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Characterizing Health Outcomes in Idiopathic Pulmonary Fibrosis using US Health Claims Data

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Keywords

Algorithms · Database · Idiopathic pulmonary fibrosis · Incidence · Insurance, health

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a life-threatening interstitial lung disease (ILD). Characterizing health outcomes of IPF patients is challenging due to disease rarity. ***Objective:*** This study aimed to identify the burden of disease in patients newly diagnosed with IPF. ***Methods:*** Patients with ≥1 claim with an IPF diagnosis were identified from a United States healthcare insurer's database (2000–2013). Patients with other known causes of ILD or aged <40 years were excluded. Subgroups were compared based on the 2011 change in International Classification of Diseases, 9th Revision (ICD-9) definition of IPF and occurrence of IPF testing. The prevalence and incidence of preselected health conditions of clinical interest were estimated. ***Results:*** Median age of newly diagnosed patients (n = 7,298) was 62 years (54.0% male). Restricting to patients with IPF diagnostic testing did not substantially affect cohort characteristics, nor did ICD-9 IPF coding change. Mean follow-up was 1.7 years; 16.8% of patients died; and a substantial proportion of patients were censored due to end of health plan enrollment (50.7%) and other causes of ILD (19.6%). The incidence of pulmonary hypertension, lung cancer, and claims-based algorithm proxy for acute respiratory worsening of unknown cause was 22.5, 17.6, and 12.6 per 1,000 person-years, respectively. ***Conclusions:*** Patients with IPF had a high disease burden with a variety of health outcomes observed, including a high rate of mortality. Database censoring due to changes in enrollment or other ILD diagnoses limited follow-up. Altering cohort entry definitions, including IPF testing or ICD-9 IPF coding change, had little impact on cohort baseline characteristics.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare, progressive, and life-threatening interstitial lung disease (ILD) of unknown etiology that leads to scarring of the lung [1, 2]. It generally occurs in patients 50 years or older. Previ-

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ously, lung transplantation was the only treatment considered to impact prognosis; however, few patients were eligible. Although pharmacotherapy has been approved for IPF in the United States (US) [3], a better understanding of the characteristics of patients with IPF is needed. The primary objective of this study was to characterize patients newly diagnosed with IPF, including prevalence and incidence estimates for selected health conditions of clinical interest.

Methods

Cohort Identification

Patients were drawn from the proprietary Optum Research Database, which contains eligibility, pharmacy, laboratory, and medical claims data from a large US commercial health plan between 1999 and 2013. This database is representative of the US's commercially insured population and has been used extensively for pharmacoepidemiology research, including postapproval safety studies [4–6].

Patients were required to have at least 1 medical claim with a diagnosis code of IPF between January 1, 2000, and December 31, 2013, and to be aged 40 years or older. During the study period, International Classification of Diseases, 9th Revision (ICD-9) codes to identify IPF were modified. Prior to October 2011, the initial inclusion diagnosis code was ICD-9 516.3 (*idiopathic interstitial pneumonia*). Effective October 2011, the inclusion diagnosis code was ICD-9 516.31 (*IPF*). Patients with other known causes of ILD recorded during the 12-month baseline period were excluded (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000504630) [7].

Patients in the newly diagnosed IPF cohort (IPF cohort) were required to have an index diagnosis of IPF within the study period (January 1, 2000 to December 31, 2013), with no IPF claims during the previous 12 months (the look-back period). A more restrictive definition was also used; patients with a procedure code related to testing for IPF during the 12-month look-back period prior to the IPF diagnosis date entered a subcohort (IPF subcohort). Procedures included either surgical lung biopsy (ICD-9 codes 33.28 and 34.21; Current Procedural Terminology codes 32602, 32607, 32608, 32609, 32095, 32096, 32097, and 32100–32160) or high-resolution computed tomography of the thorax (ICD-9 code 87.41; Current Procedural Terminology codes 71250, 71260, and 71270) [7].

Follow-up time extended from the cohort entry date until the earliest of the following: disenrollment from the health plan; death; a claim for another known cause of ILD (online suppl. Table S1); or the end of the study period.

Outcome Measures

Outcomes of clinical interest were identified by diagnosis and procedure codes, using either validated algorithms (when available) or clinical input and medical claims coding systems searches. To identify possible out-of-hospital deaths, claims data were linked to the Social Security Administration Death Master File that provides information on the occurrence (but not cause) of death for individuals aged 18 years and older.

