Morbidity and Mortality Reduction Associated with Polysomnography Testing in Idiopathic Pulmonary Fibrosis: A Population-Based Cohort Study

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Abstract

**Background:** It is not well-known if diagnosing and treating sleep breathing disorders among individuals with idiopathic pulmonary fibrosis (IPF) improves health outcomes. We evaluated the association between receipt of laboratory-based polysomnography (which is the first step in the diagnosis and treatment of sleep breathing disorders in Ontario, Canada) and respiratory-related hospitalization and all-cause mortality among individuals with IPF.

**Methods:** We used a retrospective, population-based, cohort study design, analyzing health administrative data from Ontario, Canada, from 2007-2019. Individuals with IPF were identified using an algorithm based on health administrative codes previously developed by IPF experts. Propensity score matching was used to account for potential differences in 41 relevant covariates between individuals that underwent polysomnography (exposed) and individuals that did not undergo polysomnography (controls), in order minimize potential confounding. Respiratory-related hospitalization and all-cause mortality were evaluated up to 12 months after the index date.

**Results:** Out of 5044 individuals with IPF identified, 201 (4.0%) received polysomnography, and 189 (94.0%) were matched to an equal number of controls. Compared to controls, exposed individuals had significantly reduced rates of respiratory-related hospitalization (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.24-0.75, p=0.003) and all-cause mortality (HR 0.49, 95% CI 0.30-0.80, p=0.004). Significantly reduced rate of respiratory-related hospitalization (but not all-cause mortality) was also observed among those with >=1 respiratory-related hospitalization (HR 0.38, 95% CI 0.15-0.99) and systemic corticosteroid receipt (HR 0.37, 95% CI 0.19-0.94) in the year prior to the index date, which reflect sicker subgroups of persons.

**Conclusions:** Undergoing polysomnography was associated with significantly improved clinically-important health outcomes among individuals with IPF, highlighting the potential importance of incorporating this testing in IPF disease management.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common fibrotic lung disease and its prevalence may be increasing [1, 2]. IPF is generally a progressive disease, with a median survival from diagnosis of 2–3 years [3, 4]. Acute respiratory deteriorations occur in IPF, due to a known cause (like respiratory tract infection) or due to an unknown cause (termed ‘acute exacerbations’) [3, 4]. Acute exacerbations are the leading cause of hospitalization in IPF (5,6). The recent advent of anti-fibrotic drug therapies for IPF are successful in slowing disease progression, but are not curative [7, 8]. Although lung transplantation is a definite treatment for IPF, availability is limited to a small percentage of individuals due to limited organ supply [9].

Sleep breathing disorders, including obstructive sleep apnea (OSA) [10–15] and sustained nocturnal hypoxemia [11, 16], are commonly encountered in IPF. In advanced IPF, hypoventilation may also occur,
but the prevalence of this sleep breathing disorder in IPF is not well-known. Untreated sleep breathing disorders may worsen IPF through several mechanisms. First, chronic, intermittent hypoxemia has been shown in animal models to promote pulmonary fibrosis through oxidative and inflammatory pathways [17, 18]. Second, repetitive forced inspirations against a closed glottis, which occurs in OSA, may cause recurrent tractional injury to peripheral lung tissue, which may in turn promote pulmonary fibrosis [19]. Third, gastroesophageal reflux, which can be induced by OSA [20], may lead to the development or progression of IPF [21, 22]. Finally, untreated OSA may contribute to complications of pulmonary arterial hypertension [23], the presence of which is associated with increased mortality in IPF [24]. Although sleep breathing disorders may theoretically worsen IPF, there is a paucity of published literature on whether diagnosing and treating sleep breathing disorders in the setting of IPF influences health outcomes. Two small, observational studies involving individuals with newly-diagnosed IPF and moderate-to-severe OSA showed that those adherent with positive airway pressure (PAP) therapy had significantly better survival than those that were non-adherent [14, 15] but that there was no improvement in exacerbations necessitating hospitalization [14]. A final observational study involving individuals with a variety of forms of interstitial lung disease (only 32.5% of whom had IPF) found no improvement in all-cause mortality or progression-free survival among those with OSA versus no OSA, nor among those with OSA adherent with PAP compared to those with OSA and not using PAP [25]. However, in the subset of individuals with interstitial lung disease requiring supplemental oxygen, adherence to PAP therapy for OSA was associated with significantly better progression-free survival [25]. The need for further research to clarify the importance of diagnosing and treating sleep breathing disorders in IPF has been advocated by international IPF guidelines [3].

