

# Disparities in Lung Transplant among Patients with Idiopathic Pulmonary Fibrosis

## An Analysis of the IPF-PRO Registry

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### Abstract

**Rationale:** Lung transplant offers the potential to extend life for patients with idiopathic pulmonary fibrosis (IPF); yet, this therapeutic modality is only available to a small proportion of patients.

**Objectives:** To identify clinical characteristics and social determinants of health that differentially associate with lung transplant compared with death in patients with IPF.

**Methods:** We evaluated data from the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry, a multicenter U.S. registry of patients with IPF that was diagnosed or confirmed at the enrolling center in the previous 6 months. Patients were enrolled between June 2014 and October 2018. Patients who were listed for lung transplant were not eligible to enroll in the registry, but patients could be listed for transplant after enrollment. We performed a multivariable time-to-event analysis incorporating competing risks methodology to examine differential associations between prespecified covariates and the risk of lung transplant versus death. Covariates included factors related to lung transplant eligibility, clinical characteristics of IPF, and social determinants of health. Covariates were modeled as time independent or time dependent as appropriate.

**Results:** Among 955 patients with IPF, event rates of lung transplant and death were 7.4% and 16.3%, respectively, at 2 years. Covariates with the strongest differential association were age, median zip code income, and enrollment at a center with a

lung transplant program. Lung transplant was less likely (hazard ratio [HR], 0.13 [95% confidence interval (CI), 0.06–0.28] per 5-yr increase) and death more likely (HR, 1.41 [95% CI, 1.22–1.64] per 5-yr increase) among those older than 70 years of age. Higher median zip code income was associated with lung transplant (HR, 1.22 [95% CI, 1.13–1.31] per \$10,000 increase) but not death (HR, 0.99 [95% CI, 0.94–1.04] per \$10,000 increase). Enrollment at a center with a lung transplant program was associated with lung transplant (HR, 4.31 [95% CI, 1.76–10.54]) but not death (HR, 0.99 [95% CI, 0.69–1.43]). Oxygen use with activity was associated with both lung transplant and death, but more strongly with lung transplant. A higher number of comorbidities was associated with an increased likelihood of death but not lung transplant.

**Conclusions:** For patients in the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry, median zip code income and access to a lung transplant center differentially impact the risk of lung transplant compared with death, regardless of disease severity measures or other transplant eligibility factors. Interventions are needed to mitigate inequalities in lung transplantation based on socioeconomic status.

Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01915511).

**Keywords:** interstitial lung disease; pulmonary fibrosis; organ transplants; lung transplantation

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Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal disease characterized by irreversible lung scarring (1). Antifibrotic therapy slows lung function decline (2, 3), but only lung transplant offers the potential for restoration of lung function. Over the past 15 years, there has been a marked increase in the proportion of lung transplants performed in the United States for pulmonary fibrosis, from 20.4% in 2006 to 60.0% in 2018 (4). Reasons for this increase include implementation of a need-based lung allocation system (5), which favors transplants for sicker patients, as well as the improved recognition of IPF due to standardization in diagnostic criteria (1). However, identifying the optimal timing for lung transplant in patients with IPF can be challenging because patients may progress in an unpredictable clinical course with abrupt decline.

The International Society for Heart and Lung Transplantation (ISHLT) has issued guidelines for lung transplant referral and listing in patients with IPF, along with both absolute contraindications (such as active malignancy, untreatable infection, or severe obesity) and relative contraindications, such as advanced age (6). Given the variable clinical course of pulmonary fibrosis, any patient with histopathologic or radiographic evidence of usual interstitial pneumonia is appropriate for lung transplant referral, regardless of lung function (6). Listing for lung transplant is specifically recommended for patients with IPF who experience disease progression, including development of an exertional oxygen requirement or pulmonary hypertension, hospitalization due to respiratory decline or acute exacerbation, decline in forced vital capacity (FVC), or decline in diffusing capacity of the lung for

carbon monoxide ( $DL_{CO}$ ) (6). However, only a highly selective subset of patients with IPF who experience disease progression are offered a lung transplant. Whether certain medical or nonmedical characteristics influence the occurrence of a lung transplant versus death is largely unexplored.

As clinicians and policymakers strive to ensure that eligible patients with IPF have equal opportunity to undergo lung transplant, a better understanding of factors associated with lung transplant is needed. Evaluating the impact of social determinants of health is particularly relevant because recent studies have demonstrated that patients with cystic fibrosis with poor socioeconomic status are less likely to be added to lung transplant waiting lists (7–9). The objective of our study was to identify clinical characteristics and social determinants of health that differentially associated with lung transplant compared with death in patients with IPF.

