Patient journey and treatment patterns in adults with IPF based on health care data in Sweden from 2001 to 2015

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ABSTRACT

Background: For patients with idiopathic pulmonary fibrosis (IPF), there is limited real-world data on patient journey and treatment patterns.
Aim: To explore predictors of early diagnosis and treatment initiation, and treatment patterns in IPF patients using linked data from Swedish registers and electronic medical records (EMRs).
Population: A national cohort (C1) of 17,247 pulmonary fibrosis patients (ICD-10 code J84.1; no competing diagnosis) diagnosed between 2001 and 2015, and an EMR-based regional subset (C2) comprising 1755 IPF patients diagnosed between 2004 and 2017. The time from early disease symptoms to diagnosis, use of anti-fibrotic medications, time from diagnosis to initiation of anti-fibrotic treatment, and adherence, persistence and treatment length with pirfenidone were explored in these patients.
Results: In C1, the median time to diagnosis from the first symptoms dyspnoea, cough and fatigue were 307, 563 and 639 days, respectively. Glucocorticoids were the most frequently prescribed medication. Less than 10% of patients undergoing or initiating treatment, used pirfenidone or nintedanib. Males had a higher probability of initiating anti-fibrotic treatment than females within a year of diagnosis. One-year persistence in pirfenidone patients was 42% in C1 and 25% in C2.
Conclusion: Diagnosis of pulmonary fibrosis was delayed in patients with cough and fatigue, which are early symptoms of IPF. This, and lower than expected utilisation of anti-fibrotic medications, suggests missed opportunities for early disease diagnosis and treatment. The high rate of treatment discontinuation underscores the importance of supporting and guiding patients to persist with their medications to ensure an accrual benefit of treatment.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) results from an irreversible distortion of lung architecture due to uncontrolled proliferation of fibroblasts and excessive deposition of extracellular matrix molecules [1]. IPF occurs mostly in older adults [2,3] and has a poor five-year survival rate [4]. The clinical progression of IPF patients can vary considerably ranging from slowly progressing disease to those with acute exacerbations (AE-IPF) resulting in rapid deterioration and death [5].

Currently two anti-fibrotic medications, pirfenidone and nintedanib, are approved and recommended for the treatment of patients with IPF [6,7]. Pirfenidone has anti-inflammatory and anti-fibrotic properties, but the exact mechanism of action is not fully understood [8]. Nintedanib is a tyrosine kinase inhibitor, which acts downstream of the signalling cascades to inhibit proliferation and migration of human fibroblasts [9]. Randomised clinical trials have demonstrated the efficacy of both pirfenidone [10,11] and nintedanib [12] in slowing the decline in forced vital capacity (FVC) in patients with IPF. Assessment of long-term treatment outcomes in patients enrolled in clinical trials of

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Abbreviations

AE	Adverse Event	ICD-10	International Classification of Diseases, Tenth Revision
AE-IPF	Acute Exacerbation of Idiopathic Pulmonary Fibrosis	IQR	Interquartile Range
ATC	Anatomical Therapeutic Chemical	IPF	Idiopathic Pulmonary Fibrosis
CI	Confidence Interval	NBHW	The National Board of Health and Welfare
CXP	Customised Extraction Platform	PANTHER-IPF	Prednisone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis
EMA	European Medicines Agency		
EMR	Electronic Medical Records	PDC	Proportion of Days Covered
FVC	Forced Vital Capacity	PI	Principal Investigator
HR	Hazard Ratio	SD	Standard Deviation

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pirfenidone and nintedanib have found both drugs to have an acceptable safety and tolerability profile [13,14]. Pirfenidone was approved by the European Medicines Agency (EMA) for the treatment of mild to moderate IPF in adults in 2011 [15] and received reimbursement authorisation in Sweden in June 2012. Nintedanib was approved by EMA for the treatment of IPF in adults in 2015 [16], receiving reimbursement authorisation in Sweden in May 2015.

In real-world studies, safety and tolerability of both drugs have been found to be comparable to that observed in the clinical trials [17,18]. There are, however, several knowledge gaps regarding the use of pirfenidone and nintedanib in IPF patients, such as the choice of target patient population, treatment regimen and the definition of treatment success [19]. Additionally, real-world data on-treatment patterns, effectiveness of current interventions, including assessment of adherence and persistence, is lacking.

