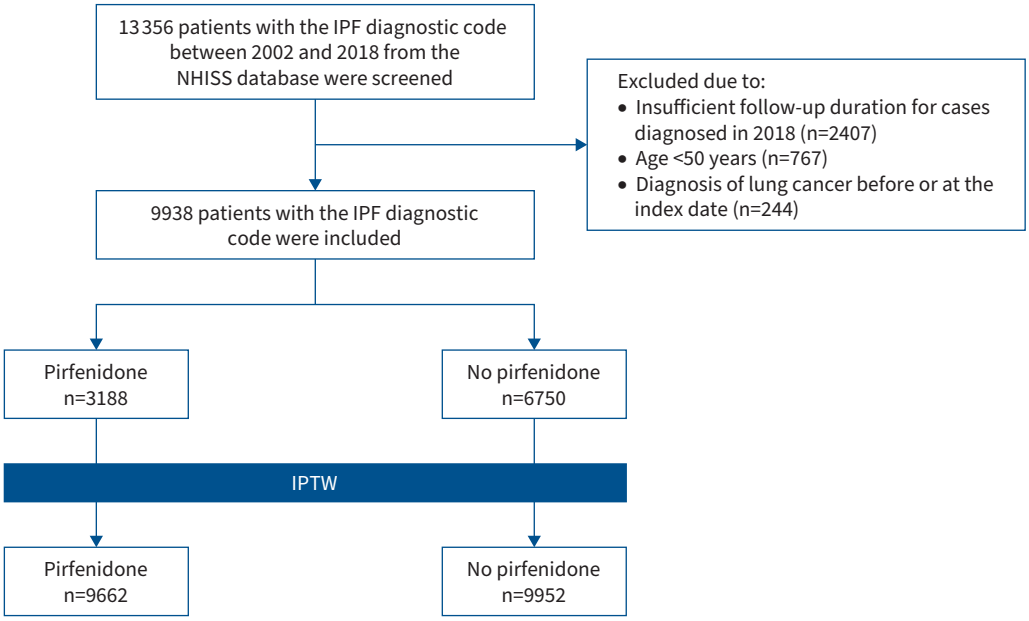

FIGURE 1 Flowchart of the study cohort enrolment process. IPF: idiopathic pulmonary fibrosis; NHISS: National Health Insurance Sharing Service; IPTW: inverse probability of treatment weighting.

Clinical cohort

Patients with IPF diagnosed between 2004 and 2019 at the Asan Medical Center were included in this study; patients with IPF were identified using diagnostic codes, verified by chart review and confirmed by multidisciplinary discussion [25, 26]. This cohort provided detailed clinical information, including lung function that was not available in the national claims database. Of 1050 patients screened, we excluded 79 patients diagnosed with lung cancer either before or simultaneously with IPF diagnosis or pirfenidone administration; 941 patients were finally included in a clinical cohort (supplementary figure S1). The clinical cohort included patients from the larger claims cohort and was used for validation using clinical data, including lung function parameters.

All patients met the diagnostic criteria based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society Clinical Practice 2018 guidelines [1]. All clinical parameters were retrospectively obtained from the medical records and/or records of the National Health Insurance of Korea.

Statistical analysis

To minimise the differences between the two groups, we used propensity score analysis with inverse probability of treatment weighting (IPTW) [27]. We chose the IPTW method for its effectiveness in balancing covariates between the pirfenidone and no pirfenidone groups in our study, thereby reducing bias [28]. IPTW creates a weighted pseudo-population by assigning weights based on the inverse probability of receiving treatment actually received, thereby balancing baseline covariates and increasing the validity of comparisons between the groups.

This method is ideal for large datasets because it preserves all data and effectively mimics the conditions of randomisation, allowing for a more accurate assessment of treatment effects. Detailed procedures for IPTW in the claims database and clinical cohort are described in supplementary table S3. Briefly, logistic regression was used to derive the propensity scores from all baseline variables. Patients were matched 1:1 using the nearest-neighbour method with a calliper of 0.2 of the logit propensity score. To reduce outlier impact, 1% of the data was removed before conducting a weighted regression analysis. Cohort balance was checked using standardised mean differences (SMDs), with an SMD of <10% being acceptable. Patients with at least one pirfenidone prescription were classified into the pirfenidone group.