## Methods

### Study Population

The study population was derived from the Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry. Details of the registry design have been published (10). Briefly, the IPF-PRO Registry is a multicenter registry of patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months according to the 2011 ATS/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society guidelines (11). Patients with malignancy (other than skin cancer) within the prior

5 years or who were listed for lung transplant or were participating in a randomized clinical trial were not eligible to enroll in the registry; however, patients could be listed for lung transplant or participate in a clinical trial after enrollment. Patients were enrolled between June 2014 and October 2018. The date of enrollment in the IPF-PRO Registry is used as the baseline time point. At enrollment, clinical data were abstracted from medical records. Patients are seen in follow-up for approximately 5 years or until death, lung transplant, or withdrawal from the registry. In addition to follow-up at site visits, a centralized call center captures information from patients on healthcare use, including hospitalizations, since the last follow-up encounter.

The study was approved by the Duke University Institutional Review Board (Pro00046131). The protocol was approved by the relevant institutional review boards and/or local independent ethics committees at each site listed in the acknowledgment at the end of the main text. All patients provided written informed consent.

### Study Outcomes

The outcomes in this study were lung transplant and death from any cause. Ascertainment of lung transplant and death was performed both by site coordinators and by the centralized call center. Rates are presented separately for the two outcomes, but in modeling, they were considered as a single endpoint; that is, death was considered as a competing risk to lung transplant and vice versa. Patients were not seen in follow-up after receiving a lung transplant; therefore, patients could experience

\*These authors contributed equally to this work.

A complete list of IPF-PRO Registry Investigators may be found before the beginning of the REFERENCES.

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**Author Contributions:** A.C.S., A.S.H., M.L.N., S.M.P., T.P.M.W., and D.F.D. contributed to the design of this study. T.P.M.W. and D.F.D. were involved in data acquisition. A.S.H. and M.L.N. were involved in the analysis of the data. All authors contributed to the interpretation of the data and the development of the manuscript. All authors approved the final version.

**Availability of data and material:** The datasets analyzed during the current study are not publicly available, but they are available from the corresponding author on reasonable request.

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transplant or death but not both. Patients without either event were censored at the time of their last follow-up.

### Clinical Characteristics and Social Determinants of Health

To examine the differential risk of lung transplant and death, we selected covariates related to lung transplant eligibility, clinical characteristics, and social determinants of health. Variables related to lung transplant eligibility included age, body mass index (BMI), and current smoking status. Clinical characteristics included sex, time since first imaging evidence of pulmonary fibrosis, FVC percent predicted, DL<sub>CO</sub> percent predicted, oxygen use at rest, oxygen use with exertion, respiratory hospitalization (from which a patient was discharged alive without a lung transplant), St. George's Respiratory Questionnaire (SGRQ) activity domain score, SGRQ symptoms domain score, emphysema on a high-resolution computed tomography scan, and a comorbidity count. The comorbidity count totaled the number of the following comorbidities in each patient: congestive heart failure (CHF), chronic kidney disease (CKD), chronic liver disease, coronary artery disease, stroke or intracranial hemorrhage, deep venous thrombosis or pulmonary embolus, atrial fibrillation, gastroesophageal reflux disease, sleep apnea, diabetes, lung or other cancer, pulmonary hypertension, and significant infection (specifically human immunodeficiency virus [HIV], hepatitis B, hepatitis C, or tuberculosis). Based on the distribution, comorbidity counts were truncated at 3 before model fitting. Respiratory hospitalizations were assessed in the 12 months before enrollment and after enrollment. The date of first imaging evidence of fibrosis was obtained by review of the medical record. The imaging study did not need to have been performed at the enrolling center.

The following social determinants of health were included as covariates: patient zip code-level median household income, distance between patient's and enrolling site's zip codes, private health insurance, and the presence of a lung transplant program at the enrolling site based on the 2020 Scientific Registry of Transplant Recipients database (12). Zip code-level median household income was obtained from the U.S. Bureau of the Census in the American Community Survey, in which estimates included 5 years of data on a

rolling basis, adjusted for inflation (13). Patients were matched to the estimate from the year in which they were enrolled in the registry.

Aside from sex, insurance, presence of lung transplant program at enrolling site, distance to enrolling site, and zip code-level income, all variables were allowed to vary over time in the models if there were any changes (i.e., were considered as time-dependent covariates). Apart from CKD, chronic liver disease, and emphysema on high-resolution computed tomography, which were only evaluated at enrollment, comorbidities were updated in the model if there were any changes.

### Statistical Analysis

For descriptive statistics, we present medians with 25th and 75th percentiles for continuous variables and frequencies with percentages for categorical variables. Time-independent variables (such as sex, race, and private insurance) are summarized at the time of enrollment. All other variables are summarized at the time of enrollment and during follow-up, apart from certain medical history variables that were collected only at enrollment. For the follow-up summary, the last reported value was used for continuous variables, and new occurrence was used for categorical variables.