Primary outcomes included a proxy measure of acute respiratory worsening of unknown cause (ARWUC) [8], pulmonary hypertension (PH) [9], pulmonary arterial hypertension (PAH) [9], lung transplantation, lung cancer [10, 11], acute myocardial infarction, and all-cause mortality. Secondary outcomes included gastrointestinal perforation [12], chronic renal failure/insufficiency [13–15], hemorrhagic diathesis or coagulopathy, venous thrombosis [16], pulmonary embolism [16], stroke, cardiac arrhythmia [17], congestive heart failure [18], ischemic heart disease [19, 20], arterial hypertension [21, 22], neutropenia [23], pneumonia [24], sepsis [25], chronic obstructive pulmonary disease [26, 27], gastroesophageal reflux disease (GERD) [28, 29], type 2 diabetes mellitus [30, 31], obstructive sleep apnea, bronchitis, upper respiratory infections, pulmonary rehabilitation, acute coronary syndrome, angina pectoris, and a series of bleeding events.

Only the first occurrence of each outcome during follow-up was counted; however, the occurrence of 1 type of outcome did not preclude counting the occurrence of a different type of outcome.

Baseline Characteristics

Selected baseline characteristics including primary and secondary outcome conditions (as listed above) and measures of healthcare utilization are given in Table 1.

The study was approved by the New England Institutional Review Board (14-341).

Statistical Methods

Baseline characteristics were compared for patients diagnosed before and after the ICD-9 coding changes for IPF diagnosis. Prevalence was calculated by dividing the number of patients in the cohort with the condition during the study period (January 1, 2000 to December 31, 2013; IPF cohort) or the 12-month look-back period (IPF subcohort) by the total number of patients in the database ("complete-period" population). Incidence rates (IRs [number of patients with the outcome divided by the sum of all observation time-to-events for all patients per cohort]) were calculated per 1,000 person-years (py). For each outcome, the IR during follow-up is presented only for patients with no evidence of this condition during baseline. Length of follow-up observed was summarized by reason for censoring.

Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The median age of the IPF cohort (n = 7,298) was 62 years (interquartile range 55–72); 54.0% were male and 72.3% were white. The most frequently observed baseline covariates were use of corticosteroids (34.3%) and GERD therapies (31.2%; Table 1). Within the IPF subcohort (n = 3,930), 93.1% had claims for high-resolution computed tomography testing only, 0.8% had surgical lung biopsy claims only, and 6.1% had claims for both.

Restricting to patients with IPF diagnostic testing did not substantially affect cohort characteristics (Table 1). Characteristics of the IPF cohorts and subcohorts were

Table 1. Characteristics of newly diagnosed IPF cohort and IPF subcohort (ORD cohort entry: January 1, 2000 to December 31, 2013)

	Overall IPF cohort (*n* = 7,298)	IPF subcohort* (*n* = 3,930)
Age, years (continuous)		
Median (IQR)	62.0 (55.0–72.0)	62.0 (55.0–71.0)
Mean (SD)	63.2 (11.6)	62.7 (11.1)
Length of health plan membership prior to cohort entry (continuous, months)		
Median (IQR)	36.0 (21.9–60.5)	37.3 (22.7–63.6)
Mean (SD)	45.4 (30.5)	47.1 (31.4)
Age, years, *n* (%)		
40–44	358 (4.9)	185 (4.7)
45–49	595 (8.2)	313 (8.0)
50–54	840 (11.5)	464 (11.8)
55–59	1,128 (15.5)	636 (16.2)
60–64	1,361 (18.6)	825 (21.0)
65–69	811 (11.1)	447 (11.4)
70–74	633 (8.7)	337 (8.6)
75–79	751 (10.3)	355 (9.0)
80–84	661 (9.1)	297 (7.6)
≥85	160 (2.2)	71 (1.8)
Gender, *n* (%)		
Male	3,940 (54.0)	2,125 (54.1)
Female	3,358 (46.0)	1,805 (45.9)
Geographic area, *n* (%)		
Northeast	803 (11.0)	459 (11.7)
Midwest	1,982 (27.2)	1,112 (28.3)
South	3,551 (48.7)	1,856 (47.2)
West	950 (13.0)	497 (12.6)
Unknown	12 (0.2)	6 (0.2)
Race, *n* (%)		
White	5,280 (72.3)	2,843 (72.3)
African American	686 (9.4)	357 (9.1)
Hispanic/Latino	387 (5.3)	214 (5.4)
Asian	130 (1.8)	74 (1.9)
Other	815 (11.2)	442 (11.2)
Cohort entry period (quartiles), *n* (%)		
January 1, 2000 to June 30, 2003	1,255 (17.2)	614 (15.6)
July 1, 2003 to December 31, 2006	2,151 (29.5)	1,118 (28.4)
January 1, 2007 to June 30, 2010	2,431 (33.3)	1,364 (34.7)
July 1, 2010 to December 31, 2013	1,461 (20.0)	834 (21.2)
Patients with at least one diagnosis, procedure, or dispensing for each of the following during the 12-month baseline period, *n* (%)		
Any corticosteroid	2,504 (34.3)	1,579 (40.2)
NAC	69 (0.9)	43 (1.1)
Azathioprine	104 (1.4)	56 (1.4)
Cyclophosphamide	55 (0.8)	43 (1.1)
Open lung biopsies	171 (2.3)	171 (4.4)
Oxygen therapy	1,181 (16.2)	734 (18.7)
GERD therapy (e.g., H2 receptor blockers, proton pump inhibitors), *n* (%)	2,276 (31.2)	1,341 (34.1)
Anticoagulation/antiplatelet therapy	1,365 (18.7)	805 (20.5)
Amiodarone	228 (3.1)	131 (3.3)
Bleomycin	13 (0.2)	12 (0.3)
Nitrofurantoin	230 (3.2)	128 (3.3)
Methotrexate	49 (0.7)	29 (0.7)
Gold salts	1 (0.0)	0 (0.0)
Epstein-Barr virus	43 (0.6)	33 (0.8)
Hepatitis C	217 (3.0)	131 (3.3)
Bronchial lavage	367 (5.0)	334 (8.5)

