

Claims-based Prevalence of Disease Progression among Patients with Fibrosing Interstitial Lung Disease Other than Idiopathic Pulmonary Fibrosis in the United States

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Abstract

Rationale: Chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype is a clinical concept describing the broad group of ILDs characterized by progressive pulmonary fibrosis. The prevalence of progressive fibrotic ILDs other than idiopathic pulmonary fibrosis (IPF) is not well understood.

Objectives: We used a novel algorithm to estimate the prevalence range of disease progression among patients with non-IPF fibrotic ILD in a U.S. claims database.

Methods: This was a retrospective study including adults with commercial or Medicare Advantage with Part D (MAPD) insurance using administrative claims data from October 2015 to September 2019. Patients likely to have non-IPF fibrosing ILD with a progressive phenotype were identified via an algorithm that incorporated ILD-related diagnosis codes (excluding IPF) and claims-based proxies for fibrotic ILD progression, including pulmonary function tests, chest imaging, oral corticosteroid (OCS) medications, immunosuppressive medications, lung transplant, oxygen therapy, palliative care, and respiratory hospitalization. The prevalence range of non-IPF fibrotic ILD with progressive disease behavior was calculated using strict and lenient case definitions to account for potential imprecision in the progression proxies.

Results: Of nearly 9 million study-eligible patients, 17,136 were identified with non-IPF fibrosing ILD. The prevalence of disease progression per 10,000 (95% confidence interval) ranged from 12.14 (11.74–12.54) to 29.05 (28.43–29.67) over a mean observation time of 1.44 years for MAPD enrollees ($n = 14,686$), and from 0.89 (0.81–0.97) to 2.36 (2.24–2.48) over a mean observation time of 1.29 years for commercial enrollees ($n = 2,450$). Prevalence estimates increased with age for both insurance types. Among patients with progression, 4,097 met at least two progression proxies not considering OCS (strict case definition) and 9,946 met at least one progression proxy (lenient case definition). The mean (standard deviation) number of proxies met was 2.1 (1.3), and the most common individual proxies met (alone or in combination with other proxies) were OCS use (48.9%), respiratory hospitalization (44.2%), and oxygen therapy (44.1%).

Conclusions: This is among the first claims-based estimates of the prevalence of non-IPF chronic fibrosing ILD with a progressive phenotype. Our analysis indicates that this phenotype is rare in the overall population but increases substantially with increasing age.

Keywords: algorithms; interstitial lung diseases; pulmonary fibrosis; retrospective studies; United States

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Chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype is a relatively new clinical concept that has been introduced to describe the broad group of ILDs characterized by the presence of progressive pulmonary fibrosis (1). Clinical effects associated with this disease behavior include worsening respiratory symptoms, lung function decline, and early mortality (1). This categorization is based on the hypothesized shared pathophysiology underlying the development of progressive fibrosis among patients with these conditions (1, 2). These disorders display similar behavior regardless of the underlying cause of disease, with fibrosis continuing via a self-sustaining disease mechanism (3). Idiopathic pulmonary fibrosis (IPF) is the most common and well-defined progressive fibrosing ILD; however, there are a wide variety of ILDs that can develop a progressive fibrosing phenotype (4).

Estimating the prevalence of progressive fibrotic ILDs presents multiple challenges. Not only does progressive fibrotic ILD constitute a disease behavior as opposed to a specific disorder, but the potential specific disorders are numerous, individually rare, and diagnostically complex. As a result, the prevalence of non-IPF progressive fibrotic ILDs is not well defined. A recent systematic literature review synthesized multiple analyses of distinct progressive fibrotic ILD subtypes to estimate an overall prevalence of 2.8 per 10,000 persons in the United States (5). However, there are few published primary analyses of the prevalence of this group of disorders.

Offering large sample sizes and geographic diversity within the United States, administrative claims provide a powerful

data source for examining questions of real-world disease prevalence. However, using claims data to estimate the prevalence of chronic fibrosing ILD with a progressive phenotype is challenging because until recently, there was no specific diagnosis code for this disease behavior. Moreover, administrative claims contain neither information about patient symptoms nor results from pulmonary function tests (PFTs), chest imaging, or other procedures integral to diagnosing and monitoring progressive fibrotic ILD. The utilization of algorithms to identify patients with specific conditions from administrative claims data is a common approach to overcoming such barriers (6). Algorithms developed to identify patients with other chronic conditions when specific diagnosis codes and/or clinical test results are unavailable have yielded high positive predictive value (7, 8).

The present study was conducted to estimate the prevalence of disease progression among patients with non-IPF fibrotic ILD in a large U.S. claims database using a novel algorithm. To account for potential imprecision in the proxies used to identify progression, we developed a range of prevalence estimates by varying the number and types of proxies.

Methods

Study Design and Data Source

This was a retrospective observational study conducted using administrative claims data from the Optum Research Database (ORD) from October 1, 2015, through September 30, 2019 (study period). Administrative claims are submitted to insurance companies

by healthcare providers for reimbursement purposes and contain codes documenting the medical reasons for services delivered. Medical claims include diagnosis and procedure codes from the *International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM)*; Current Procedural Terminology or Healthcare Common Procedure Coding System codes; site of service codes; and other information. Pharmacy claims include drug name, National Drug Code, dosage form, drug strength, and fill date for outpatient pharmacy services.

The ORD contains deidentified claims data and linked enrollment information for individuals enrolled in U.S. commercial and Medicare Advantage health plans. Medicare Advantage health plans are available to individuals over the age of 65 or younger individuals with long-term disabilities and/or end-stage renal disease. Data in the ORD are geographically diverse across the United States and represent more than 73 million unique lives since 1993.

