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Impact of Idiopathic Pulmonary Fibrosis on Longitudinal Health-care Utilization in a Community-Based Cohort of Patients

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BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a rare, chronic lung disease associated with substantial symptom burden, morbidity, and cost. Delivery of high-quality effective care in IPF requires understanding health-care resource utilization (HRU) patterns; however, longitudinal data from real-world populations are limited.

RESEARCH QUESTION: This study aimed to define HRU attributable to IPF by evaluating a longitudinal cohort of community patients with IPF compared with matched control subjects.

STUDY DESIGN AND METHODS: Incident IPF cases were identified in the Kaiser Permanente Northern California electronic health records (2000-2015) using case-validated code-based algorithms. IPF cases were compared with matched control subjects by age, sex, and length of enrollment. Annual rates of HRU measures were assessed during the 5 years pre- and postdiagnosis. Poisson generalized estimating equations were used to estimate adjusted case-control differences in HRU. IPF treatment trends were assessed before and after the availability of IPF-specific medications.

RESULTS: A total of 691 IPF cases were identified and matched with 3,452 control subjects. Adjusted rates of all diagnostic procedures were significantly increased ($P < .001$) for IPF cases compared with control subjects in both the pre- and postindex periods, including chest CT scans (pre-relative risk [RR], 80.35; post-RR, 32.79), 6-min walk tests (pre-RR, 20.81; post-RR, 34.49), and pulmonary function tests (pre-RR, 9.50; post-RR, 13.24). All-cause hospitalizations (pre-RR, 1.42; post-RR, 2.33) and outpatient visits (pre-RR, 1.22; post-RR, 1.80) were significantly higher among cases compared with control subjects during both the preindex ($P < .05$) and postindex ($P < .001$) periods. We observed use of immunosuppressive and IPF-specific therapies prior to diagnosis, and high rates of corticosteroid use before and after diagnosis.

INTERPRETATION: This study defines a marked increase in HRU in patients with IPF compared with control subjects, with accelerated use beginning at least 1 year prediagnosis and elevated use sustained over the following 5 years. To our knowledge, this is the first study to evaluate longitudinal medication trends in IPF. Collectively, this information is foundational to advancing IPF care delivery models and supporting clinical decision-making.

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KEY WORDS: health-care resource utilization; idiopathic pulmonary fibrosis; interstitial lung disease; real-world evidence

ABBREVIATIONS: HRU = health-care resource utilization; IPF = idiopathic pulmonary fibrosis; KPNC = Kaiser Permanente Northern California; RR = relative risk

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Idiopathic pulmonary fibrosis (IPF) is a life-limiting condition, characterized by chronic progressive pulmonary disease resulting in respiratory failure and premature death. IPF currently affects approximately 5 million individuals worldwide, including 200,000 in the United States, with studies demonstrating an increasing incidence.[1-3] Diagnosis and evaluation of IPF is associated with high health-care resource utilization (HRU) and direct medical costs, reflective of the extensive clinical data needed for diagnostic accuracy and the high cost of therapy.[4-6]

Overall, patients with IPF report a high symptom burden and substantial morbidity, require regular monitoring and outpatient follow-up, and may experience episodes of acute worsening requiring hospitalization or ICU-level management; a small proportion of patients will undergo lung transplantation. Currently, there is no cure for IPF; however, there are two Food and Drug Administration-approved medications that slow the progression of disease.[7,8] Metrics for chronic care delivery in IPF currently do not exist, and significant variation in long-term management are observed.

HRU management is a crucial element in advancing the delivery of high-quality care in diseases such as IPF, and requires a data-driven approach. Characterizing patterns in HRU in patients with IPF before and after diagnosis will provide insights into the burden of illness and common care pathways. Defining longitudinal HRU is an important first step in identifying areas of practice heterogeneity and inefficiency, developing decision-making support for patients and providers, and improving the health-care experience and value.