The aim of this study was to explore the patient journey before and after diagnosis of pulmonary fibrosis/IPF by identifying potential predictors associated with early disease diagnosis and treatment. Additionally, it provided insight into real-world treatment patterns, including adherence and persistence to treatment with pirfenidone during the early years of its introduction.

2. Material and methods

2.1. Study design, setting and case definition

A retrospective cohort study with linked datasets from Swedish population-based registers and electronic medical records (EMRs) was conducted. Two cohorts of patients were assembled: (A) a national cohort of patients with pulmonary fibrosis (Cohort 1); and (B) a sub-national cohort of IPF patients from Stockholm and Uppsala county councils (Cohort 2), which was an EMR-based regional subset of Cohort 1.

Patients were eligible for inclusion if they were aged 40 years and above, and had a registration of International Classification of Diseases, Tenth Revision (ICD-10) code of J84.1, *i.e.*, "Other interstitial pulmonary diseases with fibrosis" between January 1, 2001 and December 31, 2015. Patients with competing diagnosis (*i.e.*, asbestosis, berylliosis, diffuse connective tissue diseases, hypersensitivity pneumonitis, rheumatoid arthritis and other inflammatory polyarthropathies, pneumoconiosis, silicosis or talcosis) on or after the initial J84.1 registration were excluded. Patients with pulmonary fibrosis resulting from inhalation of chemicals, gases, fumes or vapours, or following radiation (radiation fibrosis) were also excluded from the study.

The regional cohort (Cohort 2) was further refined to include only those patients who had a registration of ICD-10 diagnosis code J84.1 in EMRs between November 1, 2004 and March 12, 2017 and at least one radiology procedure record in their EMR history, following the initial ICD-10 J84.1 diagnosis.

2.2. Data sources and linkages

The Swedish National Patient Register (NPR) was used to identify patients with pulmonary fibrosis. NPR maintains records of all completed in-patient admissions and out-patient visits in publicly operated hospitals [20], and has been validated in earlier studies [21–23]. Records of patients with pulmonary fibrosis were linked to the Swedish Prescribed Drug Register [24] and the Swedish Cause of Death Register [25], using their personal identity numbers, to create the database for Cohort 1. For Cohort 2, EMR data was extracted using the Pygargus Customized Extraction Platform (CXP) and linked to the national registers. CXP has been used in earlier research projects on the Swedish healthcare system [26,27].

All linkages were performed by the National Board of Health and Welfare (NBHW) in accordance with Swedish and EU data privacy legislations. Following linkage, a pseudonymised database was created by NBHW and delivered to the principal investigator (PI). The individual key code linking patient identifiers with the study database was retained by NBHW. Ethical approval for this study was obtained from the Stockholm County Ethical Committee (Regionala etikprövningsnämnden i Stockholm) with reference number: 2016/1364-31/2 dated 17-Aug-2016.

2.3. Key variables and outcomes

The following key variables/outcomes were considered for this study:

2.3.1. Index date
The date of initial registration of ICD-10 J84.1 diagnosis code (proxy for the date of disease diagnosis) in the National Patient Register or the EMR was considered as the index date. Patients were followed from the index date until the end of the study period (i.e., December 31, 2015 for Cohort 1 and March 12, 2017 for Cohort 2) or death, whichever occurred earlier.

2.3.2. Disease severity
Disease severity was measured using forced vital capacity (FVC) and was expressed as a percentage of the predicted value. Based on their FVC, patients were classified as follows: (a) normal - FVC > 100% of predicted value; (b) mild - FVC < 100- ≥80% of predicted value; (c) moderate - FVC < 80- ≥50% of predicted value; and (d) severe - FVC < 50% of predicted value.

2.3.3. Hospitalisation due to pulmonary fibrosis
The frequency and duration of hospitalisations due to pulmonary fibrosis (ICD-10 J84.1 recorded as the main diagnosis code) were extracted from the National Patient Register and from EMRs through a free text search.

2.3.4. Time to disease diagnosis and treatment
Time to disease diagnosis was defined as the time from the

appearance of the first early symptoms (dyspnoea, cough, fatigue) to the index date. The early symptoms were identified based on the ICD-10 diagnosis codes for cough, dyspnoea and fatigue, which were extracted from the EMRs and the National Registries.