In Ontario, Canada, sleep breathing disorders are diagnosed solely via laboratory-based polysomnography (PSG), with testing mandated prior to the initiation of appropriate treatments. The purpose of this study was to evaluate the association between receipt of PSG and respiratory-related hospitalization and mortality among individuals with IPF.

**Methods**

**Study design.** This was a retrospective cohort study. We analyzed health administrative data housed at ICES (formerly known as Institute for Clinical Evaluative Sciences) for the province of Ontario, Canada (13.5 million people), for the period April 1, 2007 to March 31, 2019. Because all residents of Ontario have public health insurance, with a single payer for all medically necessary health services, our analyses are population-based. ICES is a prescribed entity under Sect. 45 of Ontario’s Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. This project was conducted under Sect. 45 and received approval from ICES’ Privacy and Legal Office. This project was also approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Canada.
**Data sources.** Using unique encoded identifiers, multiple Ontario health care administrative databases were linked and analyzed at ICES, including: the Canadian Institute for Health Information Discharge Abstract database (CIHI-DAD) (contains information on all hospital discharges); the National Ambulatory Care Reporting System (NACRS) database (contains information on emergency room (ER) and hospital-based clinic visits); the Ontario Health Insurance Plan (OHIP) claims database (contains information on all physician fee-for-service patient care claims, in both ambulatory and hospital settings); the Ontario Drug Benefit (ODB) database (contains information on all publicly-funded, outpatient drug dispensings to individuals aged 65 years and older); and, the Registered Persons Database (contains information on demographics and mortality). Other databases that were used are outlined in the online supplement.

**Study population.** Ontario residents with a diagnosis of IPF aged 66 years and older between April 1, 2007 and December 31, 2017 were considered. We identified individuals with IPF from health administrative data, using an algorithm developed by a group of internationally-recognized IPF experts [1] that has been previously applied in multiple published studies [1, 26–28]. According to this algorithm [1, 26–28], individuals were considered to have IPF if the following three criteria were met: 1) there was at least one International Classification of Diseases Version 10 (ICD-10) coding for J84.1 (codes for IPF and usual interstitial pneumonia) in either Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) or National Ambulatory Care Reporting System (NACRS) between April 1, 2007 and December 31, 2017; and, 2) there was at least one claim for either a computed tomography chest scan, or a lung biopsy (including transbronchial biopsy, surgical lung biopsy, or endobronchial ultrasound and biopsy), or a bronchoscopy, in the Ontario Health Insurance Plan (OHIP) (see online supplement for relevant codes), prior to the last J84.1 coding (with a maximum look-back to April 1, 2006); and, 3) there was no coding for other forms of interstitial lung disease (see online supplement for relevant codes) in either CIHI-DAD or NACRS within the 12 months after the last J84.1 coding (with a maximum follow-up date of December 31, 2018). Although individuals with IPF younger than 66 years old were excluded from this study (because drug dispensing data were not available for them in the Ontario Drug Benefit database and we considered it important to adjust our analyses for receipt of pharmacotherapies), IPF is a disease of older adults, with an estimated 70% or more of affected individuals being older than age 65 years [2, 28].

Two exclusion criteria were applied. First, individuals receiving palliative care (based on physician service and hospitalization codes) in the year prior to the index date (defined below) were excluded, as individuals receiving such care are more likely to have poor health outcomes and less likely to undergo PSG, and their inclusion could serve to potentially introduce bias. Second, individuals that in the five years prior to the index date (defined below) underwent any PSG, or received PAP therapy, or received home supplemental oxygen, were excluded. These groups were excluded because they may have already acquired health benefits from having sleep breathing disorder diagnosed and treated, and if not excluded, their presence could then potentially introduce bias.