Kaiser Permanente Northern California (KPNC) is a nonprofit, integrated health-care delivery organization which includes 21 medical centers, 60 outpatient facilities, 110 outpatient pharmacies, and a centralized laboratory. KPNC has a current membership of 4.5 million people, accounting for 30% of the population in a 14-county area. The member population is racially and ethnically diverse with high retention rates. KPNC offers an innovative and unique opportunity to study a community-based cohort of patients with IPF with comprehensive follow-up. Studying IPF-associated HRU in a real-world setting provides the opportunity to produce high-quality, generalizable results that can be rapidly disseminated across health systems. The objective of this study was to examine real-world differences in longitudinal HRU and treatment attributable to IPF by comparing patients with IPF to matched control subjects.

Methods

Institutional review boards at the University of California, San Francisco (No. 14-15459) and the KPNC Division of Research (No. CN-15-2126-H_05) approved the study protocol.

The source population was the KPNC member population from January 1, 2000, through December 31, 2015. A start date of January 1, 2000, was selected to include patients diagnosed after publication of the first international consensus guidelines on IPF. Cases of IPF were identified using two code-based algorithms, termed the broad and narrow algorithms (e-Fig 1). Both were based on previously published algorithms using the *International Classification of Diseases, Ninth Revision* and the *International Classification of Diseases, Ninth Revision, Clinical Modification*.[2,3,9-11] Briefly, the broad algorithm required cases to be ≥ 18 years of age and to have at least one claim for a specific diagnostic code for IPF (516.3 and/or 516.31). The narrow algorithm required cases to be ≥ 50 years of age, to have at least two claims for a specific diagnostic code for IPF at least 1 month apart, and to have a chest CT scan procedural code on or before the first IPF-specific diagnostic code. In both the broad and narrow definitions, the date of the first occurrence of the IPF-specific diagnostic code was considered the index date. Cases were excluded for any one claim for an alternative diagnostic code associated with interstitial lung disease occurring on or after the index date (e-Table 1). Cases with a diagnostic code for postinflammatory fibrosis (515) were excluded because only a small minority of patients assigned this code have IPF.[12] Cases were further excluded if they did not have continuous enrollment for at least 12 months before the index date and at least 12 months after the index date or until date of death. Cases were censored at the time of death or lung transplantation.

We used a case-control analysis to estimate the burden of HRU attributable to IPF in an older, aging population. Each case was matched to between one and five control subjects from the KPNC patient population without a diagnostic code for interstitial lung disease by age (±6 months), sex, race, and length of enrollment in the KPNC system (±5 years). For control subjects, the index date was set to correspond to the index date of the matched patients with IPF. The follow-up period for control subjects was censored based on the length of the follow-up for the matched case.

Within patients with IPF, longitudinal HRU was compared pre- and postindex to assess how health-care delivery changed for this population after diagnosis. An increase in health-care utilization was previously described in the 3 months before and after diagnosis in

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TABLE 1] Characteristics of Patients Identified by Diagnostic Code-Based Broad and Narrow Algorithms

Characteristics	IPF Broad Algorithm (n = 1,698)	IPF Narrow Algorithm (n = 691)
Age, y	74 ± 11	74 ± 9
Age group, y		
< 55	87 (5)	15 (2)
55-59	84 (5)	33 (5)
60-64	132 (8)	66 (9)
65-69	193 (11)	87 (13)
70-74	269 (16)	128 (18)
75-79	328 (19)	143 (21)
> 80	605 (36)	219 (32)
Sex		
Male	968 (57)	416 (60)
Female	730 (43)	275 (40)
Race		
Asian	124 (7)	61 (9)
Black	85 (5)	34 (5)
Multiracial	91 (5)	35 (5)
Other/unknown	303 (18)	126 (18)
White	1,095 (65)	435 (63)
Index year		
2000-2005	763 (45)	279 (40)
2006-2010	298 (18)	143 (21)
2011-2015	637 (37)	269 (39)
Length of enrollment, y	21 ± 10	22 ± 10
Charlson Comorbidity Index score	3.6 ± 2.8	3.2 ± 2.5

Values are mean ± SD or No. (%). IPF = idiopathic pulmonary fibrosis.

patients with IPF.[4,5] We refer to this as the peri-index period. A sensitivity analysis was conducted to assess the effect of removing the peri-index period on the magnitude of observed pre-post changes in utilization metrics.

