Outcomes in Patients With IPF Treated With Antifibrotic Therapies Compared With Untreated Patients in the US Medicare Population

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RATIONALE

- Idiopathic pulmonary fibrosis (IPF) is a form of chronic interstitial lung disease (ILD) of unknown cause prevalent in adults ≥ 55 years old and is characterized by progressive dyspnea and cough, disability and ultimately death[1–3]
- The median survival from the time of diagnosis was 3 to 4 years prior to 2 antifibrotics, pirfenidone and nintedanib, entering the US market on 10/15/2014[4]
  - Both have been shown to slow disease progression in randomized clinical trials and were incorporated as conditional recommendations in the latest treatment guidelines[4–6]
- Despite the acceptance of antifibrotic drug therapy into IPF treatment guidelines, research has shown that many patients remain untreated[4,7,8]
- Limited real-world data are available about antifibrotic treatment effectiveness among older patients with IPF, especially those not covered by an employee-sponsored healthcare plan[9]
- This study compared mortality and all-cause and respiratory-related hospitalizations between patients with IPF who started antifibrotic therapy and those who were untreated

CONCLUSIONS AND IMPLICATIONS

- **On the basis of real-world evidence generated in this study, the use of antifibrotics confers significant health and survival benefits to Medicare beneficiaries who are diagnosed with IPF**
- **Antifibrotic therapy shows a clear protective effect against mortality and all-cause and respiratory-related hospitalizations compared with the absence of such treatment**
- **For patients with IPF who were treated with antifibrotic therapy, the risk of mortality is estimated to be 38% lower than for those not on therapy, while the risk of hospitalization is approximately 30% lower**

METHODS

Study Design:*
- Retrospective analysis of 2010–2017 administrative claims data from the 100% sample of Medicare beneficiaries (Research Identifiable Files)
- Treated patients were compared with a matched cohort of untreated historical controls

Patient Population:
- All Medicare beneficiaries with IPF defined as having ≥ 1 inpatient or ≥ 2 outpatient claims with an ICD-9-CM diagnosis code for IPF (*ICD-9-CM: 516.3, 516.30, 516.31; ICD-10-CM: J84.111, J84.112*)
- 2 groups were created relative to the US FDA approval date for antifibrotic therapy (10/15/2014):
  1. **Treated patients:** beneficiaries who initiated antifibrotics (≥ 1 prescription refill of pirfenidone or nintedanib) during a treated ID period of 10/15/2014–12/31/2017
     - The first fill date in the ID period was defined as index date (index)
  2. **Untreated patients:** beneficiaries not receiving antifibrotics during an untreated ID period of 1/1/2012–10/14/2014 (e.g., untreated historical controls)
     - ≥ 1 IPF diagnosis had to occur during the ID period, with the first IPF claim defined as index

Censoring and Follow-up Time:
- Patients who received a lung transplant after index, treated patients who switched or discontinued index treatment and untreated patients were all censored on October 14, 2014, the day before antifibrotic FDA approval
- Patients were not required to have a minimum follow-up time after index
- Each patient was observed from 2 years prior to index until end of enrollment, a censoring event, death or study end, whichever came first, up to 33.5 months following index

Matching and Study Measures:
- To optimize the balance of characteristics between the study groups, untreated patients were matched 1:1 to treated patients by using the propensity score for covariates
- Primary study outcome: death from any cause during the follow-up period
- Secondary study outcomes: all-cause (elective and non-elective) and respiratory-related hospitalizations during follow-up

Statistical Analyses:
- Descriptive statistics were generated for all baseline characteristics
- The risks of mortality and hospitalizations were compared between treated and untreated patients using Cox proportional hazards models
- Negative binomial regression was used to compare rate of hospitalizations per month
- The final statistical models included all variables used in matching including additional confounders and have been adjusted for follow-up time

ICD-9-CM, International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification; IPF, idiopathic pulmonary fibrosis.
* Additional study design elements and selection criteria are included in the Supplemental Information.