Because no identifiable protected health information was accessed in the conduct of this study, institutional review board approval or waiver of approval was not required.

Patient Selection

The study included commercial enrollees and Medicare Advantage with Part D (MAPD) beneficiaries 18 years of age or older with known sex, geographic region, and insurance type, identified between October 1, 2016, and September 30, 2019 (identification period) (Figure 1). Continuous health plan enrollment on and during the 12 months preceding September

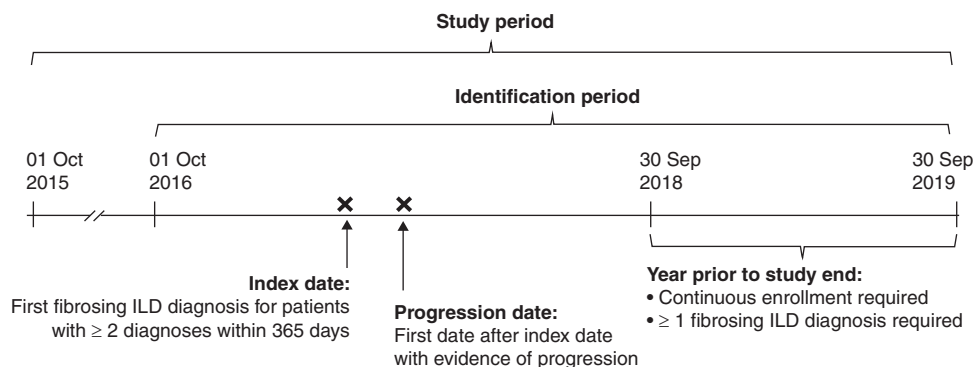


Figure 1. Study design schematic. The study was conducted using data from October 1, 2015, through September 30, 2019; patients were identified from October 1, 2016, through study end. The index date was the date of the first fibrosing interstitial lung disease diagnosis during the identification period for patients with at least two diagnoses within 365 days; the progression date was the first date with evidence of progression after the index date and before study end. ILD = interstitial lung disease.

Table 1. Administrative claims–based proxies for progression

Progression Proxy	Rationale
<ul style="list-style-type: none"> • At least 2 pulmonary function tests on different dates of service within 90 d of each other • At least 2 oxygen titration tests on different dates of service within 90 d of each other 	Sequential functional testing suggests suspicion of functional decline, which is indicative of disease progression (2, 20, 21).
<ul style="list-style-type: none"> • At least 2 inpatient or outpatient HRCT scans on different dates of service within 360 d of each other • At least 3 inpatient or outpatient chest CT scans on different dates of service within 360 d of each other 	Sequential imaging suggests suspicion of disease progression based on the extent of fibrosis (2, 21, 22).
<ul style="list-style-type: none"> • At least 1 pharmacy claim for an oral corticosteroid with a prednisone-equivalent dose greater than 20 mg/d • At least 1 pharmacy claim for a new immunosuppressive medication* 	Drug therapy suggests attempted management of observed disease progression (23).
<ul style="list-style-type: none"> • At least 1 claim for lung transplant (transplant procedure or posttransplant care) 	Lung transplant suggests that disease progression has been observed (21, 23).
<ul style="list-style-type: none"> • At least 1 claim for oxygen therapy • At least 1 claim for palliative care 	Oxygen therapy or palliative care suggests that disease progression has been observed, and in the case of palliative care, that patient is not a candidate for lung transplant (2, 21, 24).
<ul style="list-style-type: none"> • At least 1 respiratory hospitalization[†] 	Respiratory hospitalization suggests an acute exacerbation (a significant and rapid form of disease progression) or overall decline (21, 25, 26).

Definition of abbreviations: CT = computed tomography; HRCT = high-resolution computed tomography.

*Not received in the previous 12 months.

[†]Respiratory hospitalization was defined as a claim for an inpatient stay with a respiratory-related diagnosis code (Table E2) in the first position.

30, 2019, was required. Because there was not an ICD-10-CM code specific to progressive fibrotic ILD during the study period, a two-step algorithm was used to identify patients with fibrosing ILD who likely had a progressive phenotype.

Identification of fibrosing ILD. The first step in the algorithm was the identification of patients with non-IPF fibrosing ILD diagnoses using ICD-10-CM diagnosis codes selected by clinical experts (practicing pulmonologists) as being likely to indicate relevant non-IPF ILDs. These included codes for sarcoidosis, autoimmune ILDs, and hypersensitivity pneumonitis (Table E1 in the online supplement). Patients were required to have at least two non-IPF fibrosing ILD diagnoses on different dates within 365 days during the identification period. The date of the first non-IPF fibrosing ILD diagnosis was designated as the index date (Figure 1).

Identification of progressive phenotype. The second step in the algorithm was using claims-based proxies for fibrotic ILD progression to identify patients likely to have a progressive phenotype from among those with non-IPF fibrosing ILD. The proxies included PFTs, chest imaging, oral corticosteroid (OCS) medications,

immunosuppressive medications, lung transplant, oxygen therapy, palliative care, and respiratory hospitalization (Table E2) and were chosen in consultation with practicing pulmonologists (Table 1). Patient visits were analyzed for progression from the day after the index date through study end (September 30, 2019).