Incidence rates (cases per person-years) were computed as the number of observed lung cancer cases divided by the total person-years of follow-up. The cumulative incidence of lung cancer was calculated

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using Kaplan–Meier curves and differences between the groups were assessed using log-rank tests. Alternatively, to reduce potential immortal time bias, we performed a landmark analysis at 6 months after IPF diagnosis (main analysis), as well as for sensitivity analysis at 1 and 2 years after diagnosis in the IPTW cohorts. This approach ensured that follow-up time started from a fixed point and excluded subjects who were lost to follow-up or died before that time, resulting in an accurate comparison of results. The Cox proportional hazards model was used to assess the association between pirfenidone use and the risk of lung cancer, yielding unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals. The adjusted analysis included clinical (age, sex, smoking status (never *versus* former *versus* current), year of IPF diagnosis, CCI, steroid use and home oxygen supply) or socioeconomic (type of insurance, income and regional type of patient's addresses) variables collected at the index date. In the clinical cohort, we additionally adjusted for lung function (forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO})) in the analysis adjusted for clinical variables (age, sex, smoking status, year of IPF diagnosis, steroid use and CCI). We also performed a competing risk analysis to account for the potential impact of patient mortality on lung cancer development. In this analysis, we considered death as a competing event and applied the subdistribution hazard model, as proposed by Fine and Gray [29].

For sensitivity analysis, pirfenidone use was grouped, according to cumulative duration: ⩾1 month, ⩾6 months, ⩾1 year and ⩾2 years, based on total cumulative days of pirfenidone use. We performed high-dimensional propensity score (hdPS) matching analysis, which adjusts for various variables across multiple models, thereby reducing the likelihood of omitted variable bias (supplementary tables S4–S8) [30]. We also implemented time-varying analysis to examine the changes in pirfenidone use over time. Subgroup analyses were performed, according to age (⩾65 *versus* <65 years) or sex (males *versus* females). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) or SPSS version 23.0 (IBM, Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

Results

Incidence of lung cancer

Of the 9938 patients with IPF, the mean age was 69.4 years, 73.7% were men and 32.1% received pirfenidone (median (interquartile range (IQR)) treatment duration 1.0 (0.4–1.9) years; 89.3% were treated for ⩾1 month, 65.2% for ⩾6 months, 48.0% for ⩾1 year and 21.7% for ⩾2 years). During a median (IQR) follow-up period of 3.0 (1.7–5.0) years, lung cancer developed in 766 patients with IPF (7.7%; 21.9 cases per 1000 person-years).

The pirfenidone group showed younger ages, more frequent males and home oxygen use, higher body mass index (BMI), but a lower CCI than the no pirfenidone group (table 1). Through stabilised IPTW, two cohorts, comprising 9662 patients with IPF under pirfenidone treatment and 9952 without pirfenidone,

TABLE 1 Comparison of baseline characteristics between the pirfenidone and no pirfenidone groups among patients with idiopathic pulmonary fibrosis

	Before IPTW			After IPTW		
	Pirfenidone	No pirfenidone	SMD	Pirfenidone	No pirfenidone	SMD
Patients	3188	6750		9662	9952	
Age (years)	68.5±7.5	69.9±8.4	0.176	68.8±14.0	69.3±9.9	0.058
Male	2501 (78.5)	4823 (71.5)	0.162	7065 (73.1)	7314 (73.5)	0.021
Smoking status			0.042			0.012
Never-smoker	1630 (51.1)	3828 (56.7)		5206 (53.9)	5455 (54.8)	
Former smoker	1159 (36.4)	1902 (28.2)		2991 (31.0)	3060 (30.7)	
Current smoker	399 (12.5)	1020 (15.1)		1465 (15.2)	1438 (14.4)	
Smoking amount (pack-years)	11.4±12.9	10.2±12.8	0.096	10.8±22.4	10.6±15.6	0.045
BMI (kg·m^{-2})	24.5±2.9	23.7±3.1	0.260	24.1±4.9	24.0±3.8	0.020
Low household income	463 (14.5)	1037 (15.4)	0.024	1469 (15.2)	1500 (15.1)	0.003
Medical Aid	29 (0.9)	87(1.3)	0.036	134 (1.4)	116 (1.2)	0.011
CCI	1.2±0.8	1.3±0.9	0.149	1.3±1.5	1.3±1.1	0.001
Corticosteroid use	1911 (59.9)	4159 (61.6)	0.036	6064 (62.8)	6086 (61.2)	0.036
Home oxygen supply	33 (1.0)	61 (0.9)	0.202	103 (1.1)	94 (0.9)	0.011

Data are presented as n, mean±SD or n (%), unless otherwise stated. IPTW: inverse probability of treatment weighting; SMD: standardised mean difference; BMI: body mass index; CCI: Charlson Comorbidity Index.