Comorbidities were chosen a priori and included coronary artery disease, COPD, gastroesophageal reflux disease, lung cancer, and pulmonary hypertension. Comorbidities were derived based on comorbidity-specific claims for the 5-year pre- and postindex periods.

HRU during the 5-year preindex and 5-year postindex periods was determined. Annual rates of the following HRU measures were included: all-cause hospitalization, ED visit, outpatient visit, and procedures or tests commonly used in patients with IPF (CT chest scan, pulmonary function tests, 6-min walk test, surgical lung biopsy, arterial blood gas, and BAL). Inpatient deaths were based on hospital discharge status disposition data. Outpatient deaths were based on KPNC internal data, Social Security Administration, and California death certificate data.[13]

Use of medications commonly accepted for the management of IPF over the study period was assessed. This included immunosuppressive medications (corticosteroids, azathioprine, and cyclophosphamide) and IPF-specific therapies (nintedanib and pirfenidone). Trends in medication use were assessed before and after approval of IPF-specific therapies (pre- and post-September 2014). Because of this stratification, we limited the preindex period to 2 years for the medication analysis.

Baseline data were summarized using means and SDs for continuous variables and counts and percentages for categorical variables. Prevalence of comorbidities among case and control participants was compared using conditional logistic models, adjusting for age at the index visit and length of enrollment. Poisson generalized estimating equations models with robust standard errors were used to estimate adjusted case-control differences in HRU, accounting for clustering within matched sets. The data were cleaned and matched using SAS (version 9.4; SAS Institute Inc), and then analyzed using Stata (version 16.0; Stata Corp). $P < .05$ was considered statistically significant.

Results

Patient Population

A total of 1,698 patients met the broad case definition for incident IPF and were matched to 8,465 control subjects. A total of 691 patients met the narrow case definition for incident IPF and were matched to 3,452 control subjects (e-Fig 1). The mean age of the narrow cases was 74 years, 60% were men, and the mean length of enrollment was 22 ± 10 years. The baseline

characteristics of the narrow cases were similar to the broad IPF cohort (Table 1). The narrow case definition was previously demonstrated to yield an improved positive predictive value in the KPNC population; therefore, IPF cases as defined by the narrow algorithm were used in the remainder of the analysis.[9] The demographics were well balanced between patients with IPF and control subjects because of matching.

Comorbidities

Patients with IPF had a significantly higher baseline burden of disease compared with matched control subjects. The Charlson Comorbidity Index score was significantly higher for patients with IPF (3.2 ± 2.5) compared with control subjects (2.0 ± 2.2; $P < .001$).[14] All prespecified comorbidities were more prevalent for patients with IPF compared with control subjects ($P <$