Time to treatment with anti-fibrotic medication was defined as the time between the index date and the initiation of anti-fibrotic treatment (pirfenidone or nintedanib) in patients with an index date on or after January 1, 2011.

2.3.5. Use of anti-fibrotic and other medications

The use of anti-fibrotic and other medications was assessed using information on pharmacy dispensations from The Swedish Prescribed Drugs Register, which tracks all medications prescribed and subsequently dispensed to individual patients [24]. The list of concomitant medications, grouped as per their 1st level Anatomical Therapeutic Chemical (ATC) classification is presented in Table A.1. Assessment of anti-fibrotic medication use was restricted to patients initiating or continuing treatment on or after January 1, 2011; for other medications, the period from July 1, 2005 to the end of the study period was considered.

2.3.6. Treatment adherence and persistence

Persistence and adherence to pirfenidone during treatment were assessed by data collected from the Prescribed Drug Register [24] in patients with an index date on or after January 2011. Persistence was defined as the number of days on pirfenidone between initiation and end of treatment or discontinuation (*i.e.*, how long patients were taking the prescribed drug). Non-persistence occurred when there was a gap of more than 30 days from the refill due date. Once classified, patients remained non-persistent even if they re-initiated treatment at a later date. Adherence refers to the level of compliance with the provider's recommendations and was defined as the proportion of days covered

(PDC) within a three-month interval, using dosage instructions from the prescriptions.

2.4. Statistical analysis

The number of patients receiving anti-fibrotic and other medications for the treatment of pulmonary fibrosis/IPF during the pre, peri and post-index periods were described using frequencies and percentages. These periods were defined as follows: (A) *Pre-index period* - for anti-fibrotic medicines, January 1, 2011 up to the index date; for other medicines, July 1, 2005 up to the index date; (B) *Peri-index period* - time from index date until one year after; (C) *Post-index period* - time from one year after index date until data was no longer available or the patient left the cohort.

The associations between demographic characteristics (age, sex) and time to anti-fibrotic treatment initiation (in patients with index date on or after January 1, 2011) were assessed using univariate Cox proportionate hazards models, as were the association between presence of early symptoms (dyspnoea, cough, fatigue) and time to disease diagnosis. Hazard ratios (HR) and 95% confidence intervals (CI) were presented for all predictor variables; 95% CIs that did not include '1' were considered statistically significant.

Treatment persistence in pirfenidone-treated patients was described as the proportion of patients continuing treatment after 1 year of treatment initiation, as well as the median (95% CI) number of treatment days. Adherence to treatment and length of treatment were described using summary statistics (mean, median, standard deviation [SD], and interquartile range [IQR] [25th and 75th percentiles]).

3. Results

The patient journey and treatment patterns of patients with

Table 1

Cox proportionate hazards regression analysis for associations between early symptoms of pulmonary fibrosis/IPF, sex and age, respectively, and being diagnosed with pulmonary fibrosis/IPF within one year.

Cohort	Variable	Number of patients[i]	Proportion of patients undiagnosed at 1 year after first symptom, % (95% CI[b])	Median number of days from symptom to diagnosis	Unadjusted HR[e] (95% CI[b])[f]
Cohort 1[a] [d] (N = 2826)	Sex				
	Male[g]	1751	49.1 (46.7–51.4)	353	1
	Female	1075	53.5 (50.5–56.5)	426	0.93 (0.86–1.01)
	Early symptoms of pulmonary fibrosis				
	Dyspnoea[g]	1930	47.2 (45.0–49.5)	307	1
	Cough	568	58.3 (54.2–62.3)	563	0.81 (0.74–0.89)
	Fatigue	267	63.3 (57.5–69.1)	639	0.78 (0.69–0.89)
	Multiple symptoms[h]	61	37.7 (25.5–49.9)	218	1.20 (0.93–1.55)
	Age on index date	2826	50.8 (48.9–52.6)	380	0.99 (0.99–1.00)
Cohort 2[c] [d] (N = 677)	Sex				
	Male[g]	416	53.8 (49.1–58.6)	435	1
	Female	261	59.0 (53.0–65.0)	519	0.95 (0.81–1.10)
	Early symptoms of IPF				
	Dyspnoea[g]	308	48.4 (42.8–54.0)	333	1
	Cough	252	58.7 (52.7–64.8)	476	0.89 (0.76–1.06)
	Fatigue	104	72.1 (63.5–80.7)	834	0.66 (0.53–0.83)
	Multiple symptoms[h]	13	46.2 (19.1–73.3)	330	1.44 (0.82–2.51)
	Age on index date	677	55.8 (52.1–59.6)	–	0.988 (0.981–0.996)

[a] Analysis includes patients with a record on cough, dyspnoea, fatigue or multiple symptoms (≥2 symptoms recorded at the same point of contact) in the National Patient Register before the index diagnosis.