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demonstrated similar baseline demographics (all SMDs <0.1) (table 1). The pirfenidone group exhibited a lower incidence rate of lung cancer compared with that of the no pirfenidone group (10.4 *versus* 27.9 cases per 1000 person-years) (table 2). Sensitivity analysis using different treatment durations also showed consistent results (table 2).

Kaplan–Meier analysis showed that the pirfenidone group had a significantly lower cumulative incidence of lung cancer than that of the no pirfenidone group in both the original (3 years: 3.0% (95% CI 1.3–6.7%) *versus* 7.5% (95% CI 6.0–9.4%); 5 years: 4.7% (95% CI 2.8–8.0%) *versus* 12.9% (95% CI 11.2–14.9%); p<0.001) (figure 2a) and IPTW cohorts (3 years: 2.0% (95% CI 0.6–6.6%) *versus* 7.9% (95% CI 6.4–9.8%); 5 years: 3.5% (95% CI 1.7–7.2%) *versus* 13.3% (95% CI 11.6–15.3%); p<0.001) (figure 2b).

In the landmark analysis conducted at 6 months after IPF diagnosis, pirfenidone use was associated with a significantly lower cumulative incidence of lung cancer compared with no pirfenidone use (figure 3a). These findings remained consistent in landmark analyses at 1 and 2 years after IPF diagnosis (figure 3b and c).

Association with lung cancer development

The unadjusted analysis showed a significant association between pirfenidone use and a reduced risk of lung cancer in the IPTW cohort (weighted HR 0.353, 95% CI 0.315–0.396) (table 3). This association also remained after adjustment for clinical and socioeconomic variables (weighted adjusted HR 0.347, 95% CI 0.258–0.446). In terms of treatment duration, consistent risk reductions were observed for all the treatment durations: ⩾1 month (weighted adjusted HR 0.441, 95% CI 0.329–0.591), ⩾6 months (weighted adjusted HR 0.279, 95% CI 0.191–0.409), ⩾1 year (weighted adjusted HR 0.210, 95% CI 0.126–0.348) and ⩾2 years (weighted adjusted HR 0.280, 95% CI 0.156–0.504).

Considering the high mortality rate in patients with IPF, we conducted a competing risk analysis where we treated death as a competing event; the results (weighted adjusted HR 0.347, 95% CI 0.266–0.452) further support an association between pirfenidone use and a reduced lung cancer risk across all the treatment durations evaluated (table 3).

Sensitivity analysis

In the hdPS analysis, a total of 19 statistical models were derived using six dimensions: demographics, predefined covariates, and inpatient or outpatient diagnoses and procedure codes (supplementary tables S5–S8). For each model, the number of covariates used and the results are summarised in supplementary table S9. The results consistently showed that the use of pirfenidone was associated with a statistically significant reduction in the incidence of lung cancer compared with the no pirfenidone group (HR 0.385–0.442) (supplementary table S9 and supplementary figure S2). When the variable for pirfenidone use was treated as time varying, the results also consistently indicated that the pirfenidone group had a lower incidence of lung cancer compared with the no pirfenidone group, both before and after IPTW (weighted adjusted HR 0.532, 95% CI 0.471–0.600) (supplementary table S10).