* Restricted to the IPF cohort with ≥1 procedure related to testing for IPF during the 12-month baseline period. IPF, idiopathic pulmonary fibrosis; ORD, Optum Research Database; IQR, interquartile range; NAC, *N*-acetyl cysteine; GERD, gastroesophageal reflux disease.

Table 2. Healthcare utilization characteristics of the newly diagnosed IPF cohorts during the 12-month baseline period (ORD cohort entry: January 1, 2000 to December 31, 2013)

	Overall IPF cohort (*n* = 7,298), *n* (%)		IPF subcohort* (*n* = 3,930), *n* (%)	
No medication within 12 months of cohort entry	517 (7.1)		227 (5.8)	
One medication within 12 months of cohort entry	187 (2.6)		70 (1.8)	
Two medications within 12 months of cohort entry	281 (3.9)		123 (3.1)	
Three or more medications within 12 months of cohort entry	6,313 (86.5)		3,510 (89.3)	
Any hospitalization within 12 months of cohort entry (yes/no)	3,020 (41.4)		1,894 (48.2)	
Critical care evaluation and management	722 (9.9)		466 (11.9)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Physician visits†, *n*	13.5 (12.0)	11.0 (6.0–17.0)	15.6 (13.1)	12.0 (7.0–19.0)
Emergency department visits†, *n*	1.1 (2.6)	0.0 (0.0–1.0)	1.2 (2.8)	0.0 (0.0–1.0)
Inpatient stays, *n*	0.6 (1.0)	0.0 (0.0–1.0)	0.8 (1.1)	0.0 (0.0–1.0)
Inpatient days, *n*	4.3 (13.9)	0.0 (0.0–4.0)	5.5 (14.9)	0.0 (0.0–5.0)
Three-digit diagnosis codes, *n*	24.4 (13.1)	22.0 (15.0–31.0)	27.3 (13.3)	25.0 (18.0–34.0)
Surgical procedures†, *n*	4.2 (5.1)	3.0 (1.0–5.0)	5.0 (5.8)	3.0 (1.0–6.0)
Anesthesia procedures†, *n*	0.4 (0.9)	0.0 (0.0–1.0)	0.5 (1.0)	0.0 (0.0–1.0)
Unique drugs dispensed, *n*	9.8 (6.6)	9.0 (5.0–14.0)	10.6 (6.7)	10.0 (6.0–15.0)
Medical costs (US$)	4,757.8 (10,189.6)	1,999.6 (831.2–4,730.4)	6,332.9 (12,456.7)	2,873.5 (1,257.4–6,376.7)
Facility costs (US$)	14,908.5 (51,020.2)	2,474.6 (756.2–9,068.1)	20,249.2 (62,086.4)	4,029.3 (1,365.7–14,755.8)
Pharmacy costs (US$)	3,480.5 (6,887.7)	1,760.0 (496.4–4,000.1)	3,665.1 (6,779.0)	1,971.0 (599.3–4,313.3)
Total costs (US$)	23,146.8 (58,240.0)	7,985.4 (3,688.9–18,921.8)	30,247.1 (70,427.7)	10,687.1 (5,232.4–26,729.1)

* Restricted to the IPF cohort with ≥1 procedure related to testing for IPF during the 12-month baseline period. † One counted per day. IPF, idiopathic pulmonary fibrosis; ORD, Optum Research Database; IQR, interquartile range; US, United States.

similar by cohort entry stratum (i.e., entry before October 2011 compared to entry during or after October 2011), although a higher proportion of patients with later cohort entry had corticosteroid use during baseline (42.8 vs. 33.3% [IPF cohort] and 48.9 vs. 39.1% [IPF subcohort]; data not shown). These differences notwithstanding, all remaining results are reported without stratification due to the similarity of other characteristics by cohort entry time.