[b] CI: Confidence interval.

[c] Analysis includes patients with a record on cough, dyspnoea, fatigue or multiple symptoms (≥2 symptoms recorded at the same point of contact) in the National Patient Register or EMRs before the index diagnosis.

[d] Only the earliest observation of any of the symptoms considered.

[e] Separate models fitted for sex, symptoms of IPF and age, respectively; start of follow-up defined as the date when the earliest symptom was observed.

[f] Statistically significant if 95% CI does not include '1'.

[g] Reference category.

[h] ≥2 symptoms recorded at the same point of contact.

[i] For this analysis, number of patients and number of events are same.

Table 2
Adherence, persistence and length of treatment of pirfenidone-treated patients.

	Cohort 1[a] (N = 246)	Cohort 2[a] (N = 59)
Persistence		
Non-persistent patients, N	122	48
Persistence, days, median (95% CI)[b]	297 (253–360)	176 (92–297)
Patients persistent at one year, N	48	12
One year persistence, % (95% CI)[b] [f]	41.8 (34.0–49.6)	24.7 (12.7–36.6)
Length of treatment (days)		
Mean (SD)[c]	285.7 (271.6)	345.2 (286.5)
Median (IQR)[d]	182 (57–441)	257 (72–596)
Range	3–1151	9–1032
Adherence (PDC)[e]		
Mean (SD)[c]	0.9 (0.1)	0.9 (0.1)
Median (IQR)[d]	1.0 (0.9–1.0)	1.0 (0.9, 1.0)
Range	0.3–1.0	0.5–1.0

[a] Analysis based on subset of patients included in the study on or after January 1, 2011.
[b] CI, confidence interval.
[c] SD: standard deviation.
[d] IQR: interquartile range.
[e] PDC: proportion of days covered.
[f] Proportion of patients with follow-up extending at least one year beyond the index dispensation of pirfenidone.

pulmonary fibrosis/IPF are presented separately for Cohorts 1 and 2.

3.1. Cohort 1

A total of 17,247 patients fulfilled the eligibility criteria and were included in the final analysis.

3.1.1. Time to disease diagnosis

The median time to disease diagnosis from the first appearance of early symptoms (dyspnoea, cough, fatigue) was 380 days. It was shorter in men (353 days) compared with women (426 days), although the proportion of males (49.1%) and females (53.5%) diagnosed within a year of symptom appearance were comparable (Table 1). Older patients were less likely to have been diagnosed with pulmonary fibrosis within one year of symptom appearance, with each year increase in age decreasing the probability by 1%. The shortest median time to disease diagnosis was 218 days, which was observed in patients having multiple symptoms (*i.e.*, ≥2 symptoms recorded at the same point of contact).

The associations between appearance of early symptoms and diagnosis of pulmonary fibrosis are reported in Table 1. Patients with cough (HR = 0.81, 95% CI = 0.74–0.89) or fatigue (HR = 0.78, 95%

CI = 0.69–0.89) were significantly less likely to be diagnosed with pulmonary fibrosis within one year of symptom appearance than those with dyspnoea. Compared to patients with dyspnoea, those with multiple symptoms were equally likely to be diagnosed within a year of symptom appearance (Table 1).

3.1.2. Medication use

The proportion of patients using respiratory medications in the period before the index diagnosis was 54.2%. This decreased to 44.5% during the peri-index period, before increasing to 67.5% during the post-index period. Similar utilisation patterns were observed for most other medications of interest, except for systemic corticosteroids and oxygen whose use increased steadily across time (Table A.2). The three most widely used medication types in the peri-index period were those acting on the nervous (47.1%), cardiovascular (46.2%) and respiratory (44.5%) systems (Table A.2).