TABLE 2 Incidence of lung cancer in patients with idiopathic pulmonary fibrosis according to pirfenidone use and treatment duration

	Patients	Lung cancer	Incidence[#] (95% CI)
Total population	19 614	1355 (6.9)	17.8 (16.9–18.8)
Pirfenidone usage			
No	9952	925 (9.1)	27.9 (26.1–29.7)
Yes	9662	431 (4.7)	10.4 (9.5–11.4)
Duration			
<1 month	11 109	925 (8.3)	24.8 (23.2–26.4)
⩾1 month	8505	431 (5.1)	11.1 (10.1–12.2)
<6 month	13 594	1083 (8.0)	22.4 (21.1–23.8)
⩾6 months	6020	273 (4.5)	9.8 (8.7–11)
<1 year	15 303	1189 (7.8)	21.2 (20–22.5)
⩾1 year	4311	167 (3.9)	8.3 (7.1–9.6)
<2 year	17 553	1282 (7.3)	19.6 (18.6–20.7)
⩾2 years	2060	73 (3.5)	6.8 (5.4–8.5)

Data are presented as n or n (%), unless otherwise stated. [#]: cases per 1000 person-years.

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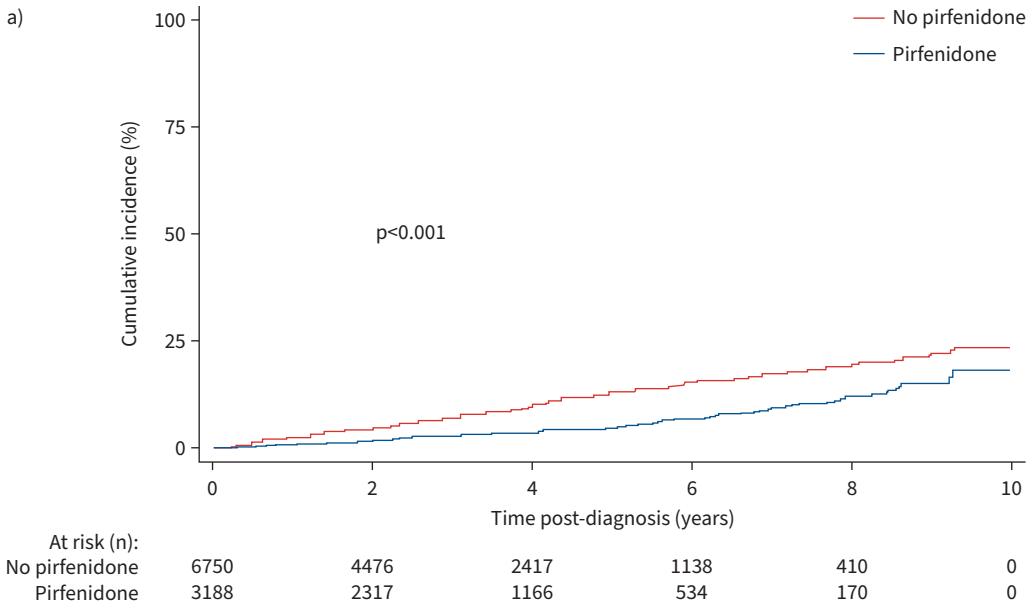