Within the IPF cohort and IPF subcohort, 41.4 and 48.2% of patients were hospitalized during baseline and 86.5 and 89.3% had dispensings for at least 3 unique medications, respectively (Table 2).

Baseline prevalence of the primary outcome conditions was low, ranging from 0.3% (*n* = 19) for PAH to 10.1% (*n* = 739) for lung cancer (Table 3). Among the secondary outcome conditions, prevalence ranged from 0.3% for gastrointestinal perforation to 55.3% for arterial hypertension (Table 3).

IRs of the nonfatal primary outcomes ranged from 2.1 per 1,000 py for PAH to 22.5 per 1,000 py for PH (Table 4). IRs for most outcomes were higher among the subcohort. Mortality was higher among the subcohort than the IPF cohort (106.4 per 1,000 py vs. 97.1 per 1,000 py). Patients with baseline occurrence of an event were not considered at risk for the event during follow-up.

The median length of time from the index diagnosis until censoring was 1.0 years (interquartile range 0.3–2.5; Table 5). For both the IPF cohort and subcohort, the most common reasons for censoring were the end of health plan enrollment (50.7 and 47.4%, respectively) and other known causes of ILD (19.6 and 23.5%, respectively). The most common censoring diagnoses were pulmonary eosinophilia (ICD-9 code 518.3: 21.8%) and other specified alveolar and parietoalveolar pneumonopathies (ICD-9 code 516.8: 13.8%; Table 6).

Discussion/Conclusion

This study used a large US healthcare insurance database to characterize health conditions among a cohort of patients with newly diagnosed IPF. Alternate cohort entry criteria were explored, including the requirement of claims for IPF testing and temporal changes in ICD diagnosis codes for IPF. The IPF cohort (diagnosis only) and

Table 3. Prevalence of comorbidities as identified during the 12-month baseline period for the newly diagnosed IPF cohorts (ORD cohort entry: January 1, 2000 to December 31, 2013)

	IPF cohort (*n* = 7,298)			IPF subcohort* (*n* = 3,930)		
	patients with condition	prevalence	95% CI	patients with condition	prevalence	95% CI
Primary outcomes						
Acute respiratory worsening of unknown cause	122	1.7	1.4–2.0	122	3.1	2.6–3.6
Pulmonary hypertension	172	2.4	2.0–2.7	120	3.1	2.5–3.6
Pulmonary arterial hypertension	19	0.3	0.1–0.4	13	0.3	0.2–0.5
Lung transplantation	36	0.5	0.3–0.7	15	0.4	0.2–0.6
Lung cancer	739	10.1	9.4–10.8	505	12.8	11.8–3.9
Acute myocardial infarction	124	1.7	1.4–2.0	75	1.9	1.5–2.3
Secondary outcomes						
GI perforation	19	0.3	0.1–0.4	9	0.2	0.1–0.4
Chronic renal failure/insufficiency	832	11.4	10.7–12.1	469	11.9	10.9–12.9
Hemorrhagic diathesis or coagulopathy	134	1.8	1.5–2.1	89	2.3	1.8–2.7
Venous thrombosis	381	5.2	4.7–5.7	251	6.4	5.6–7.2
Pulmonary embolism	178	2.4	2.1–2.8	115	2.9	2.4–3.5
Stroke (combined)	174	2.4	2.0–2.7	103	2.6	2.1–3.1
Cardiac arrhythmia	1,397	19.1	18.2–20.0	800	20.4	19.1–21.6
Congestive heart failure	1,376	18.9	18.0–19.8	789	20.1	18.8–21.3
Ischemic heart disease	1,930	26.4	25.4–27.5	1,091	27.8	26.4–29.2
Arterial hypertension	4,036	55.3	54.2–56.4	2,210	56.2	54.7–57.8
Neutropenia	126	1.7	1.4–2.0	101	2.6	2.1–3.1
Pneumonia	555	7.6	7.0–8.2	407	10.4	9.4–11.3
Sepsis	231	3.2	2.8–3.6	153	3.9	3.3–4.5
COPD	2,753	37.7	36.6–38.8	1,656	42.1	40.6–43.7
GERD	1,592	21.8	20.9–22.8	978	24.9	23.5–26.2
Type 2 diabetes mellitus	1,638	22.4	21.5–23.4	892	22.7	21.4–24.0
Obstructive sleep apnea	328	4.5	4.0–5.0	204	5.2	4.5–5.9
Bronchitis	2,610	35.8	34.7–36.9	1,533	39.0	37.5–40.5
Upper respiratory tract infection	834	11.4	10.7–12.2	471	12.0	11.0–13.0
Pulmonary rehabilitation	28	0.4	0.2–0.5	18	0.5	0.2–0.7
Acute coronary syndrome	226	3.1	2.7–3.5	128	3.3	2.7–3.8
Angina pectoris	317	4.3	3.9–4.8	177	4.5	3.9–5.2
Bleeding	616	8.4	7.8–9.1	348	8.9	8.0–9.7