We performed a time-to-event analysis incorporating competing risks methodology to determine whether differential associations existed between each covariate and lung transplant compared with death. Specifically, the method of Lunn and McNeil (14) was used to 1) test for an association between the outcomes and risk factors and 2) test whether that association, strength, and/or direction was different between lung transplant and death for each risk factor. The regression models were stratified by use of antifibrotic therapy at baseline (nintedanib/pirfenidone) versus no antifibrotic therapy at baseline, with a weighted average calculated across strata. Patients were censored at withdrawal or last known follow-up. Continuous variables were assessed for the linearity of their relationship with the outcomes; when a nonlinear relationship was found, restricted cubic splines were used in testing, and simplified versions (piecewise linear splines) were used for generating interpretable hazard ratios (HRs).

Missing data were handled using multiple imputation to generate five

imputation datasets with the fully conditional specification method to ensure that the final estimates properly reflect variability and uncertainty due to missing values. Observed data were used for descriptive analyses, and imputed data were used for inferential analyses.

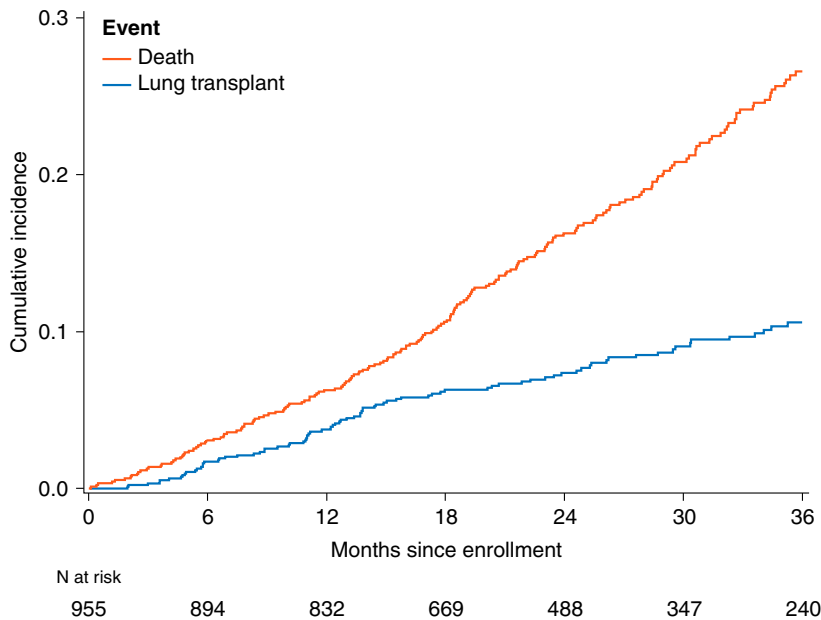
We performed sensitivity analyses to account for lung transplant eligibility and lung transplant evaluation. First, we examined the differential risk of lung transplant and death in a subgroup of patients who were likely to be eligible for lung transplant based on ISHLT guidelines (6). Specifically, we defined lung transplant eligibility as age 70 years or younger; BMI 30 kg/m<sup>2</sup> or less; no active tobacco use; and absence of CKD, CHF, chronic liver disease, or HIV. Lung transplant eligibility was assessed at baseline and, for patients not eligible at baseline, reassessed throughout follow-up; patients could enter the eligibility group at any time. Patients who entered the eligibility subgroup remained in the subgroup, regardless of age or change in BMI or health status. A patient missing data for any of these items was not considered eligible. Next, we assessed the differential risk of lung transplant versus death among patients identified as having undergone a lung transplant evaluation. Evaluation for lung transplant was captured by site coordinators both at enrollment and during follow-up. Only patients who were evaluated for lung transplant after enrollment were included in the sensitivity analysis, and if patients had multiple evaluations, the first date after enrollment was used. Of note, for all sensitivity analyses, a smaller number of potential covariates were evaluated because of the smaller sample size. Variables from the primary analysis with the largest multidegree of freedom chi-square values were examined in the sensitivity analyses.

## Results

### Study Cohort

A total of 955 patients from 48 centers were included in the analysis, with a median (interquartile range) of 15 (5–27) patients per site. Among transplant-free survivors, the median (interquartile range) duration of follow-up was 29 (20–41) months.

There were 96 lung transplants and 221 deaths during the study period. Figure 1 shows the cumulative incidence of lung transplant or death. By 1 year after registry



**Figure 1.** Time to death or lung transplant among 955 patients in the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry.

enrollment, 3.7% (95% confidence interval [CI], 2.7–5.1) of patients had undergone lung transplant, and 6.3% (95% CI, 4.8–7.9) of patients had died. At 2 years, 7.4% (95% CI, 5.8–9.2) of patients had undergone lung transplant, and 16.3% (95% CI, 13.9–18.9) had died.

Table 1 and Table E1 in the online supplement display the baseline characteristics in the cohort, grouped by eventual disposition. Patients who received lung transplants were generally younger, had private insurance, lived in a more affluent area, and were more likely to have enrolled at a site with a lung transplant program. Patients who died tended to be older, had a higher incidence of cardiac comorbidities, were more likely to use oxygen at rest, and had worse SGRQ scores.