Because the progression proxies may be imprecise, the study was designed to provide prevalence ranges based on several definitions of progression rather than a single point estimate based on one definition. To achieve this, analyses were conducted to examine progression proxy patterns and test the effect of varying the number and types of proxies required in the progressive phenotype identification algorithm. Based on the results of these analyses, the algorithm was varied to generate more strictly defined prevalence estimates by not considering the OCS proxy, by requiring that patients meet any two different proxies, and by requiring that patients meet any two different proxies without considering the OCS proxy. The OCS proxy exclusion was conducted knowing that many patients may be prescribed high-dose OCS for other conditions. This was the most common proxy, met by approximately 49% of all individuals identified with fibrosing

ILD, either alone or in combination with other proxies. When at least two progression proxies were required, chest computed tomography (CT) and high-resolution CT (HRCT) imaging were considered as a single proxy to account for partial overlap in the codes used to identify these procedures in the claims data.

Study Measures and Statistical Analysis

The prevalence of non-IPF fibrotic ILD with progression was calculated per 10,000 people as of 30 September 2019, using strict and lenient case definitions to provide a prevalence range. The denominator included patients with continuous enrollment on and during the 12 months preceding September 30 2019; known sex, geographic region, and insurance type; and age 18 or older as of September 30, 2019 (Figure 2). The numerator included denominator-eligible individuals meeting the following additional criteria for evidence of non-IPF chronic fibrosing ILD with a progressive phenotype (Figure 2):

- At least two non-IPF fibrosing ILD diagnosis codes (Table E1) on different dates within 365 days of each other

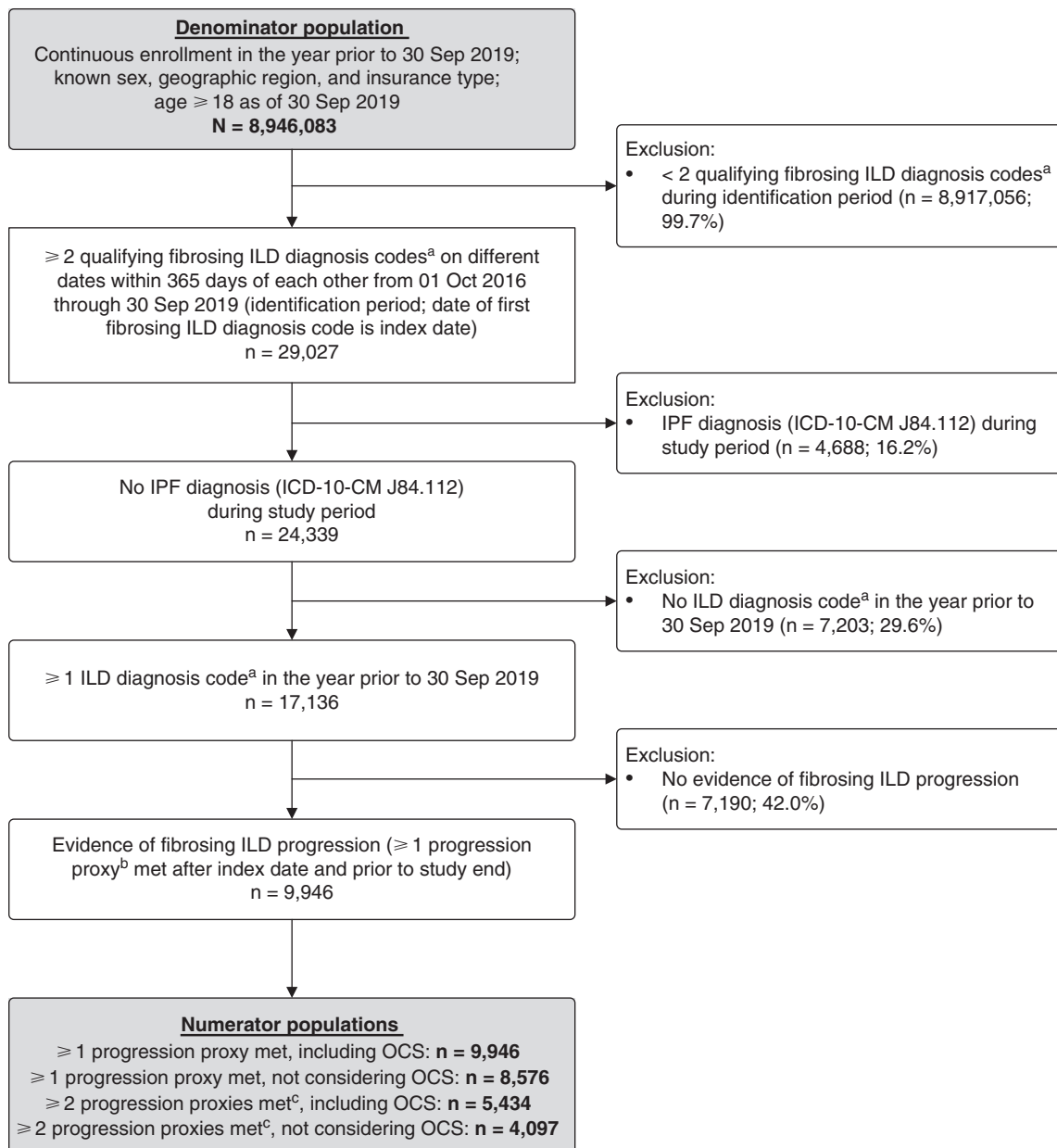


Figure 2. Identification of denominator and numerator populations: patient selection and attrition. ^aDiagnosis codes for fibrosing ILD are shown in Table E1. ^bProxies for fibrosing ILD progression include the following: at least one claim for lung transplant, respiratory-related hospitalization, oxygen therapy, or palliative care; at least two pulmonary function tests within 90 days; at least two high-resolution computed tomography scans within 360 days; at least three chest computed tomography scans within 360 days; at least two oxygen titration tests within 90 days; and at least one pharmacy claim for a new immunosuppressive medication or an oral corticosteroid with a prednisone-equivalent dose of more than 20 mg/d. ^cWhen at least two progression proxies were required, chest computed tomography and high-resolution computed tomography imaging were considered as a single proxy to account for overlap in the codes used to identify these procedures in the claims data. ILD = interstitial lung disease; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; IPF = idiopathic pulmonary fibrosis; OCS = oral corticosteroids.