* Restricted to the IPF cohort with ≥ 1 procedure related to testing for IPF during the 12-month baseline period. IPF, idiopathic pulmonary fibrosis; ORD, Optum Research Database; GI, gastrointestinal; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

subcohort (IPF testing prior to diagnosis) were similar, plausibly due to the fact that nearly half of the patients in the IPF cohort had an IPF testing procedure during baseline.

Slightly more patients were male (54.0%), in contrast to the common perception that IPF is much more prevalent in men [1]. It is, however, consistent with findings summarized by the American Thoracic Society [32], suggesting a more balanced prevalence across genders at younger ages; nearly 70% of the study population was younger than 70 years old. Furthermore, other diseases that mimic IPF are more common in women, as reflected by the slightly larger proportion of female patients that was censored due to other causes of ILD (22 vs. 18%; data not shown). During baseline, a substantial portion of patients had claims for "other and unspecified disorders of joints" (ICD-9 code 719: 25.2%; data not shown) or "other disorders of soft tissue" (ICD-9 code 729: 25.7%; data not shown), which were not in our initial exclusionary list. These patients may have had a nonspecific autoimmune disease that could be considered for exclusion in subsequent studies.

Direct comparisons to other studies are complicated by differences in cohort entry criteria, data sources, defi-

Table 4. Frequency and incidence of primary and secondary outcomes among the newly diagnosed IPF cohort and subcohort during follow-up, restricted to patients without each condition during baseline (ORD cohort entry: January 1, 2000 to December 31, 2013)

Outcomes*	Total patients eligible for outcome[†, ‡]	Patients, *n* (%)	Person-years	IR	95% CI
Primary outcomes					
Acute respiratory worsening of unknown cause	7,176	155 (2.2)	12,328	12.6	10.7–14.7
	3,808	84 (2.2)	6,013	14.0	11.1–17.3
Pulmonary hypertension	7,126	273 (3.8)	12,107	22.5	20.0–25.4
	3,810	156 (4.1)	5,911	26.4	22.4–30.9
Pulmonary arterial hypertension	7,279	26 (0.4)	12,569	2.1	1.4–3.0
	3,917	17 (0.4)	6,204	2.7	1.6–4.4
Lung transplantation[§]	7,262	75 (1.0)	12,468	6.0	4.7–7.5
	3,915	54 (1.4)	6,155	8.8	6.6–11.4
Lung cancer	6,559	200 (3.0)	11,353	17.6	15.3–20.2
	3,425	131 (3.8)	5,412	24.2	20.2–28.7
Acute myocardial infarction	7,174	169 (2.4)	12,266	13.8	11.8–16.0
	3,855	79 (2.0)	6,070	13.0	10.3–16.2
All-cause mortality	7,298	1,227 (16.8)	12,636	97.1	91.7–102.7
	3,930	665 (16.9)	6,248	106.4	98.5–114.8
Secondary outcomes					
GI perforation	7,279	44 (0.6)	12,563	3.5	2.5–4.7
	3,921	20 (0.5)	6,222	3.2	2.0–5.0
Chronic renal failure/insufficiency	6,466	720 (11.1)	10,687	67.4	62.5–72.5
	3,461	363 (10.5)	5,298	68.5	61.6–75.9
Hemorrhagic diathesis or coagulopathy	7,164	203 (2.8)	12,208	16.6	14.4–19.1
	3,841	107 (2.8)	6,017	17.8	14.6–21.5
Venous thrombosis	6,917	436 (6.3)	11,600	37.6	34.1–41.3
	3,679	234 (6.4)	5,708	41.0	35.9–46.6
Pulmonary embolism	7,120	216 (3.0)	12,178	17.7	15.5–20.3
	3,815	126 (3.3)	6,017	20.9	17.4–24.9
Stroke	7,124	233 (3.3)	12,115	19.2	16.8–21.9
	3,827	103 (2.7)	5,982	17.2	14.1–20.9
Cardiac arrhythmia	5,901	934 (15.8)	9,356	99.8	93.5–106.4
	3,130	489 (15.6)	4,546	107.6	98.2–117.5
Congestive heart failure	5,922	704 (11.9)	9,934	70.9	65.7–76.3
	3,141	339 (10.8)	4,921	68.9	61.7–76.6
Ischemic heart disease	5,368	773 (14.4)	8,470	91.3	84.9–97.9
	2,839	382 (13.5)	4,143	92.2	83.2–101.9
Arterial hypertension	3,262	965 (29.6)	4,217	228.9	214.6–243.8
	1,720	463 (26.9)	2,064	224.3	204.3–245.7
Neutropenia	7,172	119 (1.7)	12,310	9.7	8.0–11.6
	3,829	80 (2.1)	5,990	13.4	10.6–16.6
Pneumonia	6,743	460 (6.8)	11,393	40.4	36.8–44.2
	3,523	257 (7.3)	5,451	47.2	41.6–53.3
Sepsis	7,067	375 (5.3)	12,058	31.1	28.0–34.4
	3,777	204 (5.4)	5,923	34.4	29.9–39.5