### Differential Association of Clinical Characteristics and Social Determinants of Health with Lung Transplant and Death

The differential association of each variable with the outcomes of lung transplant and death are shown in Figure 2. Smoking status could not be included in the model, because there were too few current smokers. In the multivariable model, the covariates with the strongest differential association were age, median zip code income, and enrollment at a center with a lung transplant program. Specifically, lung transplant became less

likely after the age of 70 (HR, 0.13 [95% CI, 0.06–0.28] per 5-yr increase) and death more likely (HR, 1.41 [95% CI, 1.22–1.64] per 5-yr increase; *P* value for differential association, <0.001). Higher median zip code income was associated with lung transplant (HR, 1.22 [95% CI, 1.13–1.31] per \$10,000 increase) but not death (*P* value for differential association, <0.001). Finally, enrollment at a site with a lung transplant program was strongly associated with lung transplant (HR, 4.31 [95% CI, 1.76–10.54]) but not death (*P* value for differential association, 0.002).

A differential association was also seen for comorbidity count, for which more comorbidities were associated with death (HR, 1.23 [95% CI, 1.06–1.42] per one additional comorbidity) but not lung transplant (*P* value for differential association, 0.011). Higher BMI was associated with a decreased risk of death up to a BMI of 30 kg/m<sup>2</sup> (HR, 0.87 [95% CI, 0.84–0.91] per 1-point increase) but did not associate with lung transplant (*P* value for differential association, 0.03). Oxygen use with activity was associated with both lung transplant (HR, 7.95 [95% CI, 2.96–21.34]) and death (HR, 1.68 [95% CI, 1.13–2.51]) but more strongly with lung transplant (*P* value for differential association, 0.003). Distance between patient's and enrolling site's zip codes also had a different association with death than with lung transplant (*P* value for

differential association, 0.045); there appeared to be a greater risk of death with greater distance from the site.

No differential association was present for FVC percent predicted, DL<sub>CO</sub> percent predicted, or SGRQ activity score; worse values for these covariates were associated with both lung transplant and death. There was no association between respiratory hospitalization from which a patient was discharged alive without a lung transplant and either death or lung transplant.

### Sensitivity Analysis: Eligible for Lung Transplant

We examined as a sensitivity analysis the differential risk of lung transplant and death in a subgroup of patients with IPF more likely to be eligible for transplant based on ISHLT guidelines (6). Of the 906 patients in whom lung transplant eligibility could be determined, 274 (30.2%) were likely to be eligible for lung transplant based on age 70 years or younger, BMI 30 kg/m<sup>2</sup> or less, and absence of the following: active tobacco use, CKD, CHF, chronic liver disease, or HIV (Table E2). Of the 96 patients who underwent a lung transplant, 51 (53.1%) were likely to be eligible based on the above criteria, and 37 (38.5%) were not eligible, mostly because of age or BMI.

Among the 274 patients eligible for lung transplant (Table E3), 12.3% (95% CI, 8.6–16.6) had undergone lung transplant by 2 years, and 10.1% (95% CI, 6.7–14.2) had died. The variables with the strongest differential association with lung transplant and death in this subgroup were generally consistent with the primary analysis (Table 2). Specifically, higher median zip code household income and registry enrollment at a site with a lung transplant program were both significantly associated with lung transplant but not death.

### Sensitivity Analysis: Evaluated for Lung Transplant

As a second sensitivity analysis, we evaluated the differential risk of lung transplant and death among patients reported to have been evaluated for a lung transplant. Of the 955 patients in the analysis cohort, 247 patients (25.9%) were reported to have been evaluated for lung transplant at any time (before or after enrollment), and 708 (74.1%) were not (Table E4). There was inconsistency in the reporting of lung transplant evaluation because just over 10% of patients who had