**Group and index date definitions.**
Exposed group. An individual was classified as exposed if the following two criteria were met: 1) there was an OHIP claim for any PSG (see online supplement for relevant codes) between April 1, 2007 and December 31, 2017, after the first J84.1 coding; and, 2) there was an OHIP claim for spirometry (see online supplement for relevant codes) within the 12 months preceding the PSG. The latter criterion was included in order to ensure that both exposed and control individuals underwent spirometry, as controls were identified by receipt of this testing (further details outlined below) and since undergoing spirometry may influence health outcomes in IPF. Only laboratory-based (and not home-based) PSG designated exposed group classification for the following reasons: home-based testing is not currently reimbursed by OHIP, and therefore, few, if any, individuals were anticipated to have received it; in Ontario, it is mandated that prescription of any home PAP therapy be supported by a laboratory-based PSG (29); and, clinical practice guidelines do not recommend home-based sleep testing for individuals with chronic respiratory disease (like IPF) [30, 31]. If an individual underwent more than one PSG within the study accrual period, then only the first one was considered. The index date was 3 months after the date of the first PSG. The rationale for the index date being set 3 months after the PSG date, and not sooner, was to allow individuals a reasonable amount of time following their PSG to see a physician regarding the results and have possible treatment initiated.

Although receipt of certain forms of sleep breathing disorder therapy (i.e., PAP and supplemental oxygen) is partially recorded in Ontario health administrative databases, this was intentionally not selected as the exposure for several reasons. First, OSA may be reasonably treated in some individuals with either weight reduction, positional therapy or a mandibular advancement device, and receipt of these therapies are not captured in our health administrative databases. Individuals receiving such therapies would be erroneously classified as controls, if receipt of PAP and/or supplemental were selected as the exposure. Second, because there is incomplete recording of PAP therapy receipt in our health administrative databases, the control group could be contaminated by exposed individuals, had PAP receipt been selected as the exposure.

Control group. Individuals in the control group did not undergo any PSG between April 1, 2007 and December 31, 2017. Individuals entered the control group by receiving spirometry at least once between April 1, 2007-December 31, 2017 after the first J84.1 coding. Receipt of an investigation was intentionally selected to define control group entry in order to minimize bias, since exposed group entry involved investigation receipt (i.e., PSG). Spirometry was selected as the testing for control group designation, since this is commonly performed test in IPF for both diagnostic and follow-up reasons. If spirometry had been received more than once by controls during the accrual period, a spirometry receipt date was randomly selected for such individuals, and then based on the time distribution of spirometry receipt to PSG receipt in the exposed group, a random date following that distribution was assigned to controls after the spirometry receipt date. Using this approach, a fictitious PSG date was in effect created for each control. The index date was 3 months after the fictitious PSG date, consistent with the approach used for the exposed group.
Outcomes. Respiratory-related hospitalization was the primary outcome, since this is a clinically-important event among individuals with IPF, associated with high mortality risk [32, 33]. All-cause mortality was a secondary outcome. Respiratory-related hospitalization was defined by one of the following ICD-10 codes being recorded in CIHI-DAD as the reason for hospitalization: J84.1 (interstitial pulmonary disease); J96 (respiratory failure); J09-18, J20-22 and J40 (pneumonia); and, I27.0, I27.2 and I27.9 (pulmonary hypertension). Pneumonia and pulmonary hypertension were included as reasons for respiratory-related hospitalization, since these respiratory pathologies are known to occur in IPF, may necessitate hospitalization, and are associated with increased mortality risk [24, 32–33]. All outcomes were evaluated up to 12 months after the index date (with the latest possible follow-up date of March 31, 2019, assuming a PSG date of as late as December 31, 2017, which would then result in an index date of March 31, 2018 [Figure 1 depicts study time frames]), or up to the date of death, or up to date of lung transplantation (see online supplement for definition), whichever came first. Individuals were censored on the date of lung transplantation, because risk for IPF-related morbidity and mortality was anticipated to dramatically differ post-lung transplantation.