Table 4 (continued)

Outcomes*	Total patients eligible for outcome[†, ‡]	Patients, *n* (%)	Person-years	IR	95% CI
COPD	4,545 2,274	1,060 (23.3) 556 (24.5)	6,713 3,004	157.9 185.1	148.5–167.7 170.0–201.1
GERD	5,706 2,952	1,032 (18.1) 545 (18.5)	8,331 3,997	123.9 136.3	116.4–131.7 125.1–148.3
Type 2 diabetes mellitus	5,660 3,038	545 (9.6) 288 (9.5)	9,051 4,462	60.2 64.5	55.3–65.5 57.3–72.4
Obstructive sleep apnea	6,970 3,726	368 (5.3) 214 (5.7)	11,614 5,699	31.7 37.5	28.5–35.1 32.7–42.9
Bronchitis	4,688 2,397	1,201 (25.6) 601 (25.1)	6,396 2,967	187.8 202.6	177.3–198.7 186.7–219.5
Upper respiratory tract infection	6,464 3,459	698 (10.8) 338 (9.8)	9,839 4,801	70.9 70.4	65.8–76.4 63.1–78.3
Pulmonary rehabilitation	7,270 3,912	43 (0.6) 29 (0.7)	12,521 6,176	3.4 4.7	2.5–4.6 3.1–6.7
Acute coronary syndrome	7,072 3,802	212 (3.0) 108 (2.8)	11,979 5,914	17.7 18.3	15.4–20.2 15.0–22.0
Angina pectoris	6,981 3,753	289 (4.1) 141 (3.8)	11,580 5,710	25.0 24.7	22.2–28.0 20.8–29.1
Bleeding	6,682 3,582	727 (10.9) 372 (10.4)	10,488 5,175	69.3 71.9	64.4–74.5 64.8–79.6
Major GI bleeding (upper)	7,206 3,870	108 (1.5) 53 (1.4)	12,359 6,100	8.7 8.7	7.2–10.6 6.5–11.4
Major GI bleeding (lower)	6,907 3,713	476 (6.9) 235 (6.3)	11,245 5,574	42.3 42.2	38.6–46.3 36.9–47.9
Hemorrhage of the rectum or anus	7,143 3,845	203 (2.8) 99 (2.6)	11,966 5,902	17.0 16.8	14.7–19.5 13.6–20.4
Blood in stool	7,166 3,850	201 (2.8) 106 (2.8)	12,104 5,983	16.6 17.7	14.4–19.1 14.5–21.4
Epistaxis	7,165 3,848	166 (2.3) 95 (2.5)	12,169 6,013	13.6 15.8	11.6–15.9 12.8–19.3
Hemorrhoids	7,120 3,834	215 (3.0) 113 (2.9)	11,961 5,896	18.0 19.2	15.7–20.5 15.8–23.0
Hemorrhoidal bleeding	7,267 3,910	49 (0.7) 28 (0.7)	12,499 6,168	3.9 4.5	2.9–5.2 3.0–6.6
Intracranial hemorrhage	7,264 3,910	54 (0.7) 28 (0.7)	12,549 6,196	4.3 4.5	3.2–5.6 3.0–6.5

* Occurrence of one outcome did not preclude the occurrence of another, with the exception of all-cause mortality, which censored all further potential outcomes for a patient. [†] For each condition, patients (and associated person-time) who had that condition identified during baseline were not considered at risk for incident events and were excluded. [‡] For each condition, IPF cohort data presented in first row, IPF subcohort data presented in following row. [§] For lung transplantation, patients with unilateral lung transplantation during the baseline period could be "at-risk" to receive another unilateral lung transplantation during the follow-up period; however, double lung transplantations during the baseline would preclude subsequent "at-risk" person-time during the follow-up period.