**Table 1.** Patient characteristics, stratified by eventual disposition

Characteristics at Enrollment	Overall Cohort	Underwent Lung Transplant	Died without Lung Transplant
No. of subjects	955	96	221
<b>Demographics</b>			
Age, yr	70 (65–75)	65 (61–69)	72 (67–77)
Female	25.4% (243)	19.8% (19)	21.3% (47)
White	94.2% (878)	95.7% (88)	93.1% (203)
Black	1.8% (17)	2.2% (2)	2.8% (6)
Other race	4.0% (37)	2.2% (2)	4.1% (9)
Hispanic ethnicity	4.1% (36)	3.4% (3)	4.8% (10)
Private insurance	61.3% (585)	70.8% (68)	62.0% (137)
Family history of ILD	19.5% (176)	26.9% (25)	11.6% (25)
Distance to enrolling site, miles	32 (14–93)	35 (15–113)	40 (14–110)
Median zip code income, US \$1,000	60.8 (47.5–79.7)	66.4 (53.3–85.4)	55.8 (44.2–73.0)
Lung transplant center at enrolling site	77.5% (740)	93.8% (90)	82.8% (183)
<b>Disease history and severity</b>			
Time since first imaging evidence of pulmonary fibrosis, yr	0.6 (0.3–1.4)*	0.4 (0.3–1.1)	0.6 (0.3–1.4)
BMI, kg/m <sup>2</sup>	28.9 (25.9–32.4)	29.3 (26.7–32.1)	27.8 (24.9–32.4)
FVC, % predicted	70.1 (59.7–80.8)	61.1 (49.5–72.4)	64.2 (55.8–74.9)
DL <sub>CO</sub> , % predicted	42.6 (33.0–51.7)*	34.2 (27.7–43.2)	35.1 (26.3–43.8)
O <sub>2</sub> at rest	18.9% (176)	31.5% (29)	38.4% (83)
O <sub>2</sub> with exertion	32.9% (305)	54.3% (50)	52.8% (114)
Respiratory hospitalization <sup>†</sup>	16.7% (153)	19.1% (18)	24.1% (51)
<b>Medical history</b>			
Current smoker	1.7% (16)	0	1.4% (3)
Prior smoker, within 1 yr	2.5% (21)*	4.7% (4)	4.1% (8)
Comorbidity count <sup>‡</sup>	2 (1–2)*	1 (0–2)	2 (1–3)
GERD	56.3% (535)	57.3% (55)	56.1% (124)
CAD	29.3% (279)	17.7% (17)	34.5% (76)
Sleep apnea	28.2% (268)	18.9% (18)	31.7% (70)
Diabetes	20.5% (195)	18.8% (18)	21.7% (48)
Emphysema on HRCT	12.6% (120)	10.4% (10)	14.1% (31)
Atrial fibrillation or flutter	10.7% (102)	8.3% (8)	15.0% (33)
<b>Patient-reported outcomes</b>			
SGRQ total score	39.3 (25.2–52.9)	44.1 (38.1–56.6)	47.2 (36.1–62.1)
SGRQ activity score	56.1 (40.6–72.8)	59.5 (53.5–79.7)	67.9 (53.5–79.9)
SGRQ symptoms score	43.0 (29.4–60.4)	50.9 (39.9–68.2)	51.1 (37.3–68.3)
SGRQ impact score	25.9 (13.7–41.4)	32.8 (22.8–46.5)	34.2 (20.9–52.3)
<b>Medications</b>			
Antifibrotic	53.8% (514)	64.6% (62)	52.5% (116)
Oral steroid	12.7% (109)	20.5% (18)	18.0% (37)
Immunosuppressive/cytotoxic	1.3% (11)	3.4% (3)	2.0% (4)
PPI	55.0% (475)	63.6% (56)	55.3% (114)

*Definition of abbreviations:* BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; DVT = deep venous thrombosis; FVC = forced vital capacity; GERD = gastroesophageal reflux disease; HIV = human immunodeficiency virus; HRCT = high-resolution computed tomography; ICH = intracranial hemorrhage; ILD = interstitial lung disease; PE = pulmonary embolus; PPI = proton pump inhibitor; SGRQ = St. George’s Respiratory Questionnaire.

Median (interquartile range) follow-up among transplant-free survivors was 29 (20–41) months. Data are median (25th percentile–75th percentile) or percent (count).

\*Data were missing for 10–20% of the patients.