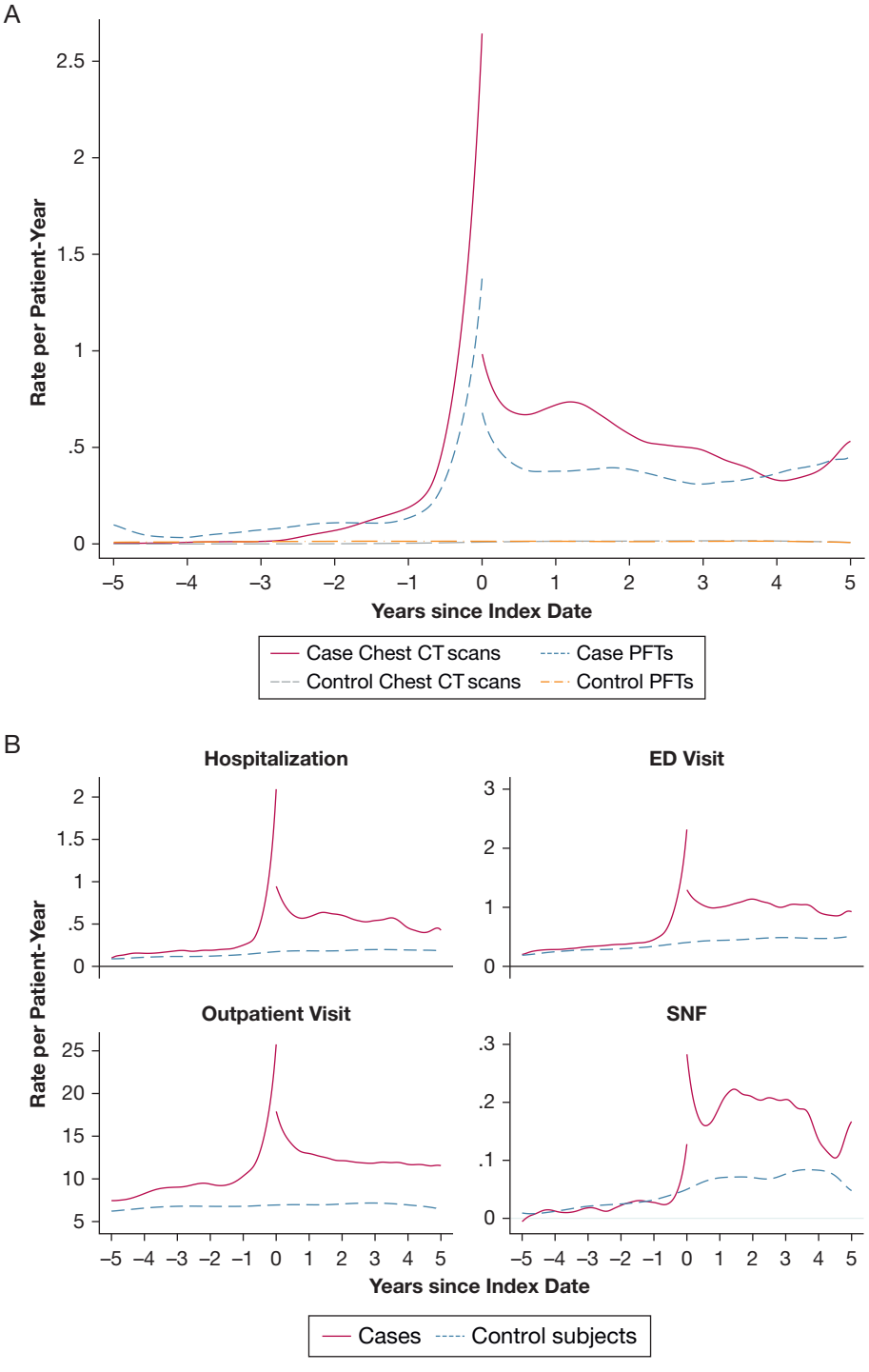

Figure 1 – *A-B, Annual pre- and postindex health-care resource utilization in idiopathic pulmonary fibrosis cases and control subjects: (A) annual diagnostic study use and (B) annual health-care visits. PFT = pulmonary function test; SNF = skilled nursing facility.*

TABLE 2] Health-care Resource Utilization Measures in Patients With IPF Compared With Control Subjects Pre- and Postindex