Propensity score matching. Propensity score matching was used to create matched samples of exposed and control individuals on baseline sociodemographic and health characteristics to reduce bias [34]. A 1:1 matching ratio was selected, since this was previously shown to minimize bias and inclusion of more controls results in minimal precision increase [35]. Following previously published recommendations, individuals were matched on the logit of the propensity score using a width caliper equal to 0.2 of the standard deviation of the logit of the propensity score [36]. A propensity score for PSG receipt was developed using logistic regression modelling incorporating 41 variables, including multiple markers of IPF severity (such as, respiratory-related hospitalization (defined above) in the year prior to the index date, intensive care unit (ICU) admission during a respiratory-related hospitalization in the year prior to the index date, physician-diagnosed congestive heart failure [CHF], and systemic corticosteroid or respiratory antibiotic receipt in the year prior to the index date), general health status, comorbidities, health care system utilization, relevant prescription medication receipt and demographics. A full list of variables included in the propensity score model can be found in Table 1. Exposed and control individuals were matched at the index date on the propensity score, as well as on the following variables in order to facilitate planned sensitivity analyses (described below): respiratory-related hospitalization in the year prior to the index date; CHF diagnosis prior to the index date; systemic corticosteroid receipt in the year prior to the index date; and, sex.
Table 1
Cohort baseline characteristics, before and after propensity score matching (abridged version*)

| Baseline characteristics                          | Prior to propensity score matching | After propensity score matching |
|---------------------------------------------------|-----------------------------------|-------------------------------|
|                                                   | Exposed  N = 201                  | Controls  N = 4843            | Exposed  N = 189                  | Controls  N = 189            | Standardized difference^† |
| Age (mean + SD)                                   | 75.9 ± 6.2                        | 78.3 ± 6.8                    | 76.2 ± 6.1                        | 76.4 ± 6.8                    | 0.37                          |
| Women (%)                                         | 33.8                               | 45.1                          | 33.3                               | 33.3                          | 0.23                          |
| Respiratory-related hospitalization past year (%) | 19.9                               | 9.1                           | 18.5                               | 18.5                          | 0.31                          |
| ICU admission during respiratory-related hospitalization past year (%) | 4.0                                | 1.5                           | 4.2                                | 4.8                           | 0.15                          |
| Congestive heart failure                          | 46.3                               | 29.8                          | 45.5                               | 45.5                          | 0.34                          |
| Systemic corticosteroid receipt past year (%)    | 37.3                               | 33.0                          | 37.0                               | 37.0                          | 0.09                          |
| Respiratory antibiotic receipt past year (%)     | 72.1                               | 66.5                          | 72.0                               | 73.5                          | 0.12                          |
| Anti-fibrotic drug§ receipt past year (%)         | ‡                                  | 0.9                           | ‡                                  | ‡                             | 0.09                          |
| Total number outpatient visits past year (mean + SD) | 19.2 ± 10.2                       | 15.7 ± 9.2                    | 18.9 ± 10.0                       | 18.1 ± 9.3                    | 0.36                          |
| CT Chest scan past year (%)                       | 67.7                               | 54.7                          | 66.7                               | 69.3                          | 0.27                          |
| Echocardiogram past year (%)                      | 65.7                               | 43.8                          | 64.0                               | 64.6                          | 0.45                          |
| Exercise oximetry past year (%)                  | 38.3                               | 31.8                          | 37.6                               | 37.6                          | 0.14                          |
| Pulmonary embolism§ (%)                           | 6.0                                | 3.2                           | 6.3                                | 6.9                           | 0.13                          |
| COPD (%)                                          | 70.6                               | 67.6                          | 69.8                               | 68.8                          | 0.07                          |

*Standardized difference: t-statistic divided by the standard deviation of the difference.

†Standardized difference: t-statistic divided by the standard deviation of the difference among the matched groups.

§§‡‡ Unavailable data.
### Baseline characteristics

|                          | Prior to propensity score matching | After propensity score matching |
|--------------------------|------------------------------------|---------------------------------|
|                          | Exposed N = 201 | Controls N = 4843 | Standardized difference† | Exposed N = 189 | Controls N = 189 | Standardized difference† |
| GERD (%)                 | 6.5 | 5.2 | 0.06 | 6.3 | 5.8 | 0.02 |
| Myocardial infarction (%)| 14.9 | 10.0 | 0.15 | 14.3 | 16.4 | 0.06 |
| Other pulmonary disease (%)| 94.5 | 87.4 | 0.25 | 94.2 | 94.7 | 0.02 |
| Opioid receipt past 3 months (%)| 17.9 | 17.8 | 0.00 | 19.0 | 19.0 | 0.00 |
| Diuretic medication receipt past 3 months (%)| 36.8 | 23.8 | 0.29 | 34.4 | 37.0 | 0.06 |
| Other cardiac drug** receipt past 3 months (%)| 77.6 | 67.3 | 0.23 | 77.2 | 77.8 | 0.01 |