during the identification period (the date of the first fibrosing ILD code was designated as the index date);

- No IPF diagnosis (ICD-10-CM J84.112) during the study period;
- At least one non-IPF fibrosing ILD diagnosis code (Table E1) in the 12

months preceding September 30, 2019; and

- Evidence of progressive phenotype (≥ 1 or ≥ 2 progression proxies [Table 1] for lenient and strict case definitions, respectively, met after the index date and prior to study end).

Prevalence results were presented separately for commercial and MAPD enrollees and stratified by sex and age group, with 95% confidence intervals (CIs) provided.

Progression proxy patterns were evaluated among patients with fibrotic ILD

identified as likely to have a progressive phenotype using the lenient case definition (≥ 1 progression proxy). Patterns assessed included the count of proxies met, the distribution of individual proxies met, and the distribution of mutually exclusive proxy combinations met. Mean and standard deviation were provided for the proxy count; numbers and percentages were provided for the distributions of individual proxies and proxy combinations.

All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc).

Results

Prevalence

Nearly 9 million patients were included in the denominator population (Figure 2). Of

these, a total of 17,136 had non-IPF fibrosing ILD, 4,097 met two or more progression proxies not considering OCS (strict definition), and 9,946 met at least one progression proxy (lenient definition) (numerator populations) (Figure 2).

Among individuals enrolled in MAPD and identified with non-IPF fibrosing ILD ($n = 14,686$), a mean of 1.44 years of continuous enrollment were available after the index date to observe progression. Prevalence of the progressive phenotype per 10,000 (95% CI) ranged from 12.14 (11.74–12.54) for those meeting at least two progression proxies not considering OCS to 29.05 (28.43–29.67) for those meeting at least one progression proxy including OCS (Table 2).

Among individuals enrolled in commercial insurance and identified with

non-IPF fibrosing ILD ($n = 2,450$), a mean of 1.29 years of continuous enrollment were available after the index date to observe progression. Prevalence of the progressive phenotype per 10,000 (95% CI) ranged from 0.89 (0.81–0.97) for those meeting at least two progression proxies not considering OCS to 2.36 (2.24–2.48) for those meeting at least one progression proxy including OCS (Table 3).

The prevalence of disease progression among patients with fibrotic ILD increased with age for both insurance types. Using the strictest case definition, the prevalence per 10,000 among MAPD beneficiaries was 8.67 (8.03–9.35) for ages 60–69, 11.17 (10.61–11.75) for ages 70–79, and 18.23 (17.21–19.31) for ages 80 and above (Table 2). Among patients with commercial insurance, women had slightly higher

Table 2. Prevalence of disease progression among Medicare enrollees with non-IPF fibrosing interstitial lung disease