IPF, idiopathic pulmonary fibrosis; ORD, Optum Research Database; IR, incidence rate per 1,000 person-years; GI, gastrointestinal; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

Table 5. Length of follow-up for the newly diagnosed IPF cohorts (ORD cohort entry: January 1, 2000 to December 31, 2013)

Cohorts		Length of follow-up, years	
		mean (SD)	median (IQR)
IPF cohort	7,298 (100.0)	1.7 (1.9)	1.0 (0.3–2.5)
Reason for censoring			
End of study period	940 (12.9)	3.3 (2.7)	2.6 (1.0–4.9)
Death	1,227 (16.8)	1.3 (1.5)	0.8 (0.2–1.8)
End of health plan enrollment	3,702 (50.7)	1.8 (1.7)	1.2 (0.5–2.5)
Exclusion criteria observed	1,429 (19.6)	1.0 (1.4)	0.4 (0.1–1.3)
IPF subcohort*	3,930 (100.0)	1.6 (1.8)	0.9 (0.3–2.3)
Reason for censoring			
End of study period	479 (12.2)	3.1 (2.7)	2.5 (1.0–4.6)
Death	665 (16.9)	1.2 (1.4)	0.7 (0.2–1.6)
End of health plan enrollment	1,862 (47.4)	1.7 (1.7)	1.1 (0.5–2.4)
Exclusion criteria observed	924 (23.5)	0.9 (1.3)	0.3 (0.1–1.1)

* Restricted to the IPF cohort with ≥1 procedure related to testing for IPF during the 12-month baseline period.
IPF, idiopathic pulmonary fibrosis; ORD, Optum Research Database; IQR, interquartile range.

Table 6. Diagnosis codes most frequently resulting in exclusion[1] due to other causes of ILD during the follow-up period (ORD cohort entry: January 1, 2000 to December 31, 2013)[2]

Description	ICD-9 diagnosis code	IPF cohort[1]		IPF subcohort[2]	
		count of patients with this code on their first day of exclusion	%	count of patients with this code on their first day of exclusion	%
Pulmonary eosinophilia	518.3	318	21.8	200	21.3
Other specified alveolar and parietoalveolar pneumonopathies	516.8	201	13.8	143	15.2
Idiopathic interstitial pneumonia, not otherwise specified	516.30	123	8.4	84	8.9
Rheumatoid arthritis	714.0	103	7.1	55	5.8
Sarcoidosis	135.0	93	6.4	69	7.3
Unspecified allergic alveolitis and pneumonitis	495.9	88	6.0	67	7.1
Sacroiliitis not elsewhere classified	720.2	49	3.4	23	2.4
Asbestosis	501.0	45	3.1	26	2.8
Systemic sclerosis	710.1	39	2.7	27	2.9
Unspecified inflammatory polyarthropathy	714.9	37	2.5	28	3.0

[1] Patients may have had claims with more than one qualifying diagnosis on the first day of exclusion, so the total does not match the cohort size. [2] Restricted to the IPF cohort with ≥1 procedure related to testing for IPF during the 12-month baseline period.
ILD, interstitial lung disease; ORD, Optum Research Database; IPF, idiopathic pulmonary fibrosis.

nition of claims-based algorithms, and reliance on Social Security Administration information for death status. Nevertheless, the prevalence and incidence of many of the health conditions were lower than expected for an IPF population for several reasons. For example, claims-based algorithms differ across studies and may not precisely identify true cases; also, sicker patients may migrate out of commercial health plans onto government insurance, and therefore their health outcomes are not observed in this database. Perhaps most importantly, other studies excluded patients diagnosed with other causes of ILD during some period of time after cohort entry [33]. Future events should not be used to define cohort entry criteria [34]. Rather, those patients should be censored at

the time those exclusionary conditions are observed, whereas events and person-time accrual until that observed exclusion should be included in IR calculations. This may affect outcome IRs, as those patients contribute person-time to the denominator for all events prior to censoring.

In this study, 2.2% of the IPF cohort was observed to have an ARWUC episode during follow-up (IR: 12.6 per 1,000 py). The incidence of ARWUC is difficult to establish due to methodological variations between studies [35], and the numerous exclusionary comorbidities included in the definition (e.g., left heart failure, pulmonary embolism, and other identifiable causes of lung injury). In addition, dyspnea – an essential component of the clinical definition of acute exacerbations of IPF – may not be well captured in claims data, so this ARWUC algorithm is a proxy for clinically defined acute exacerbations and further validation is desirable. A retrospective study of 461 hospitalized patients with diagnosed IPF reported an annual incidence of 14.2% for clinically defined acute exacerbations [36]. However, the incidence of acute exacerbations in clinical trials is generally lower and may occur in 5–10% of patients with IPF per year [33].