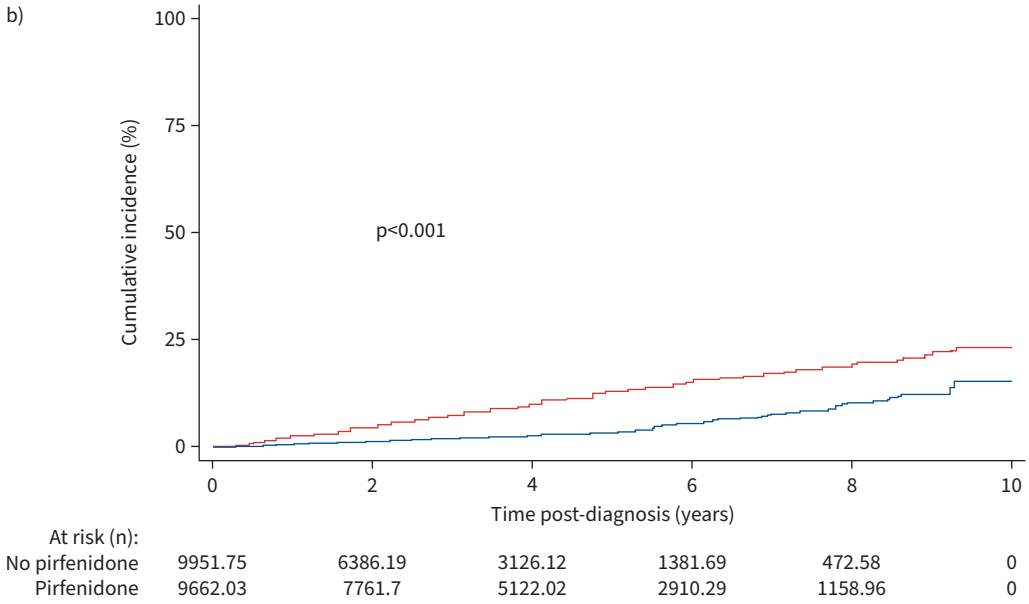

FIGURE 2 Comparison of cumulative lung cancer incidence between the pirfenidone and no pirfenidone groups in patients with idiopathic pulmonary fibrosis: a) original cohort and b) inverse probability of treatment weighting cohort. Kaplan–Meier survival curve analysis with the log-rank test was used to compare patients with and without pirfenidone treatment.

Subgroup analyses

When stratified by age (⩾65 *versus* <65 years), pirfenidone consistently reduced lung cancer risk in both age groups (<65 years: weighted adjusted HR 0.336, 95% CI 0.274–0.412; ⩾65 years: weighted adjusted HR 0.356, 95% CI 0.310–0.410) (table 4). When stratified by sex, the reduction in risk was also consistently significant in males (weighted adjusted HR 0.337, 95% CI 0.299–0.379) and females (weighted adjusted HR 0.519, 95% CI 0.327–0.823) (table 4).

Clinical cohort

Of the clinical cohort (n=941) for validation, the mean age was 66.3 years, 82.3% were men and 41.0% received pirfenidone (91.7% for ⩾1 month, 69.7% for ⩾6 months, 59.6% for ⩾1 year and 32.9% for

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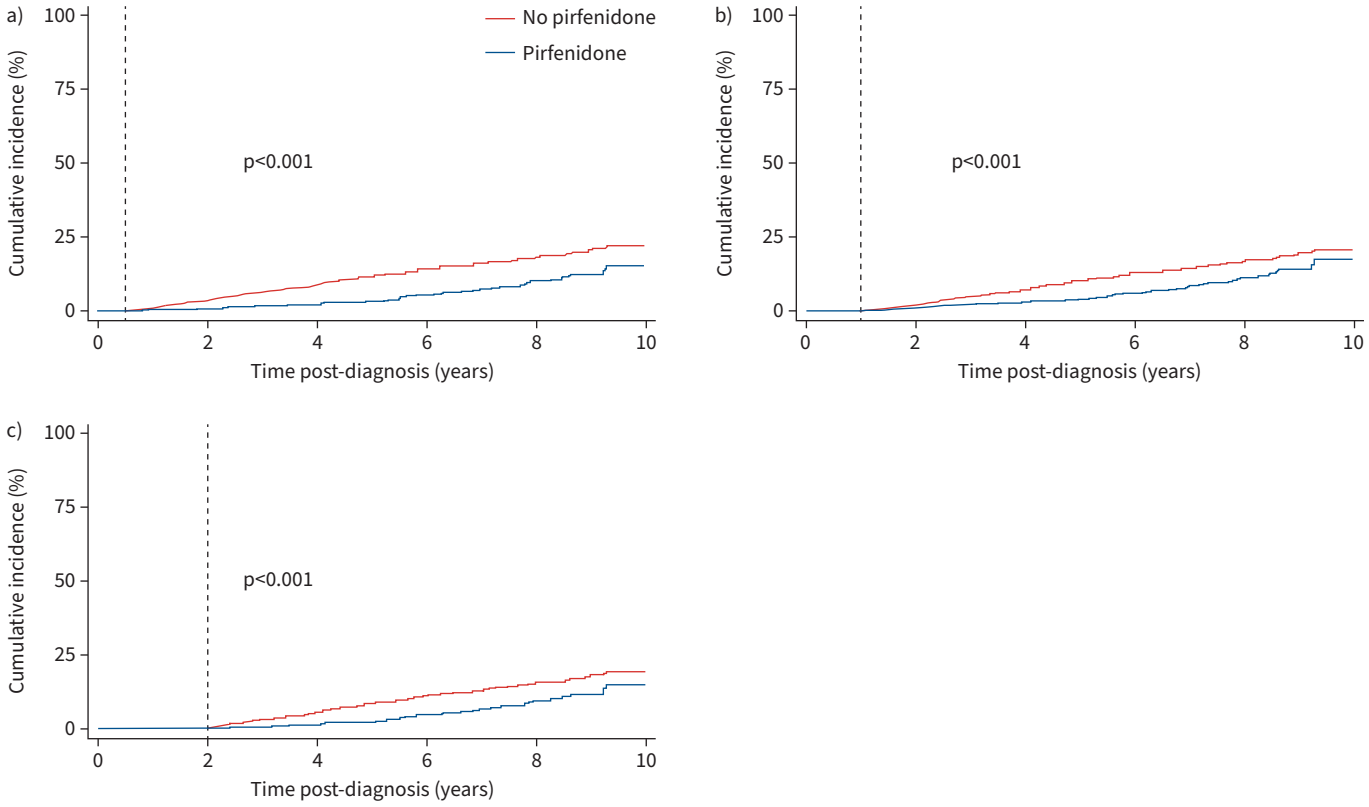