3.1.3. Treatment patterns

3.1.3.1. Anti-fibrotic medications. The extent of anti-fibrotic medication use (pirfenidone and nintedanib), as measured by pharmacy dispensations, was assessed only in patients having follow-up extending beyond 2010 or starting treatment on or after January 1, 2011. Of the 10,729 patients included in the analysis, 325 (3%) reported at least one use of pirfenidone and 39 (0.4%) patients reported at least one use of nintedanib. Pirfenidone use increased with time, from 0.9% within 6 months of disease diagnosis to 1.1% and 3.1% in the 6–12 month and ≥12 months period post-diagnosis, respectively. Similar pattern was observed for nintedanib use, which increased from 0.1% in the first 12 months post-diagnosis to 0.4% in the ≥12 month period post-diagnosis).

3.1.3.2. Other medications. In addition to anti-fibrotic treatment, the use of other medications was assessed from July 1, 2005 until the end of the study period. The most frequently prescribed medications were glucocorticoids (63.9%) followed by proton pump inhibitors (48.7%) and platelet aggregation inhibitors (44.6%). The frequency of use of most medications followed a similar pattern across time: decrease in the proportion of patients using such medications in the first 6–12 months post-diagnosis compared to the pre-index period, followed by a marked increase in use 12 months after the index date (Table A.3).

3.1.4. Adherence, persistence and length of treatment with pirfenidone

Data on adherence, persistence and length of treatment with pirfenidone were available only for 246 patients who initiated treatment on or after January 1, 2011. Patients persisted on treatment for a median period of 297 days. Of the patients whose follow-up extended for a period of at least one year beyond the index dispensation of
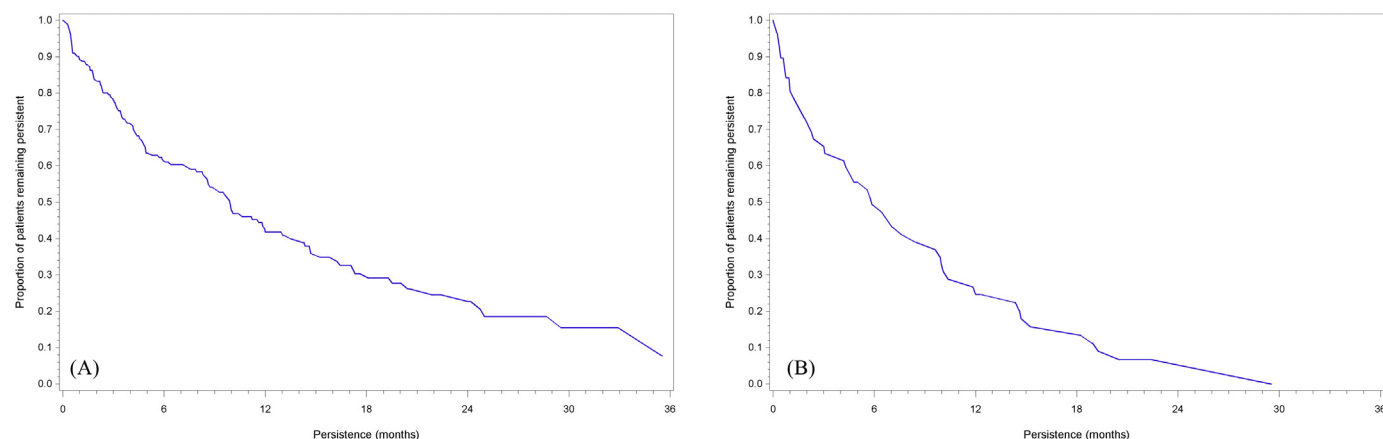
Fig. 1. Persistence curve of pirfenidone-treated patients in (A) Cohort 1 and (B) Cohort 2.

pirfenidone, the one-year persistence was 41.8%. Adherence, as defined by PDC, was high with an average of 90% of days covered (Table 2). A graphical display of the development of persistence over time is presented in Fig. 1A.

3.2. Cohort 2

A total of 1755 patients fulfilled the eligibility criteria and were included in the final analysis.

3.2.1. Time to disease diagnosis
The median time to disease diagnosis was 464 days from the appearance of the first potential symptom of IPF (dyspnoea, cough, fatigue). Although men had a shorter median time to disease diagnosis than women (435 days vs. 519 days), similar proportion of men and women (53.8% vs. 59.0%, HR = 0.95) were diagnosed with IPF within one year of symptom appearance (Table 1). Older patients were more likely to remain undiagnosed within one year of symptom appearance: each year increase in age decreased the probability of disease diagnosis by 1.2%.