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux; ICU = intensive care unit; ODB = Ontario Drug Benefit; SD = standard deviation

* A full list of the variables included in the propensity score model can be found in the Online Supplement

† Standardized differences of > 0.10 are thought to indicate potentially meaningful differences

‡ Data has been suppressed, according to ICES guidelines, because of small sample size

§ Includes Pirfenidone and Nintedanib

‖ Presence of comorbidities was based on 3-year look-back from the index date

¶ Includes asthma, bronchiectasis, occupational lung disease, pleural effusion, interstitial disease, pneumothorax, atelectasis and other

** Includes beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB)

### Statistical analysis

To assess the adequacy of the matching process, standardized differences comparing the distribution of each of the covariates between the exposed and control groups were calculated before and after propensity score matching [37]. For the respiratory-related hospitalization outcome, hazard ratios (HR) with 95% confidence intervals (CI) were calculated using cause-specific modelling that accounted for the competing risk of death. For all-cause mortality, a Cox model was used...
to regress the hazard of death on exposure status. All regression models used a robust variance estimator [38]. Number needed to treat (NNT) was estimated by calculating the inverse of the absolute risk difference. Cumulative incidence function curves were estimated for respiratory-related hospitalization (where the competing risk death was adjusted for) and Kaplan-Meier curves were estimated for all-cause mortality.

**Sensitivity analyses.** History of respiratory exacerbation, CHF complication and systemic corticosteroid receipt are all considered markers of IPF severity [32–33, 39]. Therefore, outcomes were examined stratifying by each of these variables separately, in order to further minimize confounding by indication by evaluating outcomes among healthier subsets of persons, and to further minimize ‘healthy user’ bias by evaluating outcomes among sicker subgroups of individuals. Additional sensitivity analyses are outlined in the online supplement. The propensity score was re-estimated for each specific sensitivity analysis.

**Results**

**Derivation and description of the cohort.** There were 5044 individuals with IPF identified, aged 66 years and older, of whom 201 (4.0%) received PSG during the accrual period (Fig. 2). Out of this group, 189 (94.0%) exposed individuals were matched to an equal number of controls. Before propensity score matching, compared to the control group, the exposed group had a younger mean age and consisted of a greater proportion of men and rural residents, and a smaller percentage of low income individuals, and multiple markers of IPF severity were more prevalent (such as, being admitted to hospital or ICU for respiratory-related reasons in the preceding year, having CHF, having other comorbidities, and systemic corticosteroid and respiratory antibiotic receipt). After propensity score matching, exposed and control individuals were adequately balanced on baseline characteristics, with standardized differences being below 10% for all variables, except five (rural residence, diabetes, kidney disease, antiplatelet/anticoagulant drug receipt, and year of cohort entry), where trivial imbalance remained (standardized differences ranged from 11–17%) (Table 1).

**Main analysis.** In the propensity score matched cohort, compared to controls, individuals undergoing PSG had significantly reduced rates of respiratory-related hospitalization (HR 0.43, 95% CI 0.24–0.75, p = 0.003, NNT 11) and all-cause mortality (HR 0.49, 95% CI 0.30–0.80, p = 0.004, NNT 10) (Table 2). The cumulative incidence of respiratory-related hospitalization was significantly lower and the probability of survival was significantly higher among individuals undergoing PSG versus controls (Fig. 3).
Table 2
Hazard ratios (HR) and confidence intervals (CI) for outcomes in propensity-score matched cohort (main analysis)

| Outcome                        | Exposure status | Number of events (%) | HR (95% CI)     | p-value |
|--------------------------------|-----------------|----------------------|-----------------|---------|
| Respiratory-related hospitalization | Exposed         | 15 (7.9)             | 0.43 (0.24–0.75) | 0.003   |
|                                | Controls        | 32 (16.9)            | 1.00             |         |
| All-cause mortality            | Exposed         | 21 (11.1)            | 0.49 (0.30–0.80) | 0.004   |
|                                | Controls        | 40 (21.2)            | 1.00             |         |

Sensitivity analyses.