Category	Number at Risk*	≥ 2 Progression Proxies ^{†‡}				≥ 1 Progression Proxy [†]			
		Not Considering OCS Proxy		Including OCS Proxy		Not Considering OCS Proxy		Including OCS Proxy	
		Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)
Overall	2,936,720	3,564	12.14 (11.74–12.54)	4,686	15.96 (15.50–16.42)	7,415	25.25 (24.68–27.87)	8,530	29.05 (28.43–29.67)
Sex									
Male	1,239,487	1,694	13.67 (13.02–14.33)	2,229	17.98 (17.24–18.74)	3,571	28.81 (27.87–29.77)	4,118	33.22 (32.22–34.25)
Female	1,697,233	1,870	11.02 (10.52–11.53)	2,457	14.48 (13.91–15.06)	3,844	22.65 (21.94–23.38)	4,412	26.00 (25.23–26.77)
Age									
18–39	18,218	9	4.94 (2.26–9.38)	13	7.13 (3.80–12.20)	19	10.43 (6.28–16.28)	22	12.08 (7.57–18.28)
40–49	40,724	49	12.03 (8.90–15.90)	57	14.00 (10.60–18.13)	69	16.94 (13.18–21.44)	78	19.15 (15.14–23.90)
50–59	134,391	180	13.39 (11.51–15.50)	244	18.16 (15.95–20.58)	338	25.15 (22.54–27.98)	383	28.50 (25.72–31.50)
60–69	775,141	672	8.67 (8.03–9.35)	893	11.52 (10.78–12.30)	1,368	17.65 (16.73–18.61)	1,612	20.80 (19.79–21.84)
70–79	1,323,328	1,478	11.17 (10.61–11.75)	1,979	14.95 (14.30–15.63)	3,074	23.23 (22.42–24.06)	3,557	26.88 (26.00–27.78)
80+	644,918	1,176	18.23 (17.21–19.31)	1,500	23.26 (22.10–24.46)	2,547	39.49 (37.98–41.05)	2,878	44.62 (43.01–46.28)
Age, Male									
18–39	9,189	3	3.26 (0.67–9.54)	5	5.44 (1.77–12.69)	6	6.53 (2.40–14.21)	8	8.71 (3.76–17.15)
40–49	18,687	26	13.91 (9.09–20.38)	28	14.98 (9.96–21.65)	34	18.19 (12.60–25.41)	37	19.80 (13.94–27.28)
50–59	62,077	72	11.60 (9.08–14.60)	98	15.79 (12.82–19.24)	140	22.55 (18.97–26.61)	156	25.13 (21.34–29.39)
60–69	336,404	278	8.26 (7.32–9.29)	386	11.47 (10.36–12.68)	617	18.34 (16.92–19.84)	744	22.12 (20.56–23.76)
70–79	566,541	735	12.97 (12.05–13.94)	965	17.03 (15.98–18.14)	1,523	26.88 (25.55–28.27)	1,762	31.10 (29.67–32.59)
80+	246,589	580	23.52 (21.65–25.51)	747	30.29 (28.16–35.54)	1,251	50.73 (47.97–53.61)	1,411	57.22 (54.28–60.28)
Age, Female									
18–39	9,029	6	6.65 (2.44–14.46)	8	8.86 (3.83–17.45)	13	14.40 (7.67–24.61)	14	15.50 (8.48–26.00)
40–49	22,037	23	10.44 (6.62–15.66)	29	13.16 (8.81–18.89)	35	15.88 (11.07–22.08)	41	18.61 (8.48–26.00)
50–59	72,314	108	14.93 (12.25–18.03)	146	20.19 (17.05–23.74)	198	27.38 (23.70–31.47)	227	31.40 (27.45–35.74)
60–69	438,737	394	8.98 (8.12–9.91)	507	11.56 (10.57–12.61)	751	17.12 (15.91–18.38)	868	19.78 (18.49–21.14)
70–79	756,787	743	9.82 (9.12–10.55)	1,014	13.40 (12.59–14.25)	1,551	20.49 (19.49–21.54)	1,795	23.72 (22.63–24.84)
80+	398,329	596	14.96 (13.79–16.21)	753	18.90 (17.58–20.30)	1,296	32.54 (30.79–34.35)	1,467	36.83 (34.97–38.76)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; OCS = oral corticosteroids.

*Number at risk was among patients who had continuous enrollment with medical and pharmacy coverage during the continuous enrollment period and who were aged ≥ 18 yr with known sex and geographic region at study end.

[†]Proxies for fibrosing ILD progression include the following: at least one claim for lung transplant, respiratory-related hospitalization, oxygen therapy, or palliative care; at least two pulmonary function tests within 90 days; at least two HRCT scans within 360 days; at least three chest CT scans within 360 days; at least two oxygen titration tests within 90 days; and at least one pharmacy claim for a new immunosuppressive medication or an oral corticosteroid with a prednisone-equivalent dose of more than 20 mg/d.

[‡]When at least two progression proxies were required, chest CT and HRCT scans were considered as a single proxy to account for overlap in the codes used to identify these procedures in the claims data.

Table 3. Prevalence of disease progression among commercial insurance enrollees with non-IPF fibrosing interstitial lung disease

Category	Number at Risk*	≥2 Progression Proxies ^{†‡}				≥1 Progression Proxy [†]			
		Not Considering OCS Proxy		Including OCS Proxy		Not considering OCS proxy		Including OCS proxy	
		Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)	Events	Prevalence per 10,000 (95% CI)
Overall	6,009,363	533	0.89 (0.81–0.97)	748	1.24 (1.16–1.34)	1,161	1.93 (1.82–2.05)	1,416	2.36 (2.24–2.48)
Sex									
Male	3,068,327	249	0.81 (0.71–0.92)	343	1.12 (1.00–1.24)	552	1.80 (1.65–1.96)	669	2.18 (2.02–2.35)
Female	2,941,036	284	0.96 (0.86–1.08)	405	1.38 (1.25–1.52)	609	2.07 (1.91–2.24)	747	2.54 (2.36–2.73)
Age									
18–39	2,574,993	31	0.12 (0.08–0.17)	40	0.16 (0.11–0.21)	59	0.23 (0.17–0.29)	80	0.31 (0.25–0.39)
40–49	1,281,403	57	0.44 (0.34–0.58)	93	0.72 (0.58–0.89)	134	1.05 (0.88–1.24)	178	1.39 (1.19–1.61)
50–59	1,308,552	138	1.05 (0.89–1.25)	197	1.51 (1.30–1.73)	299	2.28 (2.03–2.56)	367	2.80 (2.53–3.11)
60–69	729,766	172	2.36 (2.02–2.74)	240	3.29 (2.88–3.73)	380	5.21 (4.70–5.76)	468	6.41 (5.84–7.02)
70–79	82,494	78	9.46 (7.47–11.80)	106	12.85 (10.52–15.54)	154	18.67 (15.84–21.86)	176	21.33 (18.30–24.73)
80+	32,155	57	17.73 (13.43–22.96)	72	22.39 (17.52–28.19)	135	41.98 (35.21–49.67)	147	45.72 (38.64–53.71)
Age, Male									
18–39	1,320,937	11	0.08 (0.04–0.15)	13	0.10 (0.05–0.17)	21	0.16 (0.10–0.24)	28	0.21 (0.14–0.31)
40–49	652,334	28	0.43 (0.28–0.62)	42	0.64 (0.46–0.87)	63	0.96 (0.74–1.23)	77	1.18 (0.93–1.47)
50–59	661,808	46	0.70 (0.51–0.93)	70	1.06 (0.82–1.34)	112	1.69 (1.39–2.04)	140	2.11 (1.78–2.50)
60–69	374,984	87	2.32 (1.86–2.86)	116	3.09 (2.56–3.71)	191	5.09 (4.40–5.87)	237	6.32 (5.54–7.18)
70–79	43,692	45	10.30 (7.51–13.78)	61	13.96 (10.68–17.93)	87	19.91 (15.95–24.56)	99	22.66 (18.42–27.58)
80+	14,572	32	21.96 (15.03–30.99)	41	28.14 (20.20–38.15)	78	53.53 (42.33–66.76)	88	60.39 (48.46–74.35)
Age, Female									
18–39	1,254,056	20	0.16 (0.10–0.25)	27	0.22 (0.14–0.31)	38	0.30 (0.21–0.42)	52	0.41 (0.31–0.54)
40–49	629,069	29	0.46 (0.31–0.66)	51	0.81 (0.60–1.07)	71	1.13 (0.88–1.42)	101	1.61 (1.31–1.95)
50–59	646,744	92	1.42 (1.15–1.74)	127	1.96 (1.64–2.34)	187	2.89 (2.49–3.34)	227	3.51 (3.07–4.00)
60–69	354,782	85	2.39 (1.91–2.96)	124	3.50 (2.91–4.17)	189	5.33 (4.59–6.14)	231	6.51 (5.70–7.41)
70–79	38,802	33	8.50 (5.85–11.94)	45	11.60 (8.46–15.52)	67	17.27 (13.38–21.92)	77	19.84 (15.66–24.80)
80+	17,583	25	14.22 (9.20–20.98)	31	17.63 (11.98–25.02)	57	32.42 (24.56–41.98)	59	33.56 (25.55–43.26)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; OCS = oral corticosteroids.