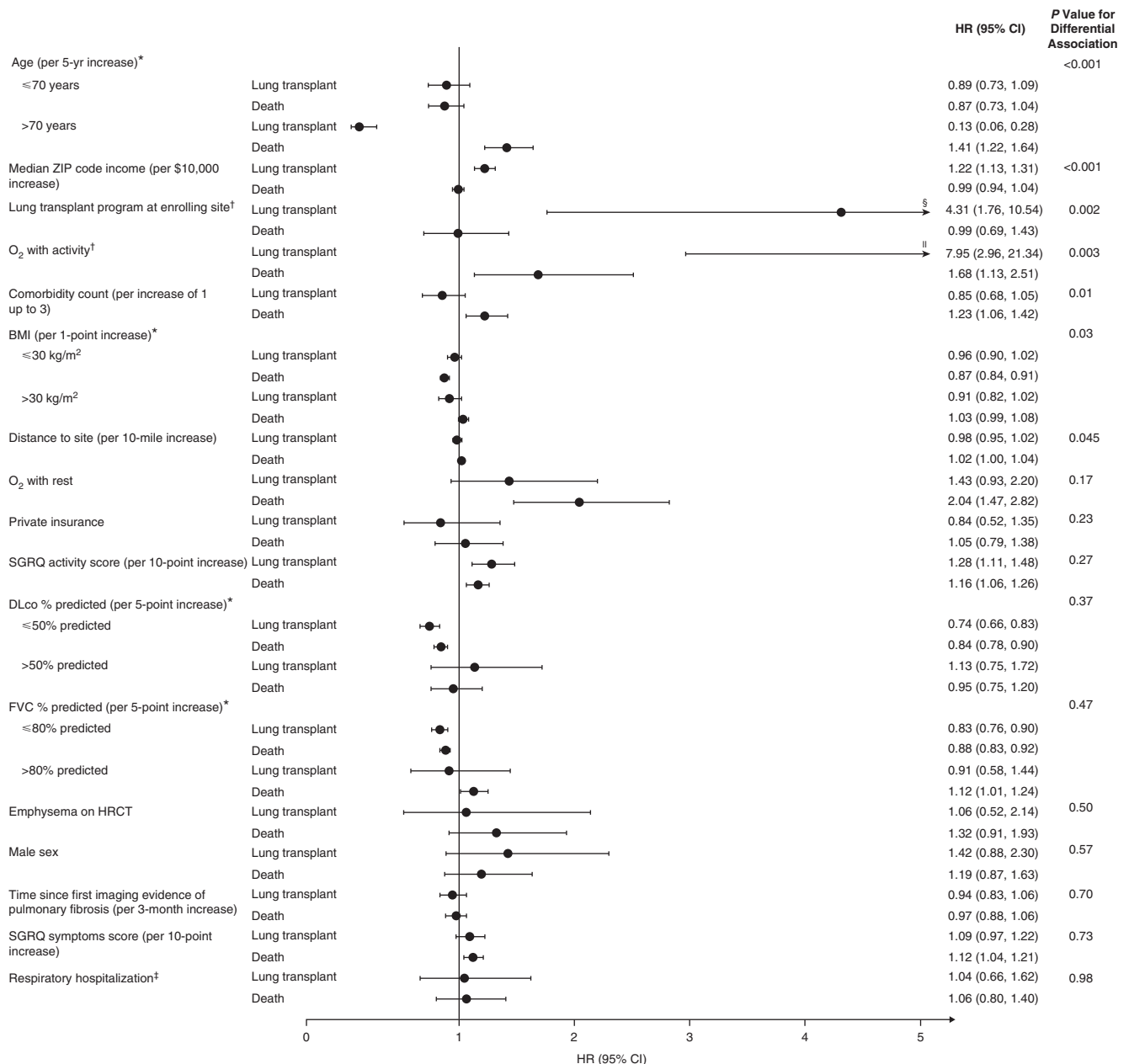
<sup>†</sup>In the 12 months before enrollment in the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry.

<sup>‡</sup>Sum of the following comorbidities: CHF; CKD; chronic liver disease; CAD; stroke or ICH; DVT or PE; atrial fibrillation or flutter; GERD; sleep apnea; diabetes; lung or other cancer; pulmonary hypertension; and HIV, hepatitis B or C, or tuberculosis. Comorbidity count was calculated only among patients who had data for all 15 comorbidities. Comorbidities reported in more than 10% of patients in the overall cohort are shown individually in this table.

undergone a lung transplant were not reported to have had a lung transplant evaluation. Patients who were evaluated for

a lung transplant tended to be younger and to have worse physiologic measures of disease severity and quality of life, but they

also had fewer comorbidities than patients who did not undergo lung transplant evaluation (Table E5).



**Figure 2.** Differential association of covariates with lung transplant and death. The model included all the covariates shown. Variables are shown in order of greatest to least differential association. \*These continuous variables had a nonlinear relationship with at least one outcome. For generating *P* values, they were fit with restricted cubic splines. For generating hazard ratios, the relationships were approximated with piecewise linear splines. †The confidence interval for lung transplant is wide for these variables because there are very few events among patients at non-transplant program sites, or patients not on O<sub>2</sub> with activity at any time. ‡From which the patient was discharged alive without a lung transplant. §Upper limit of 95% CI was 10.54. ||HR 7.95 (95% CI: 2.96–21.34). BMI = body mass index; CI = confidence interval; DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio; HRCT = high-resolution computed tomography; SGRQ = St. George’s Respiratory Questionnaire.

Among the 135 patients evaluated for lung transplant after registry enrollment, 29.0% (95% CI, 22.7–35.6) had undergone lung transplant at 2 years,

and 11.7% (95% CI, 7.6–16.8) had died. Among patients evaluated for a lung transplant, registry enrollment at a site with a lung transplant program and

shorter distance between patient’s and enrolling site’s zip codes were associated with lung transplant but not death (Table 3).

**Table 2.** Differential association of covariates with lung transplant and death among patients likely eligible for lung transplant\*