RESULTS

Study Population

- We identified 4993 patients diagnosed with IPF who initiated treatment with antifibrotics (pirfenidone [n = 2587] and nintedanib [n = 2406]) during the study period (**Table 1**)
- After matching, there were 4641 treated patients (93.0%) with 4641 matched untreated controls

Table 1. Patient Demographics

	Treated (n = 4641)	Matched Untreated (n = 4641)	*P* Value*
Age, mean (SD), years	76.0 (5.6)	76.1 (5.8)	0.642
Age category, n (%)			0.151
67–74 years	2025 (43.6)	2086 (44.9)	
75–84 years	2202 (47.4)	2188 (47.1)	
≥ 85 years	414 (8.9)	367 (7.9)	
Female, n (%)	1735 (37.4)	1674 (36.1)	0.189
White, n (%)	4394 (94.7)	4411 (95.0)	0.424
Modified CCI, mean (SD)†	3.3 (2.9)	3.2 (2.8)	0.103
No. of chronic conditions, mean (SD)	7.8 (2.0)	7.7 (2.0)	< 0.001
COPD, including emphysema, n (%)	2768 (59.6)	2816 (60.7)	0.309
Obstructive sleep apnea, n (%)	1585 (34.2)	988 (21.3)	< 0.001
Lung cancer, n (%)	119 (2.6)	232 (5.0)	< 0.001
Pneumothorax, n (%)	326 (7.0)	135 (2.9)	< 0.001
Gastroesophageal reflux, n (%)	2724 (58.7)	2397 (51.6)	< 0.001
Obesity, n (%)	1174 (25.3)	733 (15.8)	< 0.001
Cardiovascular conditions, n (%)			
Atrial fibrillation	1043 (22.5)	1013 (21.8)	0.453
Congestive heart failure	1404 (30.3)	1408 (30.3)	0.928
Cor pulmonale	200 (4.3)	234 (5.0)	0.095
Ischemic heart disease	2669 (57.5)	2687 (57.9)	0.705
Pulmonary hypertension	483 (10.4)	514 (11.1)	0.299
Stroke	288 (6.2)	266 (5.7)	0.335
Venous thromboembolism	386 (8.3)	353 (7.6)	0.206
Smoking cessation therapy, n (%)	186 (4.0)	144 (3.1)	0.019
Pulmonary rehabilitation within 1 year prior to index, n (%)	651 (14.0)	381 (8.2)	< 0.001
Respiratory diagnostic services within 1 year prior to index, n (%)	4450 (95.9)	3800 (81.9)	< 0.001
Newly diagnosed patients with IPF, n (%)	2989 (64.4)	2961 (63.8)	0.545

CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis
* Statistical comparisons of means and percentages were conducted using t-tests and χ^2 tests, respectively.
† Excludes chronic pulmonary disease.

Frequency of Mortality and Hospitalization

- Patients treated with antifibrotic therapy vs. untreated patients had fewer deaths, and mean all-cause and respiratory-related hospitalizations per month
- There was a significantly lower rate of all-cause hospitalizations per patient-month among treated vs. untreated groups (incidence rate ratio [IRR], 0.65; 95% CI, 0.60, 0.71)
- There was also a significantly lower rate of respiratory-related hospitalizations per patient-month among treated vs. untreated groups (IRR, 0.65; 95% CI, 0.58, 0.73)

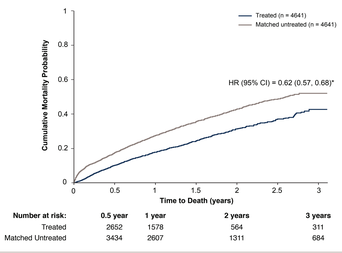
Table 2. Number of Deaths and Hospitalizations in the Variable Follow-Up Period Among Medicare Beneficiaries With IPF

	Treated (n = 4641)	Matched Untreated (n = 4641)	*P* Value
Death, n (%)	826 (17.8)	1777 (38.3)	< .001*
Hospitalizations per patient-month			
All-cause hospitalization	0.104 (0.33)	0.160 (0.41)	< .001†
Respiratory-related hospitalization‡	0.052 (0.24)	0.085 (0.31)	< .001†

* χ^2 test.
† Wald χ^2 test based on negative binomial model.
‡ Inpatient claims with primary diagnosis of respiratory disease (*ICD-9-CM*: 460.xx–519.xx; *ICD-10-CM*: J00.xx–J99.xx) or outpatient claims with any diagnosis of respiratory disease.