	Preindex				Postindex			
Diagnostic Procedure	Case Incident Rate per 100 Patient-Years (n = 691)	Control Incident Rate per 100 Patient-Years (n = 3,452)	Incident Rate Ratio (95% CI)	*P* Value	Case Incident Rate per 100 Patient-Years (n = 691)	Control Incident Rate per 100 Patient-Years (n = 3,452)	Incident Rate Ratio (95% CI)	*P* Value
6MWT	1.33	0.064	20.81 (12.67, 34.17)	< .001	2.87	0.083	34.49 (19.66, 60.49)	< .001
Arterial blood gas	3.78	1.26	3.00 (2.59, 3.49)	< .001	3.55	0.642	5.53 (4.13, 7.41)	< .001
BAL	0.423	0.012	35.10 (10.79, 1114.11)	< .001	1.16	0.011	–	–
Chest CT scan	6.84	0.085	80.35 (44.62, 144.71)	< .001	38.6	1.18	32.79 (22.98, 46.78)	< .001
Pulmonary function test	2.37	0.250	9.50 (7.20, 12.54)	< .001	5.60	0.423	13.24	< .001
Surgical lung biopsy	0.217	< .01	–	–	1.60	< .01	–	–
Health-care Visits	Case Incident Rate per 100 Patient-Years (n = 691)	Control Incident Rate per 100 Patient-Years (n = 3,452)	Incident Rate Ratio (95% CI)	*P* Value	Case Incident Rate per 100 Patient-Years (n = 691)	Control Incident Rate per 100 Patient-Years (n = 3,452)	Incident Rate Ratio (95% CI)	*P* Value
All-cause hospitalization	6.92	4.88	1.42 (1.23, 1.64)	< .001	41.0	17.6	2.33 (2.03, 2.67)	< .001
ED visit	13.5	12.0	1.12 (0.99, 1.27)	.08	70.2	39.5	1.78 (1.57, 2.02)	< .001
Outpatient visit	257.7	226.0	1.22 (1.13, 1.31)	< .001	989.8	549.4	1.80 (1.66, 1.96)	< .001
Skilled nursing facility	0.570	0.901	0.63 (0.44, 0.91)	.012	12.8	6.34	2.02 (1.62, 2.52)	< .001

6MWT = 6-min walk test; – = too few events for the model to provide a reliable estimate. See Table 1 legend for expansion of other abbreviation.

.001) (e-Fig 2). The greatest relative differences in comorbidity prevalence were found in preindex lung cancer (OR, 37.7), pneumothorax (OR, 15.1), pneumonia (OR, 9.4), pulmonary hypertension (OR, 8.9), and COPD (OR, 7.3) (e-Table 2). For a number of comorbidities, the incidence in control subjects was too low to calculate an OR.

HRU

For patients with IPF, HRU throughout the study period was characterized by an increase in all HRU measures beginning in the year prior to diagnosis, with a peak in HRU around the index date, followed by sustained increased HRU for the remainder of the study period. This pattern differed significantly compared with non-IPF control subjects, in which HRU measures remained relatively stable throughout the pre- and postindex periods (Fig 1).

Patients with IPF had significantly higher rates of all selected diagnostic procedures in both the pre- and postindex periods ($P < .001$) (Table 2), in both unadjusted analysis and after adjusting for

comorbidities. The greatest relative difference in the rates of HRU measures was observed with use of chest CT scan in both the preindex (relative risk [RR], 80.35; 95% CI, 44.62-144.71) and postindex periods (RR, 32.79; 95% CI, 22.98-46.78). Increased use of chest CT scans and pulmonary function tests was observed throughout the 5-year postindex study period (Fig 1A). For a number of preselected HRU measures, the incidence in control patients was too low to calculate a postindex incidence rate (Table 2).

Analysis of annual health-care visits demonstrated significantly different utilization for patients with IPF compared with control subjects. In the preindex period, patients with IPF had higher rates of all-cause hospitalizations (RR, 1.42; $P < .001$) and outpatient visits (RR, 1.22; $P < .001$) than control subjects, similar rates of ED visits, and lower rates of skilled nursing facility visits (RR, 0.63; $P < .12$) (Table 2). The rates of all in- and outpatient visits peaked around the index date (Fig 1B) followed by significantly ($P < .001$) higher rates of all visit types in the postindex period for patients with IPF compared with control subjects (all-cause hospitalizations: RR, 2.33; ED visits: RR, 1.78; outpatient visits: RR, 1.80; skilled nursing facility stay: RR, 2.02).