*Number at risk was among patients who had continuous enrollment with medical and pharmacy coverage during the continuous enrollment period and who were aged at least 18 years with known sex and geographic region at study end.

†Proxies for fibrosing ILD progression include the following: at least one claim for lung transplant, respiratory-related hospitalization, oxygen therapy, or palliative care; at least two pulmonary function tests within 90 days; at least two HRCT scans within 360 days; at least three chest CT scans within 360 days; at least two oxygen titration tests within 90 days; and at least one pharmacy claim for a new immunosuppressive medication or an oral corticosteroid with a prednisone-equivalent dose of more than 20 mg/d.

‡When at least two progression proxies were required, CT and HRCT were considered as a single proxy to account for overlap in the codes used to identify these procedures in the claims data.

prevalence per 10,000 than men (range 0.97 [0.86–1.08] to 2.54 [2.36–2.73] for women, and range 0.81 [0.71–0.92] to 2.18 [2.02–2.35] for men) (Table 3). However, this trend was reversed in the MAPD group (range 11.02 [10.52–11.53] to 26.00 [25.23–26.77] for

women, and range 13.67 [13.02–14.33] to 33.22 [32.22–34.25] for men) (Table 2).

Progression Proxy Patterns

Among the total patient population identified as likely to have a progressive

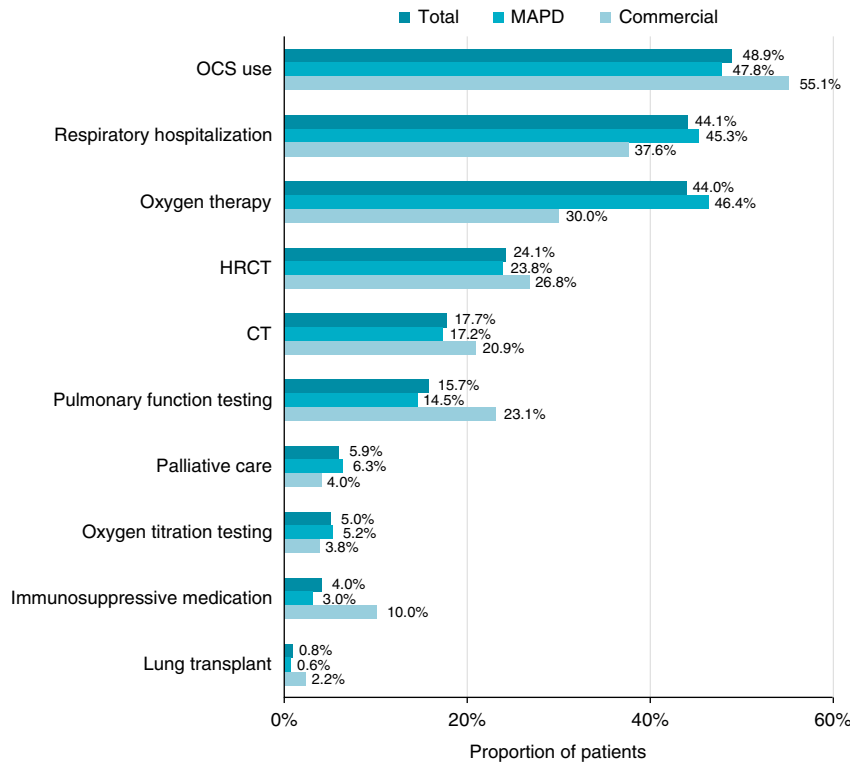
phenotype, the mean (standard deviation) number of progression proxies met was 2.1 (1.3), with the majority of patients (56.2%) meeting 2 or more proxies (Table 4). The most common individual proxies met (alone or in combination with other proxies) were OCS use (48.9% of patients), respiratory hospitalization (44.2% of patients), and oxygen therapy (44.1% of patients) (Figure 3A). The most common mutually exclusive proxy combinations met were OCS use only (13.8% of patients), oxygen therapy only (10.3%), respiratory hospitalization only (9.1%), and OCS use + oxygen therapy + respiratory hospitalization (5.1%) (Figure 3B). Proxy patterns when examined by insurance type were generally similar for patients with commercial versus MAPD insurance, with some exceptions; for example,