Risk of Mortality and Hospitalization

Figure 1. Risk of Mortality

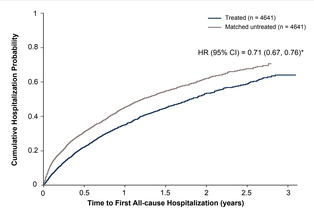


Number at risk:	0.5 year	1 year	2 years	3 years
Treated	2652	1578	564	311
Matched Untreated	3434	2607	1311	684

- There was a significantly lower risk in mortality between the treated and untreated groups

HR, hazard ratio.
* Adjusted for baseline covariates as described in Supplemental Information.

Figure 2. Risk of All-Cause Hospitalization

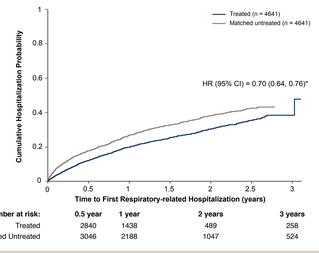


Number at risk:	0.5 year	1 year	2 years	3 years
Treated	2277	1246	374	195
Matched Untreated	2625	1731	718	339

- There was a significantly lower risk in all-cause hospitalizations among treated vs. untreated groups

HR, hazard ratio.
* Adjusted for baseline covariates as described in Supplemental Information.

Figure 3. Risk of Respiratory-Related Hospitalization



Number at risk:	0.5 year	1 year	2 years	3 years
Treated	2840	1438	489	258
Matched Untreated	3046	2188	1047	524

- There also was a significantly lower risk in respiratory-related hospitalizations among treated vs. untreated groups

HR, hazard ratio.
* Adjusted for baseline covariates as described in Supplemental Information.

REFERENCES

1. Lederer DJ, Martinez FJ. *N Engl J Med.* 2018;378:1811–1823.
2. Collard HR, et al. *Ann Am Thorac Soc.* 2015;12:981–987.
3. Raghu G, et al. *Lancet Respir Med.* 2014;2:566–572.
4. Maher TM, Strek ME. *Respir Res.* 2019;20:205.
5. Saito S, et al. *J Thorac Dis.* 2019;11(suppl 14):S1740–S1754.
6. Raghu G, et al. *Am J Respir Crit Care Med.* 2015;192:e3–e19.
7. Maher TM, et al. *BMC Pulm Med.* 2017;17:124.
8. Salisbury M, et al. *Am J Respir Crit Care Med.* 2020;201 [abstract A5622].
9. Dempsey TM, et al. *Am J Respir Crit Care Med.* 2019;200:168–174.

DISCLOSURES

J Mooney has participated as a clinical trial investigator for Boehringer Ingelheim and Genentech/Roche.

M Corral is an employee of Genentech, Inc.

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Supplemental Information

https://bit.ly/2CBVJja

https://bit.ly/2UVTRYW

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METHODS

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PATIENT DEMOGRAPHICS

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Methods

Inclusion criteria

- All Medicare beneficiaries diagnosed with IPF, defined as having ≥ 1 inpatient or ≥ 2 outpatient claims with an International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnosis code for IPF (*ICD-9-CM*: 516.3, 516.30, 516.31; *ICD-10-CM*: J84.111, J84.112) during the study period (1/1/2010–12/31/2017). Two groups of patients with IPF were created relative to the US Food and Drug Administration approval date for antifibrotic therapy (10/15/2014):
  1. Beneficiaries who initiated antifibrotic treatment (≥ 1 prescription fill of pirfenidone or nintedanib) during a treated ID period of 10/15/2014–12/31/2017 (i.e., treated patients)
  2. Beneficiaries not receiving antifibrotic treatment during an untreated ID period of 1/1/2012–10/14/2014 (i.e., untreated historical controls)
- Treated patients
  - The first fill date in the ID period was defined as index date (index)
  - Patients could not have any claims for pirfenidone or nintedanib prior to index and had to have ≥ 1 IPF diagnosis before index
- Untreated controls (e.g, historical untreated controls)
  - ≥ 1 IPF diagnosis had to occur during the ID period, with the first IPF claim defined as index
  - Untreated controls were allowed in the treatment group if they initiated treatment after regulatory approval date to avoid introducing selection bias, as patients with IPF who were not prescribed antifibrotic therapy once approved may be very different than patients who initiated such therapy
- Treated and untreated groups also met the following criteria:
  - ≥ 67 years old on index
  - Continuously enrolled in fee-for-service Medicare Parts A/B and Part D for 2 years prior to index (baseline period)
  - ≥ 1 CT scan occurring during baseline period, with an IPF diagnosis after a CT scan