By respiratory-related hospitalization. In the subgroup of individuals that experienced no respiratory-related hospitalization in the year prior to the index date, compared to controls, individuals undergoing PSG had significantly reduced rate of all-cause mortality (HR 0.34, 95% CI 0.23–0.83, p = 0.01), but not respiratory-related hospitalization (Table 3). In the subgroup of individuals with ≥ 1 respiratory-related hospitalization in the year prior to the index date, significantly reduced rate of respiratory-related hospitalization (HR 0.38, 95% CI 0.15–0.99, p = 0.05) was observed among individuals undergoing PSG relative to controls, but there was no significant difference all-cause mortality rate.
Table 3
Hazard ratios (HR) and confidence intervals (CI) for outcomes in propensity-score matched cohort, stratifying by respiratory-related hospitalization

| Respiratory-related hospitalization status | Outcomes                          | Exposure status | Number of events (%) | HR (95% CI)   | p-value |
|-------------------------------------------|-----------------------------------|-----------------|----------------------|----------------|---------|
| No respiratory-related hospitalization in year prior to index date | Respiratory-related hospitalization | Exposed         | 9 (5.9)              | 0.47 (0.21–1.06) | 0.07    |
|                                            |                                    | Controls        | 18 (11.8)            | 1.00           |         |
|                                            | All-cause mortality                | Exposed         | 14 (9.2)             | 0.34 (0.23–0.83) | 0.01    |
|                                            |                                    | Controls        | 30 (19.6)            | 1.00           |         |
| >=1 respiratory-related hospitalization in year prior to index date | Respiratory-related hospitalization | Exposed         | *                    | 0.38 (0.15–0.99) | 0.05    |
|                                            |                                    | Controls        | 10 (34.5)            | 1.00           |         |
|                                            | All-cause mortality                | Exposed         | *                    | 0.42 (0.17–1.05) | 0.06    |
|                                            |                                    | Controls        | 10 (34.5)            | 1.00           |         |

*Data has been suppressed, according to ICES guidelines, because of small sample size

By CHF. Compared to controls, there were no significant differences in rates of respiratory-related hospitalization or all-cause mortality among those undergoing PSG, in both the subgroup without CHF complication and in the subgroup with CHF complication (Table 4).
### Table 4
Hazard ratios (HR) and confidence intervals (CI) for outcomes in propensity-score matched cohort, stratifying by congestive heart failure (CHF)

| Sex          | Outcomes                      | Exposure status | Number of events (%) | HR (95% CI)    | p-value |
|--------------|-------------------------------|-----------------|----------------------|----------------|---------|
| Without CHF | Respiratory-related hospitalization | Exposed        | 9 (8.7)              | 0.57 (0.25–1.33) | 0.19    |
|              |                               | Controls        | 15 (14.4)            | 1.00            |         |
|              | All-cause mortality           | Exposed        | 10 (9.6)             | 0.75 (0.33–1.72) | 0.49    |
|              |                               | Controls        | 13 (12.5)            | 1.00            |         |
| With CHF    | Respiratory-related hospitalization | Exposed        | 6 (7.1)              | 0.41 (0.16–1.05) | 0.06    |
|              |                               | Controls        | 14 (16.7)            | 1.00            |         |
|              | All-cause mortality           | Exposed        | 9 (10.7)             | 0.45 (0.20–1.02) | 0.06    |
|              |                               | Controls        | 19 (22.6)            | 1.00            |         |

By systemic corticosteroid receipt. In the subgroup of individuals with no systemic corticosteroid receipt in the year prior to the index date, there were no significant differences among individuals having undergone PSG versus controls in respiratory-related hospitalization and all-cause mortality rates (Table 5). In the subgroup of individuals that received a systemic corticosteroid in the year prior to the index date, there was significantly lower rate of respiratory-related hospitalization (HR 0.37, 95% CI 0.14–0.94, p = 0.04), but not all-cause mortality, among those undergoing PSG relative to controls.
Table 5
Hazard ratios (HR) and confidence intervals (CI) for outcomes in propensity-score matched cohort, stratifying by systemic corticosteroid receipt