HRU Within IPF

Among patients with IPF, higher rates of HRU were observed in the postindex period compared with the preindex period, in both unadjusted analysis and after adjusting for comorbidities. This included chest CT scans (RR, 5.64; $P < .001$) and pulmonary function tests (RR, 2.36; $P < .001$), commonly used for both diagnosis and monitoring of IPF. Increased rates of all health-care visit types were also observed in the postindex period compared with the preindex period for patients diagnosed with IPF (Table 3). e-Table 3 summarizes the results of the sensitivity analysis. After excluding the peri-index period, slightly increased rates of all HRU metrics were observed in the postindex period compared with the preindex period. The P value for all measures was $< .001$, supporting the robustness of this finding. Finally, within the cohort of patients diagnosed with IPF, there was significant variability in utilization metrics. Although most patients with IPF had between zero and five hospitalizations and ED visits, there were patients hospitalized more than five times during the study period and patients who had $>$ 10 ED visits (e-Fig 3).

Treatment

Treatment trends in patients with IPF over the study period are displayed in Figure 2. Analysis was divided into two study periods, pre-2014 and post-2014, reflecting approval and availability of IPF-specific medications. In both study periods, we observed initiation of therapy prior to a definitive diagnosis, as defined as the index date. This included preindex use of both immunosuppressive medications (corticosteroids, azathioprine, and cyclophosphamide) and IPF-specific therapies (nintedanib and pirfenidone). Azathioprine and cyclophosphamide were not commonly used in the management of IPF. The use of both medications declined in the postindex period, and an overall decline in their use was observed after 2014 (Fig 2B). In contrast, high rates of corticosteroid use were observed before and after 2014 (e-Fig 4). Corticosteroid use prior to a definitive diagnosis was common. Furthermore, we observed high use of corticosteroids in patients with IPF in the postindex period, extending as far as 5 years postdiagnosis. As expected, prescriptions of IPF-specific medications (nintedanib and pirfenidone) were observed after their approval in 2014. Rates of nintedanib and pirfenidone use increased throughout the study period. However, their use remained uncommon among patients with IPF.

Discussion

This study was a longitudinal retrospective analysis of patients with IPF who received care at KPNC, a large, community-based, integrated health-care system in the United States. The objective of the study was to broaden our understanding of HRU in a complex disease by characterizing the utilization and treatment trends attributable to IPF both pre- and postdiagnosis.

This study demonstrates increased HRU in patients with IPF compared with control subjects, with accelerated use beginning at least 1 year prediagnosis and elevated use that is sustained in the following 5 years. This HRU pattern differed significantly from that observed among matched control subjects, thought to represent an aging population with increasing comorbidities. To our knowledge, this is the first study to describe the long-term HRU in IPF, an important first step to improving our understanding of the associations among the natural history of the disease, clinical practice patterns, and patient outcomes. Within patients with IPF, we observed higher rates of diagnostic procedures and visits in the

TABLE 3] Health-care Resource Utilization Measures in Patients With IPF in the Postindex Period Compared With the Preindex Period

Diagnostic Procedure	Incident Rate Ratio (95% CI)	*P* Value
6MWT	2.16 (1.32, 3.55)	.002
Arterial blood gas	0.94 (0.68, 1.31)	.71
BAL	2.75 (1.09, 6.93)	.031
Chest CT scan	5.64 (3.51, 9.07)	< .001
Pulmonary function tests	2.36 (1.65, 3.37)	< .001
Surgical lung biopsy	7.40 (2.64, 20.75)	< .001
Health-care Visits	**Incident Rate Ratio (95% CI)**	***P* Value**
All-cause hospitalizations	5.93 (4.65, 7.56)	< .001
ED visits	5.22 (4.28, 6.35)	< .001
Outpatient visits	3.59 (3.19, 4.03)	< .001
Skilled nursing facility	22.48 (12.91, 39.14)	< .001

See Table 1 and 2 legends for expansion of abbreviations.

postindex period compared with the preindex period, demonstrating the high burden of illness associated with the diagnosis and long-term management of IPF. Furthermore, we demonstrate heterogeneity in HRU within patients with IPF, exemplified in both the use of procedures and health-care visits. This heterogeneity may reflect practice variability among providers, the importance of which is best defined in future comparative effectiveness studies. Alternatively, IPF subtypes with distinct natural histories may drive the observed heterogeneity in HRU. Further exploration of a potential association between HRU, IPF phenotypes, and outcomes could inform future health-care delivery models.