CT, computed tomography; ICD-9/10-CM, International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnosis; ID, identification period; IPF, idiopathic pulmonary fibrosis.

Methods

Exclusion criteria

- Claim for another ILD diagnosis after the last observed IPF claim (to avoid potential misclassification) or lung transplant prior to index

ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

Methods

Censoring and follow-up time

- Patients who received a lung transplant after index were censored at the time of transplant
- Treated patients who switched or discontinued index treatment were censored at the time of switching or 60 days after discontinuing therapy (discontinuation was defined as a gap in use of > 60 days)
- Untreated patients were censored on 10/14/2014 (the day before antifibrotic approval)
- Patients were not required to have a minimum follow-up time after index; thus, each patient was observed from 2 years prior to index until end of enrollment, a censoring event, death or study end, whichever came first, up to 33.5 months following index

Methods

Propensity score matching

- To optimize the balance of characteristics between the study groups, untreated patients were matched 1:1 to treated patients by using the propensity score (nearest neighbor with caliper = 0.2 of the SD of the logit of the propensity score)
- The propensity for initiating antifibrotic treatment was estimated using logistic regression containing several baseline variables:
  - Age, sex, geographic region, quartile of median income of patient residential area, distance from patient residential area to an ILD specialty center (miles)
  - Charlson Comorbidity Index (CCI; modified to exclude chronic pulmonary disease), COPD, selected cardiovascular conditions (atrial fibrillation, congestive heart failure, ischemic heart disease, pulmonary hypertension, stroke and venous thromboembolism)
  - Proxies for disease severity (pneumonia, CT scan, respiratory-related hospitalization [defined below] or OCS use within 3 months prior to index; oxygen use and number of respiratory-related office visits in the year prior to index; newly diagnosed IPF)
- All main effects and significant 2-way interactions were retained
- Treated patients without a match were excluded

COPD, chronic obstructive pulmonary disease; CT, computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; OCS, oral corticosteroids.

Methods

Measures

- Outcomes
  - Primary study outcome: death from any cause during the follow-up period
  - Secondary study outcomes: all-cause and respiratory-related inpatient hospitalizations during follow-up
    - Respiratory-related hospitalization was defined as an inpatient claim with a primary diagnosis of respiratory disease (*ICD-9-CM: 460.*xx–519.xx; *ICD-10-CM*: J00.xx–J99.xx)
- Baseline measures (in addition to the variables used in matching) were:
  - Race, number of chronic conditions, obstructive sleep apnea, lung cancer, pneumothorax, gastroesophageal reflux, obesity, cor pulmonale, pulmonary rehabilitation and respiratory diagnostic services (in the year prior to index) and smoking cessation history
- All measures were calculated using Medicare claims and the applicable *ICD-9-CM* or *ICD-10-CM* diagnosis or procedure codes, Current Procedural Terminology codes and prescription drug codes

ICD-9/10-CM, International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification diagnosis.