| Sex                                      | Outcomes                    | Exposure status | Number of events (%) | HR (95% CI)  | p-value |
|------------------------------------------|-----------------------------|-----------------|----------------------|--------------|---------|
| No corticosteroid receipt in year prior to index date | Respiratory-related hospitalization | Exposed         | 8 (6.8)              | 0.54         | (0.23–1.30) | 0.17    |
|                                          |                             | Controls        | 14 (11.9)            | 1.00         |         |
|                                          | All-cause mortality         | Exposed         | 10 (8.5)             | 0.47         | (0.22–1.02) | 0.06    |
|                                          |                             | Controls        | 20 (17.0)            | 1.00         |         |
| Corticosteroid receipt in year prior to index date | Respiratory-related hospitalization | Exposed         | 6 (8.6)              | 0.37         | (0.14–0.94) | 0.04    |
|                                          |                             | Controls        | 15 (21.4)            | 1.00         |         |
|                                          | All-cause mortality         | Exposed         | 9 (12.9)             | 0.57         | (0.25–1.28) | 0.17    |
|                                          |                             | Controls        | 15 (21.4)            | 1.00         |         |

**Discussion**

Our population-level study demonstrates the novel and important finding that undergoing PSG is associated with significantly lower rates of respiratory-related hospitalization and all-cause mortality among individuals with IPF. The credibility of our findings is further corroborated by significantly reduced respiratory-related hospitalization in association with PSG receipt amongst sicker subgroup of individuals, like those with prior history of respiratory-related hospitalization and prior systemic corticosteroid receipt.

Obviously, PSG in of itself is not responsible for the observed positive health outcomes. Rather, subsequent downstream events following PSG (i.e., diagnosis and treatment of sleep breathing disorders) are presumed to explain the observed benefits, with PSG simply reflecting a surrogate marker for these events. Although our study is the first population-based study demonstrating positive outcomes in IPF following PSG, our findings are consistent with the results of two earlier, smaller observational studies that showed improved survival among individuals with combined IPF and OSA in association
with PAP adherence [15, 16]. Our results are also consistent with three, small observational studies reporting improvements in scores on multiple quality-of-life instruments in association with treatment of OSA in IPF [15–16, 40]. Our findings of improved health outcomes differ from another observational study, where neither having OSA, nor being adherent with PAP therapy, generally influenced all-cause mortality or progression-free survival, although in this study only a minority of individuals with interstitial lung disease had IPF (32.5%) [25]. Although significant reductions in morbidity and mortality were observed in association with PSG receipt among individuals with IPF, only a very small proportion of our cohort (4.0%) underwent this beneficial testing, underscoring its wide under-utilization in the IPF population.

To account for measured differences between our exposed and control groups, we performed rigorous propensity score matching, adequately balancing on 41 covariates, including on multiple markers on IPF severity, general health status, comorbidities and health care system utilization. Furthermore, the fact that, as with the exposed group, control group entry was based on receipt of a test (i.e., spirometry) serves to makes it less likely that changes in overall health status or health-seeking behaviour explain our results. Reduced respiratory-related hospitalization in association with PSG in the subgroups of individuals with prior history of respiratory-related hospitalization and previous systemic corticosteroid receipt (which are sicker subgroups of individuals) decreases the likelihood that our findings are as result of 'healthy user' bias. Small sample size may account for the fact that rate of all-cause was not significantly lower in association with PSG in the aforementioned two subgroups, and that significantly improved outcomes were not observed in the sensitivity analyses by CHF comorbidity, as point estimates were below 1.00 for all outcomes across all subgroups.