Among the early symptoms of IPF, the shortest median time to disease diagnosis was observed in patients with multiple symptoms (330 days). Compared to patients with dyspnoea, those with cough (HR = 0.89, 95% CI = 0.76–1.06) or fatigue (HR = 0.66, 95% CI = 0.53–0.83) were less likely to have been diagnosed with IPF within one year of symptom appearance, although, this difference was statistically significant only for the fatigue symptom. Patients with multiple early symptoms had a similar probability of being diagnosed with IPF within one year of symptom appearance as those with dyspnoea (Table 1).

3.2.2. Medication use
As per the pharmacy dispensation records, 73.6% of IPF patients used respiratory medications before the index diagnosis. The proportion of patients using respiratory medications during the peri-index and post-index periods were 56.5% and 69.2%, respectively (Table A.2). Other than systemic corticosteroids and oxygen whose use steadily increased over time, other medications of interest followed a similar pattern to what was observed for respiratory medications: decrease in use during the peri-index period as compared to the pre-index period, followed by an increase in use in the post-index period (Table A.2). Respiratory (56.5%), cardiovascular (51.6%) and nervous system (46.6%) medications were the three most common medications prescribed during the peri-index period.

3.2.3. Treatment patterns
3.2.3.1. Anti-fibrotic medications.
Anti-fibrotic medication use was assessed in 1554 patients with follow-up extending beyond 2010 or starting treatment on or after January 1, 2011. A total of 121 (7.8%) patients reported at least one use of pirfenidone during the follow-up period and 41 (2.6%) reported at least one use of nintedanib. Pirfenidone use increased with time, from 2% within 6 months of disease diagnosis to 7.8% in ≥12 months period post-diagnosis, respectively. Similar pattern was observed for nintedanib use, which increased from 0.8% in the first 6 months post-diagnosis to 2% in the ≥12 month period post-diagnosis.

3.2.3.2. Other medications.
The use of other medications in IPF patients from July 1, 2005 until the end of the study period was also assessed. Glucocorticoids were the most commonly prescribed medications and were used by 34.6%, 32% and 53.6% of patients in the 0–6 months, 6–12 months and >12 months post-index periods, respectively. Overall, 72.6% of patients used glucocorticoids at least once, either before or after their disease diagnosis. Other commonly prescribed medications were proton pump inhibitors (59%), N-acetylcysteine (53.1%) and platelet inhibitors (47.4%). Compared to the pre-index period, the use of most medicines decreased in the first 12 months following the disease diagnosis, but increased thereafter (Table A.4).

3.2.4. Time to initiation of anti-fibrotic treatment
The association between demographic variables, disease severity (based on FVC) and time to initiation of anti-fibrotic treatment was assessed only for those with the index date on or after January 1, 2011. Overall, 113 (11%) of the 1028 patients included in this analysis initiated treatment with anti-fibrotic medications, the majority (93.3%) of whom remained untreated during the first year of their index diagnosis. Compared to male patients, female patients were significantly less likely to have initiated anti-fibrotic treatment within one year of their index diagnosis (Table 3). Data on disease severity was available for 305 patients: there were no statistically significant differences in the treatment initiation rates between patients with mild, moderate or severe disease. Additionally, no statistically significant association between age at index date and treatment initiation was noted (Table 3).

3.2.5. Adherence, persistence and length of treatment with pirfenidone
This analysis was conducted only for 59 patients who initiated treatment with pirfenidone on or after January 1, 2011, and for whom data on treatment adherence, persistence and length of treatment were available. The median persistence in these patients was 176 days.

Table 3
Cox proportionate hazards regression analysis for associations between sex, disease severity and age at index, respectively, and initiation of anti-fibrotic treatment within one year of disease diagnosis in Cohort 2 patients (N = 1028).