Nearly 17% of patients died during follow-up (97.1 per 1,000 py), and a substantial percentage were censored for other reasons (19.6% for other causes of ILD and 50.7% due to end of health plan enrollment). However, from November 1, 2011, protected state records could no longer be disclosed; therefore, some deaths may not be available in the Death Master File, and mortality may be underestimated in this study. Among 622 patients randomized to placebo in the CAPACITY studies evaluating pirfenidone (n = 347) and the INSPIRE study evaluating interferon-γ1b (n = 275), the rate of claims-identified deaths due to all causes were 6.6% at 1 year and 13.7% at 2 years [37]. Similarly, during the 52-week treatment period of the INPULSIS-1 trial of nintedanib, 7.8% of patients in the placebo group died from any cause [38]. In a pooled analysis of the INPULSIS and TOMORROW trials, 8.3% of the patients in the placebo group died from any cause over 52 weeks [39]. However, drawing conclusions about the mortality of patients with IPF from clinical trial data is challenging. Patients in the "real-world," such as those in this study, tend to have more comorbidities, whereas those eligible for clinical trials tend to be fitter and are closely monitored, which may explain the lower death rates described above.

The percentage of patients with surgical lung biopsy (7% of the IPF subcohort) is lower than the 34% value reported by Behr et al. [40]. Reported dispensings of common IPF medications were also lower than expected. Many of these key medications are administered during inpatient stays, so utilization is not well captured in claims data due to the bundled payment mechanisms. Also, physician-provided samples and over-the-counter medications are not observed in claims data. Given that there were no efficacious or approved treatments available during these study periods, patients may have received additional healthcare and medications via clinical trials, which would not be observed in claims data.

This study has some key limitations. While claims data are extremely valuable to determine healthcare outcomes, claims databases have inherent limitations given the duration of follow-up, which can be restricted for example due to changes in health insurance enrollment. Particularly, severity of IPF could lead to disability or retirement, resulting in a shift to government insurance for some patients meaning outcomes that occur post-enrollment do not contribute to IRs. Also, the presence of a diagnosis code on a medical claim does not positively indicate the presence of disease, as diagnosis codes may be incorrect or included as rule-out criteria. This may be especially relevant in the current study due to the difficulty in diagnosing IPF when patients first present to the medical provider.

Validation by comparison to medical records may improve the accuracy of a claims-based algorithm for IPF case identification. Since these data were analyzed, 2 algorithms for the identification of patients with IPF in claims databases have been published. Each has limitations for application to the commercially insured population due to heavy weighting toward the elderly [41], and both have potentially low specificity [42].

The population in the Optum Research Database is representative of those commercially insured in the US; however, findings may be less generalizable to uninsured, publicly insured, older, or non-Caucasian populations. Lifestyle behaviors such as exercise, diet, smoking, and alcohol consumption are not captured in claims data and therefore cannot be described.

However, there are several advantages to this study. Unlike site- or registry-based studies that are typically limited in sample size, claims databases contain millions of lives, allowing for broader investigation of health outcomes within populations with rare conditions such as IPF. In addition, linkage of patient characteristics with pharmacy dispensings and medical encounters allows for more timely investigations and more completely captures the covered health services across the broad spectrum of healthcare providers. Defined health plan enrollment pe-

riods provide specific person-time accrual, allowing the calculation of IRs. These factors contribute to both cost and time efficiencies, while maintaining study validity and avoiding selection, observation, or recall biases inherent in clinical trials.

Efforts were made to minimize other potential sources of bias. When available, validated algorithms were used to identify particular health conditions. Where validated algorithms were unavailable, a comprehensive approach to literature reviews and descriptive analyses was undertaken to correctly identify outcomes or comorbidities.

In conclusion, this study characterized patients newly diagnosed with IPF and showed that there are a variety of health conditions observable among these patients. The most prominent primary outcomes were mortality, PH, and lung cancer, and for secondary outcomes, the highest IRs were observed for arterial hypertension, bronchitis, GERD, and chronic obstructive pulmonary disease. Alternate cohort entry definition, including IPF testing and changes in ICD-9 coding for IPF, had little impact on cohort baseline characteristics.

Statement of Ethics

Ethics approval was not required for this retrospective database analysis study.

Disclosure Statement

J.Y., R.G., and C.E. are employees of Optum Epidemiology. K.M.M. was an employee of Optum Epidemiology at the time the study was conducted. N.H. is an employee of Boehringer Ingelheim. D.B.B. and J.C. were employees of Boehringer Ingelheim at the time the study was conducted.

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This study was sponsored by a research contract between Optum and Boehringer Ingelheim. The authors were responsible for all content and editorial decisions, were involved in the study development, and approved the final version. As the guarantor of this work, Optum had full access to all the data in the study. As such, Optum takes responsibility for the integrity of the data, the accuracy of the data analysis and interpretation, and the final wording of the manuscript.

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