FIGURE 3 Landmark analysis for cumulative lung cancer incidence between the pirfenidone and no pirfenidone groups in patients with idiopathic pulmonary fibrosis (IPF): a) 6 months, b) 1 year and c) 2 years post-diagnosis. Kaplan–Meier survival curve analysis with the log-rank test was used to compare patients with and without pirfenidone treatment after landmark time. The index date was defined as the first date of the IPF diagnosis code assignment for both groups. The dashed vertical lines represent the landmark points at each time-point.

⩾2 years) (supplementary table S11). During a median (IQR) follow-up of 2.8 (1.0–5.3) years, lung cancer developed in 26 (6.7%) patients in the pirfenidone group and 61 (11.0%) in the no pirfenidone group. The cumulative incidence of lung cancer was significantly lower in the pirfenidone groups compared with the no pirfenidone group (3-year: 8.5% (95% CI 5.7–12.6%) *versus* 11.3% (95% CI 8.3–15.4%); 5-year: 11.0% (95% CI 7.2–15.4%) *versus* 19.8% (95% CI 15.0–26.0%); p=0.012) (supplementary figure S3a). This finding was consistent with the results of landmark analyses performed at 6 months, 1 year and 2 years after IPF diagnosis (supplementary figure S3b–d).

TABLE 3 Association between pirfenidone use and risk of lung cancer in patients with idiopathic pulmonary fibrosis

	Weighted HR		Weighted adjusted HR[#]		Competing risk weighted adjusted HR[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Pirfenidone use	0.353 (0.315–0.396)	<0.001	0.347 (0.258–0.466)	<0.001	0.347 (0.266–0.452)	<0.001
Duration						
⩾1 month	0.431 (0.384–0.483)	<0.001	0.441 (0.329–0.591)	<0.001	0.441 (0.340–0.572)	<0.001
⩾6 months	0.421 (0.368–0.481)	<0.001	0.279 (0.191–0.409)	<0.001	0.279 (0.200–0.391)	<0.001
⩾1 year	0.378 (0.321–0.445)	<0.001	0.210 (0.126–0.348)	<0.001	0.210 (0.127–0.346)	<0.001
⩾2 years	0.331 (0.261–0.418)	<0.001	0.280 (0.156–0.504)	<0.001	0.280 (0.155–0.505)	<0.001

HR: hazard ratio. [#]: adjusted HR was calculated by adjusting for clinical (age, sex, year of diagnosis, Charlson Comorbidity Index, smoking status, steroid use and home oxygen supply) and socioeconomic (type of insurance, income and regional type of patient's address) variables.

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TABLE 4 Age- and sex-stratified subgroup analysis for association between pirfenidone and risk of lung cancer in patients with idiopathic pulmonary fibrosis

	Weighted HR		Weighted adjusted HR[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age[¶]		0.941[+]		0.549[+]
<65 years	0.351 (0.288–0.429)	<0.001	0.336 (0.274–0.412)	<0.001
⩾65 years	0.356 (0.310–0.409)	<0.001	0.356 (0.310–0.410)	<0.001
Sex[¶]		0.119[+]		0.096[+]
Male	0.338 (0.300–0.380)	<0.001	0.337 (0.299–0.379)	<0.001
Female	0.503 (0.318–0.796)	0.003	0.519 (0.327–0.823)	0.005

HR: hazard ratio. [#]: adjusted HR was calculated by adjusting for clinical (age, sex, year of diagnosis, Charlson Comorbidity Index, smoking status, steroid use and home oxygen supply) and socioeconomic (type of insurance, income, regional type of patient's address) variables; [¶]: adjusted analyses were performed, excluding the stratification covariates in the subgroup model; [+]: p-value for interaction between pirfenidone use and age or sex.