Risk Factor <sup>†</sup>	Lung Transplant-Specific HR (95% CI)		Death-Specific HR (95% CI)		P Value for Differential Association
Median zip code income	1.31 (1.16–1.47)	Per \$10,000 increase	0.97 (0.83–1.12)	Per \$10,000 increase	0.001
Lung transplant program at the enrolling site <sup>‡</sup>	14.87 (3.27–67.68)		3.11 (1.14–8.44)		0.03
DL <sub>CO</sub> , % predicted <sup>§</sup> (HR shown per 5% increase)	0.65 (0.55–0.77)	Up to 50	0.77 (0.66–0.91)	Up to 50	0.12
	1.20 (0.71–2.06)	Over 50	1.37 (0.84–2.22)	Over 50	
FVC, % predicted <sup>§</sup> (HR shown per 5% increase)	0.74 (0.67–0.82)	Up to 80	0.85 (0.75–0.96)	Up to 80	0.29
	0.95 (0.57–1.59)	Over 80	0.82 (0.50–1.37)	Over 80	
Comorbidity count (up to 3)	1.01 (0.75–1.36)	Per one additional	1.34 (0.98–1.85)	Per one additional	0.30
O <sub>2</sub> at rest	1.10 (0.58–2.08)		0.84 (0.44–1.63)		0.51
O <sub>2</sub> with activity <sup>‡</sup>	10.15 (2.22–46.51)		7.14 (2.27–22.44)		0.63
SGRQ activity score	1.41 (1.17–1.70)	Per 10-point increase	1.31 (1.08–1.58)	Per 10-point increase	0.76
Distance to site	0.98 (0.93–1.03)	Per 10-mile increase	0.96 (0.91–1.01)	Per 10-mile increase	0.95

Definition of abbreviations: CI = confidence interval; DL<sub>CO</sub> = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio; SGRQ = St. George's Respiratory Questionnaire.

The model included all the covariates in the table. Variables are shown in order of greatest to least differential association.

\*Patients were deemed eligible if they were ≤70 years old, had body mass index of ≤30 kg/m<sup>2</sup>, were not an active smoker, and had no history of chronic kidney disease, congestive heart failure, chronic liver disease, or human immunodeficiency virus. Eligibility was assessed at baseline and, for patients not eligible at baseline, reassessed throughout follow-up; patients could enter the eligibility group at any time.

<sup>†</sup>The nine variables from the primary analysis that had the strongest overall association with the endpoints were considered in this model, except for age and body mass index, which were eligibility criteria.

<sup>‡</sup>The CI for lung transplant is wide for these variables because there were very few events among patients at non-transplant program sites or patients not receiving O<sub>2</sub> with activity at any time.

<sup>§</sup>These continuous variables had a nonlinear relationship with at least one outcome in the overall cohort. For generating *P* values, they were fit with restricted cubic splines. For generating HRs, the relationships were approximated with piecewise linear splines.

## Discussion

We evaluated the contributions of clinical characteristics and social determinants of health to the differential risk of lung transplant compared with death in patients with IPF. We found that regardless of IPF disease severity measures and lung transplant eligibility factors (i.e., age, BMI, comorbidities), higher median zip code income and registry enrollment at a center with a lung transplant program were associated with an increased risk of lung transplant but not death. Oxygen use with activity was associated with both lung transplant and death, but more strongly with lung transplant. Our results were consistent across several sensitivity analyses.

Our study adds to a growing body of literature that suggests that social disadvantage is associated with meaningful clinical consequences in patients with IPF (15–17). Consistent with our finding of an association between median zip code income and lung transplant, a recent study found a lower odds of lung transplant in patients with IPF who had greater neighborhood-level

disadvantage (18). This suggests that although zip code areas can be large and heterogeneous, zip code-level median income may still be a reliable measure of neighborhood or individual socioeconomic status within certain regions (19). Prior studies have demonstrated that low zip code-based income decreases the likelihood of wait-listing for a kidney transplant (20) and a lung transplant among patients with cystic fibrosis (7, 9), although the clinical outcome of non-wait-listed patients is unclear. Our study extends this work and determines the association of covariates with firm patient-centered outcomes of lung transplant and death using a competing risks framework. The finding that residing in a more affluent area increases the probability of lung transplant but not death has implications for efforts to address inequalities in donor organ allocation based on socioeconomic status. Lung transplant can be financially burdensome, with costs related to pretransplant evaluation and testing, surgery, follow-up care, rehabilitation, and relocation. Preevaluation financial screening may propagate

socioeconomic inequalities by limiting evaluation to individuals with resources to afford this process. Health policies that supplement the cost of a lung transplant for individuals who cannot afford this process may ensure more equitable care for patients with IPF.

Another important finding from this study is that access to a lung transplant center, as captured by the presence of a lung transplant program at the enrolling site, was associated with lung transplant but not death. Prior research has evaluated access to a lung transplant center using both geographic distance and rural dwelling and found that living farther away from a lung transplant center decreases the likelihood of lung transplant listing (21). In contrast, a more recent analysis found that a longer travel distance was associated with favorable wait-list outcomes in patients seeking a lung transplant (22). Longer travel distance to a clinic has also been associated with an increased risk of death or lung transplant in patients with other fibrotic interstitial lung diseases (23). The distance between the patient's and enrolling site's zip codes had a

**Table 3.** Differential association of covariates with lung transplant and death among patients evaluated for lung transplant after registry enrollment