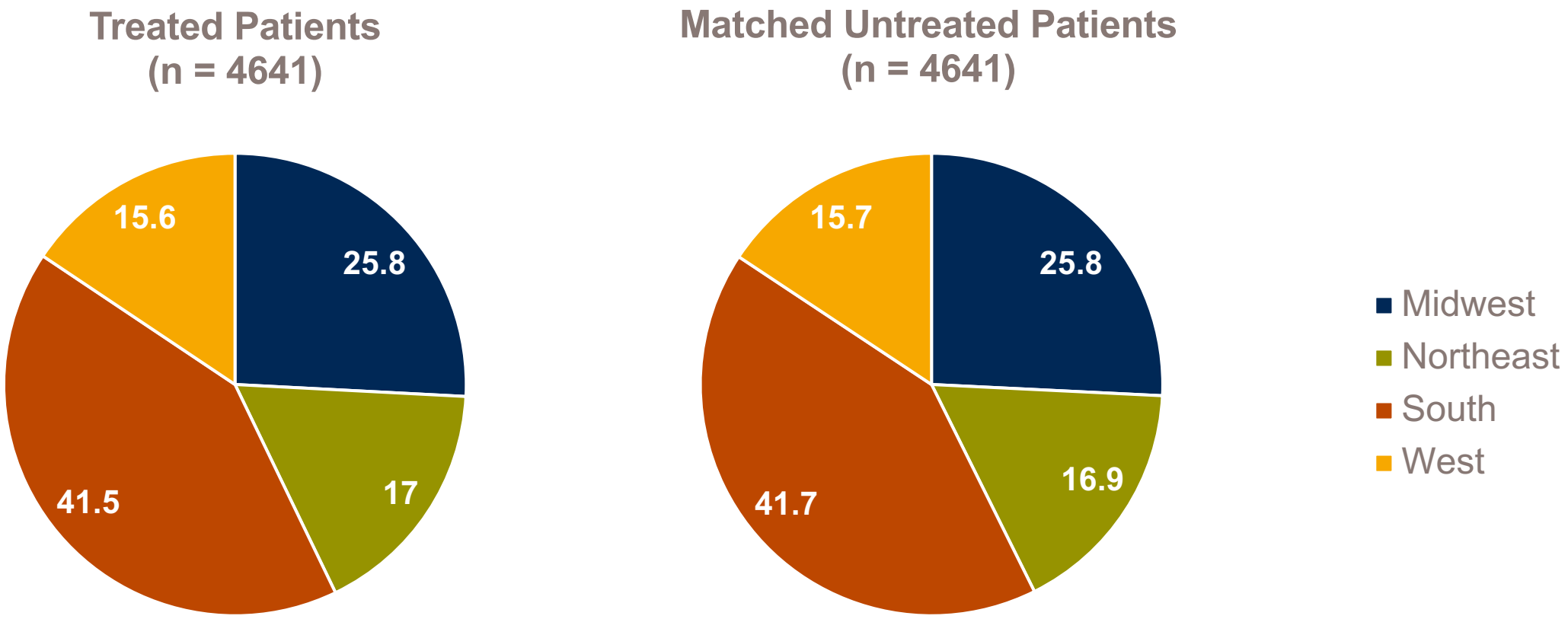
Methods

Statistical analysis

- Descriptive statistics were generated for all baseline characteristics
- Means and SDs were reported for continuous variables, and frequencies and percentages were reported for categorical data
  - Statistical comparisons of means and percentages were conducted using t-tests and X^2 tests, respectively
- The risks of mortality and hospitalization (all cause and respiratory related) were compared between treated and untreated patients by using cumulative probability curves and Cox proportional hazards regression
  - The proportional hazards assumption was checked for all covariates
- The rate of hospitalizations per month was compared using negative binomial regression
- The final Cox models and negative binomial models were adjusted for follow-up time and included all variables used in matching, in addition to the following variables, irrespective of statistical significance, to adjust for potential residual confounding:
  - Obstructive sleep apnea, lung cancer, pneumothorax, gastroesophageal reflux, obesity, pulmonary rehabilitation and respiratory diagnostic services in the year prior to index
- All statistical tests were performed as 2-sided and at a significance level of 0.05
- All data transformations and statistical analyses were performed using SAS version 9.4