To our knowledge, this is the first study to evaluate longitudinal medication trends in IPF. The introduction of nintedanib and pirfenidone in 2014 changed the landscape of IPF management, a change well demonstrated by treatment of this community-based IPF population. We observed decreased use of azathioprine and cyclophosphamide post-2014. This change is likely reflective of both the availability of IPF-specific medications and evidence that treatment with chronic immunosuppression is associated with increased morbidity and mortality in patients with IPF.[15] However, the observed early use of immunosuppressive medications prior to a definitive IPF diagnosis warrants further evaluation because this may be an opportunity for targeted clinical decision-making support.

The use of corticosteroids, historically part of the conventional approach to IPF treatment, has been challenged by evidence suggesting harm in chronic IPF.[15] Corticosteroids remain a common, albeit controversial, treatment decision in the management of sudden disease decompensations, known as acute exacerbations of IPF.[16] There is limited evidence to support corticosteroid use in this context and more recently a signal that corticosteroids in acute exacerbations of IPF may cause harm.[17] Despite this uncertainty, our study demonstrated disproportionate use of corticosteroids compared with all other medications studied. Unfortunately, we were unable to capture the indication for corticosteroids use to better understand potential drivers for this trend. However, we did not observe a parallel increase in annual hospitalizations, suggesting that the trend in corticosteroids use is not fully explained by episodes of acute disease decompensation. Additional characterization of the patterns of use and drivers of continued corticosteroids use in IPF is important to advancing on-going efforts to deliver high-quality care in the face of evolving guidelines.

Finally, KPNC is a closed health system offering integrated care to patients. This offers a unique opportunity to ensure complete capture of utilization metrics across all aspects of health care, including medication use. In addition, the availability of comprehensive patient-level data presents future opportunities to investigate the associations among disease behavior and management patterns to better inform the delivery of high-quality, safe, and effective IPF care.