Table 4. Count of proxies among patients meeting progression criteria

Progression Proxies Met	Total N = 9,946	MAPD n = 8,530	Commercial n = 1,416
Count of proxies, mean (SD)	2.1 (1.3)	2.1 (1.3)	2.1 (1.4)
Count of proxies, n (%)			
1	4,352 (43.8)	3,709 (43.5)	643 (45.4)
2	2,609 (26.2)	2,259 (26.5)	350 (24.7)
3	1,512 (15.2)	1,324 (15.5)	188 (13.3)
4	836 (8.4)	714 (8.4)	122 (8.6)
5	409 (4.1)	340 (4.0)	69 (4.9)
6+	228 (2.3)	184 (2.2)	44 (3.1)

Definition of abbreviations: MAPD = Medicare Advantage with Part D; SD = standard deviation.

A Individual proxies met (alone or in combination).



B Mutually exclusive proxy combinations met. Of 309 unique proxy combinations observed, the 10 most common are shown.

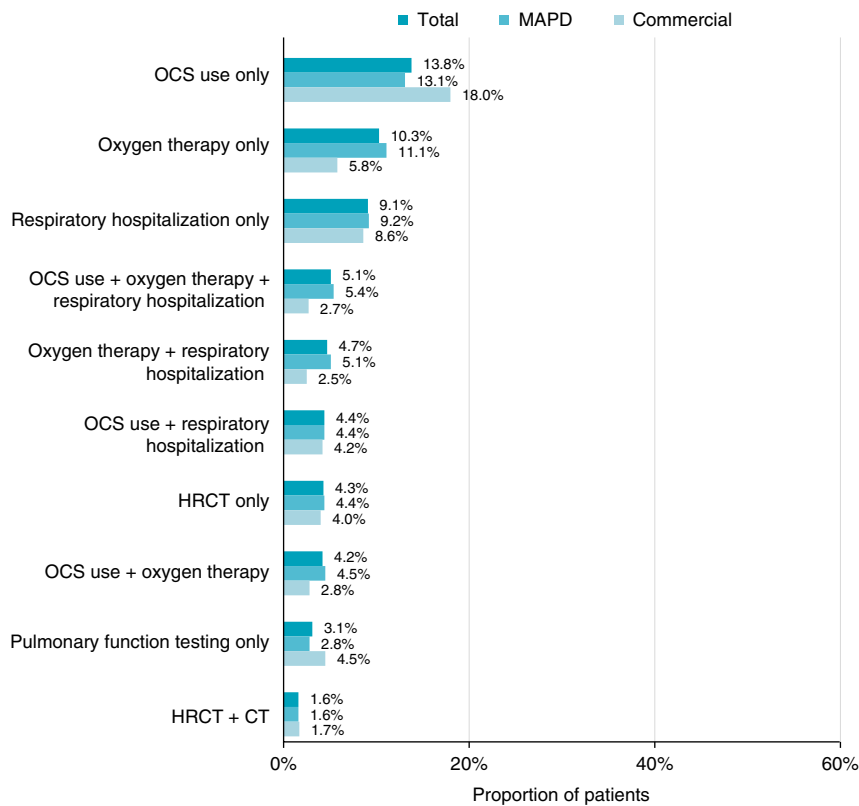


Figure 3. Proxy patterns among patients meeting progression criteria (A) Individual proxies met (alone or in combination). (B) Mutually exclusive proxy combinations met. Of 309 unique proxy combinations observed, the 10 most common are shown. CT = computed tomography; HRCT = high-resolution computed tomography; MAPD = Medicare Advantage with Part D; OCS = oral corticosteroids.

immunosuppressive medication use was numerically more common among patients with commercial insurance, whereas oxygen therapy was more common among MAPD enrollees.

Discussion

This retrospective observational analysis is among the first claims-based estimates of the prevalence of progressive disease behavior among patients with non-IPF chronic fibrosing ILD. Our study builds upon previous attempts to estimate the prevalence of progressive fibrosing ILD using a variety of other data sources (5, 9) and provides a valuable addition to the evolving understanding of this clinical concept.

The prevalence of disease progression among patients with non-IPF fibrotic ILD was estimated to range from 0.89 per 10,000 to 2.36 per 10,000 for those with commercial insurance, similar to the 2.8 per 10,000 estimated by Olson and colleagues in a systematic literature review (5). This prevalence is quite low compared with more common lung conditions such as chronic obstructive pulmonary disease and asthma, which have prevalence estimates of approximately 483 per 10,000 and 757 per 10,000, respectively, in the United States (10–12). Because IPF represents a more extensively studied progressive fibrotic ILD, its prevalence, estimated at 0.7 per 10,000 in a U.S. commercially insured population in 2010 (13), provides valuable context for estimates of progressive behavior in non-IPF fibrotic ILD. Our prevalence estimate is closest to that for IPF when the strictest case definition is used but is higher when using the most lenient case definition, highlighting the impact of progression proxy choice on prevalence estimates.