Variable	Number of patients[a]	Proportion of patients not initiating treatment at 1 year after disease diagnosis, % (95% CI[b])	Number of events	Unadjusted HR[b] (95% CI)[f]
Sex				
Male[d]	669	91.9 (89.6–94.2)	82	1
Female	359	95.8 (93.5–98.1)	31	0.63 (0.41–0.97)
Disease severity at index[e]				
Mild (FVC[c] ≥80%, < 100%)[d]	70	90.6 (83.4–97.8)	10	1
Moderate (FVC[c] ≥50%, < 80%)	164	93.3 (89.3–97.3)	24	1.09 (0.52–2.31)
Severe (FVC[c] < 50%)	42	94.4 (87.0–100.0)	3	0.62 (0.17–2.25)
Normal (FVC[c] ≥100%)	29	94.7 (84.7–100.0)	1	0.28 (0.04–2.16)
Age at index	1028	93.3 (91.6–95.0)	113	0.996 (0.978–1.013)

[a] Analysis restricted to patients with index date on or after January 1, 2011; separate models fitted for sex, disease severity and age at index.
[b] CI: Confidence interval.
[c] FVC: Forced vital capacity.
[d] Reference category.
[e] Parameter estimates of 723 patients with 'unknown' FVC status not presented.
[f] Statistically significant if 95% CI does not include '1'.

Persistence was low with only 24.7% of patients (among those with follow-up extending for a period of one or more years beyond the index dispensation of pirfenidone) persisting treatment for a period of at least one year (Table 2 and Fig. 1B). Treatment adherence, however, was high with 90% of days covered during the treatment period (Table 2).

4. Discussion

This retrospective cohort study explored the patient journey and the real-world treatment patterns of pulmonary fibrosis/IPF patients in Sweden. On average, the median time to disease diagnosis was greater than one year from the time of appearance of first potential symptoms. Less than 10% of patients received pirfenidone or nintedanib, reflecting the low anti-fibrotic medication usage during the early years of introduction. Among those prescribed pirfenidone, less than half in the national cohort and one-fourth in the regional cohort continued treatment for a year or more, although adherence during the treatment period was very high.

In this study, patients with cough or fatigue were less likely to have been diagnosed with pulmonary fibrosis/IPF compared to patients with dyspnoea. Although cough, dyspnoea and fatigue are among the most frequently reported symptoms in IPF patients [28], they are non-specific symptoms and are also associated with other respiratory diseases such as COPD. The early disease diagnosis in patients reporting dyspnoea, as opposed to those with cough or fatigue, can be partly attributed to its late onset as well as its association with AE-IPF [29]. Dyspnoea has also been associated with an impaired quality of life in IPF patients [30,31]. The shortest median time to disease diagnosis, from the first appearance of symptoms, was about 7 months for Cohort 1 patients and 11 months for Cohort 2 patients, which underscores the importance of early disease diagnosis. Early diagnosis of IPF in patients can help arrest the irreversible deterioration of lung function which, in turn, may improve treatment outcome and survival [32].

General medication use, as measured by pharmacy dispensation of relevant drugs, was substantial in both cohorts, possibly due to the high burden of comorbidities observed in IPF patients [33,34]. Glucocorticoids were the most common medication dispensed to patients in both cohorts, before and after the disease diagnosis. As this study included prescription data from 2005 onwards, the high glucocorticoid use probably reflects the conventional use of corticosteroids for treatment of IPF [35]. Following publication of the PANTHER trial in 2012 [36], the use of corticosteroids in IPF patients has been severely restricted and is currently not recommended for IPF treatment, except to manage AE-IPF [6,37]. Alternately, this may be indicative of the lack of specificity of the case definition, resulting in inclusion of patients with pulmonary fibrosis disease other than IPF where corticosteroid use may be warranted. Furthermore, some of the glucocorticoid medications would have been prescribed by primary care physicians who may not be aware of the latest treatment guidelines.

Even though pirfenidone was approved by the EMA for use throughout the European Union in February 2011 [15], a relatively small proportion of patients diagnosed with pulmonary fibrosis/IPF between 2011 and 2015 received the medicine post-diagnosis. A possible reason for this low drug utilisation could be the initial hesitancy among practitioners to prescribe pirfenidone due to the restrictive treatment guidelines [37] and the limited reimbursement policy in some counties. In a study evaluating anti-fibrotic medication usage in Finnish and Swedish patients between 2014 and 2016, a much higher prescription rate was noted among the Swedish IPF patients [38]. It is also important to note that a sizeable proportion of patients in both cohorts (approximately 70% in Cohort 1 and 43% in Cohort 2) were diagnosed by non-pulmonologists, which would have further limited their probability of being prescribed an anti-fibrotic medication early on during treatment. Nevertheless, the low drug utilisation highlights a missed opportunity for patients to receive an effective treatment at an early stage of their disease.