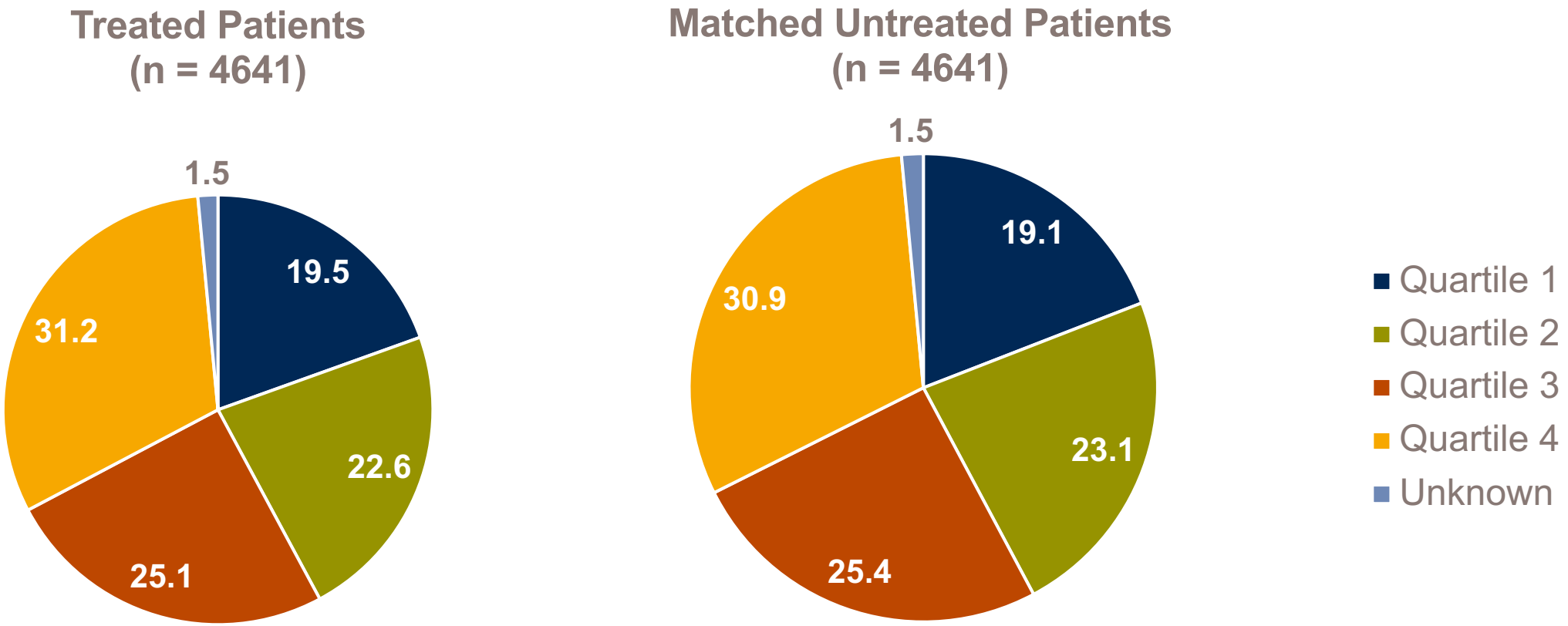
Patient demographics

Region (P = 0.998)



Patient demographics

*Median income of living area (P = 0.957)**



* Income quartiles based on an external population derived from Healthcare Cost and Utilization Project Nationwide Inpatient Sample.

Patient demographics

Other characteristics

Characteristic	Treated (n = 4641)	Matched Untreated Controls (n = 4641)	*P* value*
Distance from residential area to ILD specialty center, mean (SD) miles	100 (161.51)	101 (172.02)	0.824
Respiratory hospitalization within 3 mo. prior to index, n (%)	567 (12.2)	549 (11.8)	0.566
Pneumonia (bacterial or viral) within 3 mo. Prior to index, n (%)	577 (12.4)	545 (11.7)	0.308
CT scan within 3 mo. prior to index, n (%)	2195 (47.3)	2123 (45.7)	0.134
OCS use within 3 mo. prior to index, n (%)	1584 (34.1)	1664 (35.9)	0.082
Oxygen use within 1 year prior to index, n (%)†	2739 (59.0)	2810 (60.5)	0.133
Respiratory-related hospital visits within 1 year prior to index, mean (SD)	7.32 (5.54)	7.11 (7.03)	0.119

CT, computed tomography; ILD, interstitial lung disease; OCS, oral corticosteroids.
* Statistical comparisons of means and percentages were conducted using t-tests and X^2 tests, respectively
† Five patients who used pirfenidone and 4 who used nintedanib had evidence of an oxygen flow rate of ≥ 4 L/min.