Notably, the estimated prevalence of progressive disease was higher among MAPD enrollees in the present study, ranging from 12.14 per 10,000 to 29.05 per 10,000. This is comparable to the 14.6 per 10,000 prevalence of IPF estimated in a previous study of a U.S. Medicare population in 2011 (14). Given that fibrosing ILDs become more common with age (9) and prevalence estimates increased with age in the present study, these findings may be partly attributable to higher mean age among MAPD beneficiaries (*see* Table E3 for age distribution). However, prevalence estimates were remarkably high even among younger

age groups in the MAPD population compared with commercial enrollees. Although most Medicare beneficiaries are over the age of 65 (15), individuals of any age who have long-term disability are also eligible for the program. As severe lung disease can result in substantial disability, we speculate that patients with progressive disease who qualified for Medicare before the age of 65 likely contributed to the high prevalence observed among younger individuals in the MAPD population.

Prevalence ranges based on several definitions of progression were provided in this study to account for the expected imprecision in the progression proxies—for instance, OCS are prescribed for a variety of conditions, immunosuppressants may be initiated to manage underlying autoimmune disease rather than as a treatment for fibrosis, and respiratory hospitalization may be due to reasons other than fibrosis progression. The ability of the proxies to identify progressive disease accurately is also dependent on coding and utilization patterns that may be affected by factors unrelated to clinical progression; for example, healthcare providers may have different protocols for the routine frequency and timing of diagnostic procedures. Furthermore, patients who tend to have higher overall healthcare utilization, such as older individuals and those with more comprehensive health insurance coverage (16, 17), may be more likely to meet nonspecific progression proxies. Validation studies utilizing electronic health record (EHR) data (e.g., medical charts abstracted manually and/or using natural language processing) should be conducted to evaluate algorithm performance. In particular, it is important to determine whether patients identified via the claims-based proxies have EHR evidence of lung function decline and radiographic progression of fibrosis, the hallmark features of progressive fibrosing ILD (2).

It should also be noted that some of the progression proxies—in particular, PFTs and HRCT/CT—are involved in routine ILD disease monitoring and therefore may identify patients with ILD who are being closely followed but do not have progressive disease. To ensure that use of these proxies did not artificially inflate our prevalence estimates, we conducted sensitivity analyses in which 1) the PFT and HRCT/CT proxies were excluded, and 2) a composite proxy was created, comprising two PFTs within 90 days combined with two HRCT scans within the

same year. The results of these sensitivity analyses (Tables E4 and E5) were not appreciably different from those of the original analysis. Our estimates may also have been impacted by follow-up time, which averaged 1.44 years and 1.29 years for the MAPD and commercially insured populations, respectively. Given that reported diagnostic criteria for progressive fibrosing ILD generally specify progression within 2 years of fibrosing ILD diagnosis (2, 18), more patients may have been identified with progression if the observation time had been longer.

This study used a series of simple proxy variations to adjust the strictness of the case definition for progressive fibrotic ILD, but many other variations are possible, such as changing the dosage cutoff for OCS or changing the time interval for proxies that required multiple events to help account for real-world factors that can affect scheduling. For example, receipt of 2 HRCT scans within 360 days was considered a proxy for progression in the present study, but adjusting this proxy to use a 330-day window may make the case definition more strict by excluding patients who received a routine annual scan that occurred a few weeks early.

Limitations

This study has several limitations. First, our analysis lacked access to information on lung function decline and radiographic progression of fibrosis. We were therefore unable to definitively ascertain whether patients identified via the claims-based proxies indeed had progressive fibrosing ILD. Our analysis was further complicated by the lack of a specific diagnosis code for progressive fibrotic ILD at the time the study was conducted. Approximately 85% of patients in our study population were included on the basis of ICD-10-CM code J8410, which is not specific for fibrotic disease and may have affected the results. Additional studies are therefore required to validate the algorithm against EHR data, which contain clinical information that is unavailable in administrative claims. The new ICD-10-CM diagnosis code for progressive fibrotic ILD that was recently announced (19) may also facilitate patient identification in future studies.

Second, diagnosis codes must be recorded correctly for the fibrosing ILD algorithm to identify patients accurately. Error will be introduced if diagnosis codes are coded incorrectly or included as a rule-

out diagnosis. To minimize this error, we required patients to have at least two qualifying diagnosis codes on different dates of service within 365 days of each other.

Third, because progressive fibrosing ILD has conventionally been defined as disease progression despite standard care, it is possible that some patients whose fibrosis stabilized after treatment may have been misclassified with progression on the basis of the OCS and immunosuppressant proxies. Given the frequency of OCS use, we accounted for this potential limitation by providing prevalence ranges based on inclusion or exclusion of the OCS proxy. Although we did not include a similar offset for the immunosuppressant proxy, the percentage of patients identified on the basis of this criterion was small; therefore, it is

unlikely that the results were substantially affected.

Finally, because this study was conducted among patients with commercial or MAPD insurance, the results may be less generalizable to other populations (e.g., uninsured individuals or those enrolled in Medicaid or fee-for-service insurance plans).

Conclusion

Chronic fibrosing ILD with a progressive phenotype is a relatively new clinical concept, and there are minimal data available regarding the prevalence of non-IPF forms. This study used a claims-based algorithm to estimate ranges of disease progression prevalence among patients with non-IPF fibrotic ILD in the United States. Our findings indicate that this disease behavior is rare in the overall population;

however, there is a substantially higher prevalence with increasing age, reflected among both patients with MAPD and those with commercial insurance. Future work will focus on better understanding the performance of these algorithms and on applying them to assess the disease burden in this patient population. ■

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