Risk Factor*	Lung Transplant-Specific HR (95% CI)	Death-Specific HR (95% CI)	P Value for Differential Association
Site transplant program	3.06 (1.21–7.71)	0.69 (0.31–1.54)	0.01
Distance to site	0.96 (0.92–0.99) Per 10-mile increase	1.02 (0.97–1.07) Per 10-mile increase	0.02
Comorbidity count (up to 3)	0.87 (0.70–1.08) Per one additional	1.49 (1.02–2.19) Per one additional	0.02
SGRQ activity score	1.43 (1.23–1.65) Per 10-point increase	1.17 (0.96–1.43) Per 10-point increase	0.10
O <sub>2</sub> at rest	1.61 (1.02–2.53)	2.99 (1.34–6.67)	0.20
Median zip code income	1.04 (0.96–1.13) Per \$10,000 increase	0.99 (0.86–1.14) Per \$10,000 increase	0.53
O <sub>2</sub> with activity <sup>†</sup>	3.97 (1.40–11.23)	7.65 (1.00–58.78)	0.79

*Definition of abbreviations:* CI = confidence interval; HR = hazard ratio; SGRQ = St. George's Respiratory Questionnaire.

The model included all the covariates in the table. Variables are shown in order of greatest to least differential association.

\*The seven variables from the primary analysis that had the strongest overall association with the endpoints were considered in this model, except for age and body mass index.

<sup>†</sup>CI is wide for this variable because, among patients evaluated for lung transplant, very few were not receiving O<sub>2</sub> with activity at any time, and among these patients, there were only a few events.

differential association in our study, particularly in individuals evaluated for lung transplant, in whom shorter distances were associated with lung transplant. However, other factors may also influence access to lung transplant. For example, it is conceivable that physicians caring for patients with IPF at centers with lung transplant programs are more aware of lung transplant as a therapeutic option or are more likely to refer patients with higher-risk features such as older age. Alternatively, it is possible that patients with IPF who want to undergo lung transplant preferentially transition their IPF care to a lung transplant center. Importantly, lung transplant events were distributed among many centers, and the multicenter nature of the cohort is reflective of various listing practices. Pulmonologists may have the opportunity to increase access to transplant by educating patients with IPF about lung transplant early in the course of the disease.

The variable and rapid disease progression that can occur in patients with IPF may increase the difficulty of timely lung transplant evaluation and listing. As such, there has been a recent emphasis on oxygen use and respiratory hospitalization in the timing of lung transplant listing (6). Respiratory hospitalizations (before or after enrollment) from which a patient was discharged alive did not associate with subsequent lung transplant or death in our analysis. Although seemingly contrasting with data from clinical trials (24–26) and retrospective studies (27, 28) that demonstrated an association between respiratory hospitalizations and increased

mortality in patients with IPF, our finding is likely related to the inclusion of only respiratory hospitalizations from which the patient was discharged alive without a transplant. Furthermore, the inclusion of other clinical factors that may associate with increased risk of hospitalization, such as oxygen use and lung function, may influence the relationship between respiratory hospitalization and death in this analysis (29).

Only 25.9% of patients in the IPF-PRO Registry were listed as ever having undergone a lung transplant evaluation. Although this likely underestimates the proportion of patients who underwent a formal or informal referral, it suggests that lung transplant may be underused in patients with IPF. Interestingly, 39% of patients who underwent a lung transplant in our cohort were not considered “likely to be eligible for transplant” based on age older than 70 years, BMI greater than 30 kg/m<sup>2</sup>, or specific comorbidities (CKD, CHF, chronic liver disease, or HIV). These patients were spread across multiple centers, highlighting the nuanced nature of transplant candidacy assessment. This finding emphasizes the importance of transplant consideration for all patients and the need for strong relationships between IPF providers and their regional transplant programs. Furthermore, the transition of > 50 patients from “ineligible for transplant” at registry enrollment to “eligible” later demonstrates the value of continually reassessing for transplant eligibility.

This analysis could not account for several important factors that may differentially impact the probability of lung

transplant and death, including a patient's preferences and functional status. In addition, our comorbidity count weighted each medical problem equally, which does not reflect clinical practice. The social determinants of health that we captured were not exhaustive and did not include factors such as social support, education, individual income, or race. Because our cohort was predominantly White, we were unable to evaluate the impact of race and ethnicity. Prior studies have demonstrated that patients who are members of ethnic minority groups are less likely to survive to transplant (30, 31) and have greater severity of illness at the time of listing. Few patients in our cohort were uninsured or had Medicaid coverage, which limited the evaluation of insurance type. The absence of such disadvantaged patients in the IPF-PRO Registry may have resulted in an underestimation of the disparities in lung transplantation in this analysis. Finally, post-transplant outcomes are uncertain because patients were not followed after receiving transplants. A notable strength of our study is the incorporation of time-dependent covariates, which is particularly relevant in IPF, given its unpredictable course.

## Conclusions

Regardless of disease severity measures and factors associated with lung transplant eligibility, patients with IPF who have access to a lung transplant center and live in a more affluent area have a higher probability of receiving lung transplant. Given the continued progression of IPF despite current treatment strategies, lung transplant is underused in IPF. Future



interventions should focus on mitigating inequalities based on socioeconomic and geographic factors. ■

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