Approximately 42% of patients in Cohort 1 and 25% of patients in Cohort 2 continued treatment with pirfenidone for a period of at least 1 year following treatment initiation. This is lower than what has earlier been reported from real-world studies [17,39,40], although the mean length of treatment and adherence to therapy were higher in both cohorts [39,40]. A possible reason for the apparently low treatment persistence can be the short prescription refill window of 30 days, beyond which a patient was considered to have discontinued treatment; other studies have used wider window periods [39,40]. However, as patients are required to take the medications daily, the 30-day window after the refill due date was considered a reasonable time frame for treatment discontinuation. Adverse events (AEs) following treatment initiation can be another reason for the low treatment adherence. AEs are the primary drivers of treatment discontinuation in pirfenidone-treated patients [41], majority of which occur during the first 6 months of treatment [42]. In this study too, a large proportion of discontinuation occurred within the first 6 months of treatment initiation (Fig. 1). Creating awareness about the potential AEs and ways to mitigate them at the time of treatment initiation can be a potential strategy to improve treatment persistence [32].

The main limitations of this study are those inherent to real-world studies using secondary data. This includes the potential for disease misclassification in the National Patient Register and the EMRs, even though detailed exclusionary criteria were applied to refine the disease diagnosis. Another potential limitation is the possibility of under-reporting of the diagnoses reflecting symptoms of pulmonary fibrosis/IPF (e.g., dyspnoea, cough, fatigue) as only ICD-10 codes were used to identify these symptoms. It should, however, be acknowledged that some of the conditions may have been managed in primary care rather than in the hospital setting and were therefore not captured in the National Patient Register. Similarly, the FVC measurements may have been performed but not recorded in the EMR, resulting in a large number of patients with an 'unknown' disease severity.

Medication use in this study was based on prescription refills through pharmacy dispensations, which do not account for the possible stockpiling of medicines. It was also assumed that all medications dispensed were consumed, and that the first day of consumption was equal to the day of dispensation, which may not have been the case in all instances. This may have resulted in overestimation of treatment persistence and duration. Although PDC has been widely used as an indirect measure of adherence in studies using electronic databases [43,44], it is possible that some patients may not have ingested the correct drug or the correct dose [44]. Furthermore, as nintedanib was commercially not available until 2015 (last year of the study period) [16], only a small number of nintedanib-treated patients could be included in this study; hence, assessment of persistence and adherence to nintedanib could not be ascertained.

The ability to obtain a more complete overview of the clinical profile and treatment patterns of pulmonary fibrosis/IPF in relatively large number of Swedish patients, by linking patient-level data from National Registers with EMRs, is a major strength of this study. This allowed for extensive and virtually complete follow-up information on all patients.

5. Conclusions

In this study, the diagnosis of pulmonary fibrosis/IPF was delayed in patients with cough and fatigue, which are early symptoms of IPF. This, along-with the lower than expected utilisation of anti-fibrotic medications, suggest potential missed opportunities for early disease diagnosis and treatment. Furthermore, the high rate of pirfenidone discontinuation underscores the importance of supporting and guiding patients to persist with their medications to ensure an accrual benefit of treatment.

Conflicts of interest

The authors have reported to Respiratory Medicine the following conflicts of interest:

C. Magnus Sköld: C. Magnus Sköld has received research grants from Boehringer Ingelheim, F. Hoffmann-La Roche and Sandoz, and consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, Novartis, Mundipharma, Sandoz, Chiesi, Almirall, InterMune and F. Hoffmann-La Roche, Ltd.

Lisen Arnheim-Dahlström: Lisen Arnheim Dahlström was an employee of IQVIA, and now is an employee of Celgene. She has received research funding for Karolinska Institutet from GlaxoSmithKline, MSD and SPMSD.

Karen Bartley: Karen Bartley is an employee of Roche-Genentech and holds Roche-Genentech shares.

Christer Janson: Christer Janson has received consultancy or speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, Novartis, and TEVA.

Klaus-Uwe Kirchgässler: Klaus-Uwe Kirchgässler is an employee of F. Hoffmann-La Roche Ltd. and holds Roche shares.

Aaron Levine: Aaron Levine is an employee of IQVIA.

Giovanni Ferrara: Giovanni Ferrara has received fees for lectures from Boehringer Ingelheim and Roche.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.06.001.

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