Our study has several limitations. Causation cannot be concluded as the explanation for our findings. Unmeasured differences between our exposed and control groups could explain our findings. Information on symptoms, lung function and exercise capacity measures, oxygenation status, and extent of fibrosis on imaging, were not available in our health administrative databases. Nevertheless, we balanced the exposed and control groups on a number of important IPF severity markers, including history of respiratory-related hospitalization, history of ICU admission, CHF, and previous systemic corticosteroid and respiratory antibiotic receipt. Furthermore, any unmeasured IPF severity markers would most likely track disease severity markers that we did have information on, and these were in fact consistently more prevalent among exposed versus control individuals, before propensity score matching. Specifically, before propensity score matching, compared to controls, individuals undergoing PSG were more frequently admitted to hospital or ICU for respiratory-related reasons in the preceding year, had CHF and other forms of cardiovascular disease, had other pulmonary comorbidities, and received a systemic corticosteroid and a respiratory antibiotic. Any unmeasured IPF severity markers would logically be anticipated to track these, and if persistently unbalanced after propensity score matching, then bias the analysis against the exposed group, and yet, better health outcomes were observed in association with PSG receipt among these individuals. Our IPF identification algorithm, while developed by internationally-recognized IPF experts [1] and previously applied [1, 26–28], has not been validated. The IPF algorithm largely relies on a J84.1 coding occurring in the context of a hospitalization or emergency room (ER) visit,
which has the potential to under-capture individuals with milder degrees of disease, who would less likely present to hospital. Therefore, our results may not be applicable to all individuals with IPF. However, if individuals with milder degrees of IPF were less likely included in our study, this would only serve to decrease possible 'healthy user' bias influencing our results. Our study used a surrogate marker for diagnosis and treatment of sleep breathing disorder (i.e., PSG receipt). A sensitivity analysis by PAP or supplemental oxygen receipt was not feasible because of small sample size (only 37/201 [18%] of our cohort of IPF undergoing PSG were recorded as having subsequently received PAP or supplemental oxygen) and this is as a result of known incomplete recording of these therapies in our health administrative databases. While we propose that our findings of better health outcomes in association with PSG testing are likely as a result of diagnosis and treatment of sleep breathing disorder, the institution of other cardio-pulmonary interventions/treatments as a consequence of PSG results may have also possibly contributed to observed improvements. It is possible that undergoing PSG testing is reflective of having a more thorough health care provider, and that the observed improved health outcomes in association with PSG are then as a consequence of receipt of more thorough overall medical care, rather than direct downstream consequences following PSG. However, our propensity score model included multiple markers of health care utilization, including number of outpatient physician visits in the preceding year, receipt of other types of investigations (including chest computed tomography, echocardiography and exercise oximetry testing) and receipt of multiple types of pharmacotherapies (including anti-fibrotic therapy, systemic corticosteroids, respiratory antibiotics, inhalers, smoking cessation drugs and cardiac medications), and exposed and controls were well-balanced on all these variables, thereby making it less likely that differences in overall medical care received explain our findings. Our health administrative databases also do not contain objective information relating to sleep breathing disorder diagnosis (e.g., apnea-hypopnea index, oxygen desaturation measures). Our findings also potentially do not apply to individuals with IPF under the age of 66 years old, who were excluded from our study.

Receipt of PSG was found to be associated with significantly lower rates of respiratory-related hospitalization and all-cause mortality among individuals with IPF. Our findings have potentially enormous implications for the management of IPF, a disease that is progressive and for which there are limited treatment options. Although our study used PSG as a surrogate, our results suggest that evaluation for and treatment of sleep breathing disorders is highly beneficial in IPF. Further research, particularly clinical trials, would be needed to exclude possible unresolved confounding and establish causation.

**Abbreviations**

CHF
congestive heart failure
CIHI-DAD
Canadian Institute for Health Information Discharge Abstract Database
CI
Declarations

Ethics approval: ICES is a prescribed entity under section 45 of Ontario’s Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and approved by ICES’ Privacy and Legal Office. This project was also approved by the Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Canada. All methods were performed in accordance with ICES guidelines and regulations.

Consent for study participation: This study was conducted under Section 45 of Ontario’s Personal Health Information Protection Act, which authorizes ICES to collect personal health information, without consent,
for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. This project was conducted under section 45, and approved by ICES' Privacy and Legal Office. The Research Ethics Board at Sunnybrook Health Sciences Centre, Toronto, Canada, also approved the waiving of informed consent.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used in this study are held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Competing interests: None of the authors have financial or non-financial competing interests to declare.

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Authors contributions: Study conception and funding acquisition: NTV; Study design: NTV, ASW, PAC, TK, CMR and ASG; Manuscript preparation: NTV; Review and editing of manuscript: NTV, ASW, PAC, TK, CMR and ASG

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Figures
Figure 1

Study time frames
Figure 2
Flow diagram outlining exposed and control group identification

5044 individuals with idiopathic pulmonary fibrosis (IPF) aged 66 years and older were identified between April 1, 2007 and December 31, 2017

201 (4.0%) received polysomnography (PSG)

189 (94.0%) were propensity-score matched to an equivalent number of individuals not receiving PSG

4843 (96.0%) did not receive PSG

189 (3.9%) individuals not receiving PSG were included in the analysis
Figure 3

(a) Cumulative incidence function curves for respiratory-related hospitalization and (b) Kaplan-Meier curves for all-cause mortality

Supplementary Files
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