The pirfenidone group had higher BMI, lower D_{LCO} and total lung capacity, and less frequent use of corticosteroids than the no pirfenidone group before IPTW. After IPTW, baseline demographics, except for lung function, were balanced with SMDs <0.1 (supplementary table S12). Pirfenidone use was associated with a significant reduction in the risk of lung cancer development in both the unadjusted analysis (weighted HR 0.662, 95% CI 0.485–0.903) and in the analysis adjusted for clinical variables and lung function (FVC and D_{LCO}) (weighted adjusted HR 0.716, 95% CI 0.517–0.991) (table 5). The results were consistent regardless of treatment duration, but were more significant with longer treatment duration, especially in the groups treated for ⩾2 years (weighted adjusted HR 0.504, 95% CI 0.330–0.769). The competing risk analysis also showed consistent results (table 5).

Discussion

Our study showed an association between the use of pirfenidone and a reduced risk of lung cancer in both cohorts from a national claims database and a clinical cohort of patients with IPF. The treatment with pirfenidone was significantly associated with the lower risk of lung cancer in patients with IPF, irrespective of treatment duration, age or sex.

Our study found that pirfenidone treatment significantly reduced the risk of lung cancer, similar to previous findings [17, 18]. In a study among 261 patients with IPF, Miura *et al.* [18] showed that the use of pirfenidone was associated with a lower risk of lung cancer (n=41) (HR 0.11, 95% CI 0.03–0.46; p=0.003) after adjustment for emphysema and *N*-acetylcysteine use. In a Japanese multicentre IPF study (n=345), Naoi *et al.* [17] also showed that the use of antifibrotics (pirfenidone n=137 and nintedanib n=52) was associated with a reduced risk of lung cancer (n=35) (HR 0.298, 95% CI 0.106–0.835; p=0.021) in patients with IPF, after adjustment for age, sex, smoking status and FVC. In contrast to

TABLE 5 Association between pirfenidone use and risk of lung cancer in patients with idiopathic pulmonary fibrosis in the clinical cohort

	Weighted HR		Weighted adjusted HR[#]		Competing risk weighted adjusted HR[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Pirfenidone use	0.662 (0.485–0.903)	0.009	0.716 (0.517–0.991)	0.044	0.716 (0.517–0.991)	0.044
Duration						
⩾1 month	0.693 (0.508–0.946)	0.021	0.744 (0.538–1.028)	0.073	0.744 (0.538–1.028)	0.073
⩾6 months	0.859 (0.626–1.178)	0.345	0.916 (0.663–1.264)	0.592	0.916 (0.663–1.264)	0.592
⩾1 year	0.830 (0.599–1.149)	0.262	0.886 (0.623–1.203)	0.390	0.886 (0.623–1.203)	0.390
⩾2 years	0.493 (0.324–0.751)	0.001	0.504 (0.330–0.769)	0.002	0.504 (0.330–0.769)	0.002

HR: hazard ratio. [#]: adjusted HR was calculated by adjusting for clinical (age, sex, year of diagnosis, Charlson Comorbidity Index, smoking status, forced vital capacity and diffusing capacity for carbon monoxide, and steroid use) variables.

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previous studies with limited sample sizes, our large study population allowed for robust statistical analyses with adjustment for clinical and socioeconomic variables. As a result, our study confirmed a significant association between pirfenidone use and a reduced risk of lung cancer in patients with IPF.