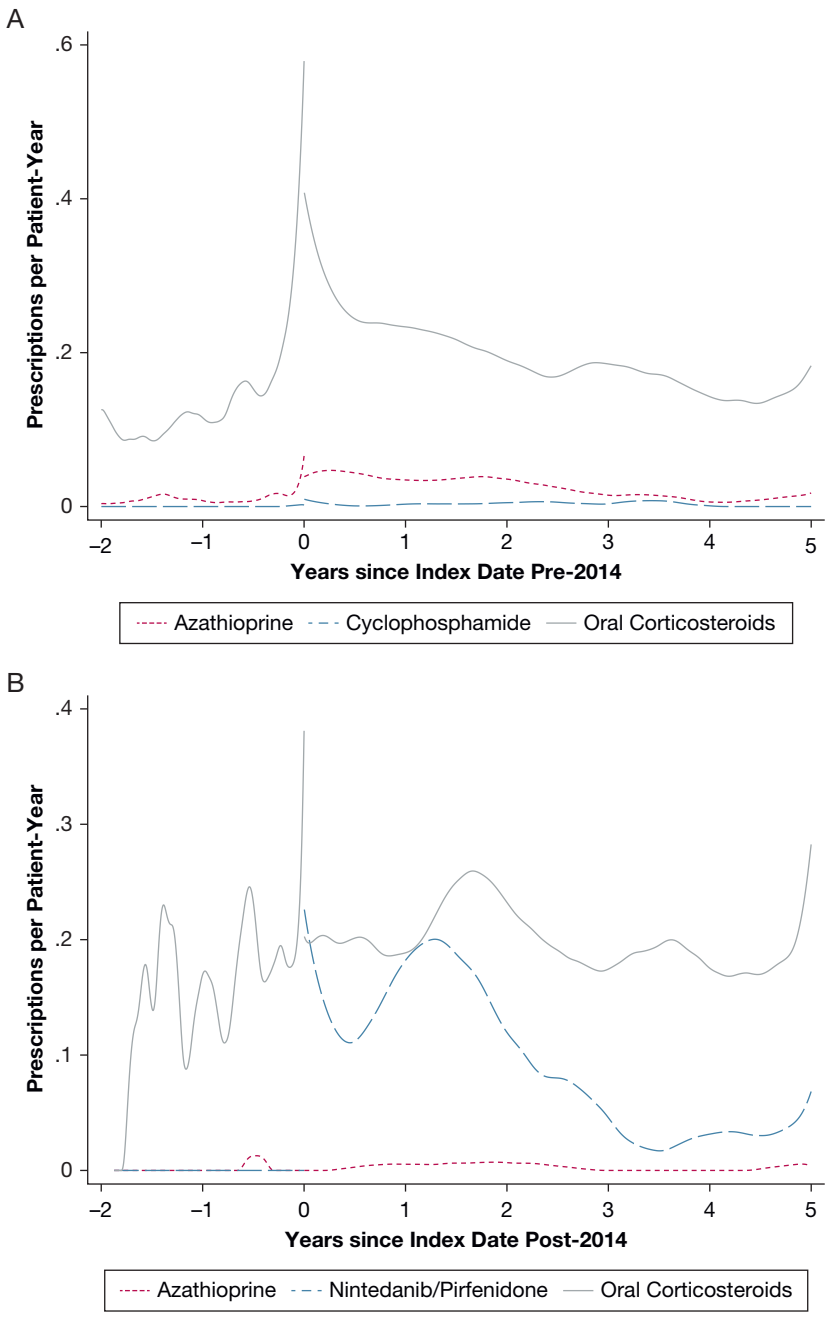

Figure 2 – *A-B, Pre- and postindex treatment for idiopathic pulmonary fibrosis: (A) medication use prior to 2014 and (B) medication use post-2014.*

There are several limitations of our study. First, the case-validated IPF algorithms used in our study were developed in the KPNC population, thereby improving accurate identification of patients with IPF and minimizing the challenges of misclassification in this cohort. However, the algorithms' performance and applicability in other cohorts is unknown. KPNC is a dynamic cohort. If there was a difference in the migration of cases in or out of the system relative to the larger member population, this could have biased our estimates. However, we anticipate this to be a minor issue in a large, integrated health system such as KPNC. Second, the narrow IPF algorithm included an HRU metric (ie, chest CT scan), which may have resulted in an overestimation of HRU. Third, comorbid conditions and HRU metrics were assessed using diagnostic codes. Inaccurate or inconsistent primary use of the codes introduces the potential for misclassification. Although the estimated prevalence and incidence of comorbidities in this study may be impacted by misclassification, leading to an over- or underestimation of the burden of illness, the RR in IPF cases compared with control subjects should be unaffected. Finally, significant variation in HRU was

observed among patients with IPF. However, the association between this variation and disease risk (as estimated by the GAP index) or patient outcomes remains unknown and requires further study.

Interpretation

Our results demonstrate high HRU in patient with IPF that begins prior to diagnosis and is sustained for years after diagnosis, reflecting the burden of long-term management. Interventions to improve the delivery of complex, chronic care to patients with IPF must take into consideration the impact of this burden on care delivery models. Further efforts to characterize and understand evidence-practice gaps and HRU heterogeneity within IPF are important to supporting clinical decision-making.

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Author contributions: E. F. had access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E. F., C. I., E. V., T. L.-H., B. L., G. M., and H. R. C. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript.

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Additional information: The e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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