Previous studies have proposed potential mechanisms for the effect of pirfenidone on lung cancer development [31, 32]. Fujiwara *et al*. [32] reported that pirfenidone inhibited both lung and cancer-associated fibroblasts (human non-small cell lung cancer (NSCLC) lines), as well as tumour growth in an NSCLC mouse model. The anti-inflammatory and antioxidant effects of pirfenidone [33] may inhibit the pathways involved in lung carcinogenesis stimulated by the production of reactive oxygen species (ROS) in IPF lungs [34, 35]. These ROS can damage DNA and other cellular components, leading to genetic mutations and carcinogenesis [36]. Marwitz *et al*. [31] have also shown that pirfenidone induces cell cycle arrest, downregulated SMAD expression and reduced proliferation in human NSCLC cells. Furthermore, pirfenidone effectively reduced tumour growth and promoted T-cell and natural killer cell infiltration in an NSCLC mouse model [31]. These findings suggest that pirfenidone may have a protective role in reducing the risk of lung cancer in patients with IPF.

Our study showed that pirfenidone treatment reduced the risk of lung cancer, regardless of the duration of treatment. This effect of treatment duration was not investigated in the studies by Naoi *et al*. [17] and Muira *et al*. [18]. Although pirfenidone has been used as a standard treatment for IPF and has been shown to improve prognosis in some studies [15, 16], its use is limited due to the high rate of accompanying side-effects and poor compliance [37]. However, in our study, pirfenidone showed consistent results regardless of the duration of treatment. A small-sample-sized Japanese retrospective study also found that short-term pirfenidone therapy (<1 year; n=16) resulted in similar changes in FVC (change in FVC at 6 months after PFD therapy: –2%) when compared to long-term treatment (>1 year; n=30: change in FVC at 6 months after PFD therapy: 0%; p=not significant) [38]. However, our data suggest that there appears to be a trend toward a lower risk (a reduction in hazard ratio) with longer duration of treatment in both cohorts, suggesting that the effect of long-term treatment may be more pronounced. Furthermore, in the subgroup analysis, pirfenidone was significantly associated with a lower risk of lung cancer, regardless of age or sex. Although hazard ratios were slightly higher in female patients, there was no significant interaction between pirfenidone and sex. It is worth noting that the high 95% confidence interval ranges in female patients could be attributed to the smaller sample size, as both IPF and lung cancer are less common in female patients [5]. Collectively, these findings suggest that considering the use of pirfenidone might be a valuable strategy to reduce the risk of lung cancer in patients with IPF, given the elevated comorbidity and mortality associated with lung cancer in this population, irrespective of age and sex.

This study has limitations. First, the diagnosis of IPF cases may be overestimated due to the use of the national claims database. To mitigate this limitation, we used the RID registration code to define IPF cases and performed validation using the clinical IPF cohort to replicate our findings. Second, due to the limitations of the claims data, we were unable to adjust for all potential confounding variables, such as lung function. To minimise this limitation, we used the IPTW analysis to adjust for confounding variables between the two groups and performed hdPS analysis to reduce the likelihood of omitted variable bias. We also performed subgroup analyses with validation using clinical data including lung function parameters. Third, our study was a retrospective study that included patients who underwent medical health check-ups, which may lead to selection bias. However, the National Health Insurance Service in our country provides medical health check-ups to the entire population, which minimises the potential impact of patient selection bias on the representativeness of the study. Fourth, treatment may not have been started at the time of the first IPF diagnosis, potentially leading to differences in disease stage between the pirfenidone and no pirfenidone groups. Despite adjustment for oxygen use and lung function, this confounding factor remains unaddressed. Lastly, as our study was conducted in a Korean population, further validation in different populations is needed given the ethnic differences in the epidemiology and genetic predisposition of IPF. Despite these limitations, our study benefits from a large sample size, various statistical methods and a clinical cohort, which increases the reliability and generalisability of the findings.

In conclusion, our study suggests an association between the use of pirfenidone and a reduced risk of lung cancer in patients with IPF. Further research is needed to elucidate the underlying mechanisms and to validate these findings through prospective cohort studies in diverse populations.

Ethics statement: This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (approval number S2021-1136) and informed consent was waived due to the retrospective study design.

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Author contributions: J.W. Song was responsible for the conception and design of the study. J.W. Song also serves as guarantor and takes full responsibility for the content of the manuscript, including the data analysis. J.W. Song was responsible for data acquisition. H. Kim and Y. Bae performed the statistical analysis and data interpretation. H-Y. Yoon and J.W. Song were responsible for writing the first draft. All authors reviewed and approved the final version of the manuscript.

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