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Racial and Ethnic Disparities in Idiopathic Pulmonary Fibrosis: A UNOS/OPTN Database Analysis

D. J. Lederer^a, S. M. Arcasoy^a, R. G. Barr^{a,c}, J. S. Wilt^a, E. Bagiella^d, F. D'Ovidio^b, J. R. Sonett^b, and S. M. Kawut^{a,c,*}

^aDepartment of Medicine, Joseph L. Mailman School of Public Health, Columbia University, New York, NY, USA

^bDepartment of Surgery, College of Physicians and Surgeons, Joseph L. Mailman School of Public Health, Columbia University, New York, NY, USA

^cDepartment of Epidemiology, Joseph L. Mailman School of Public Health, Columbia University, New York, NY, USA

^dDepartment of Biostatistics, Joseph L. Mailman School of Public Health, Columbia University, New York, NY, USA

Abstract

We previously reported poorer survival among non-Hispanic blacks and Hispanics with idiopathic pulmonary fibrosis (IPF) compared to non-Hispanic whites at our center. In the current study, we hypothesized that these disparities would exist in a nationwide cohort of wait-listed patients with IPF. We performed a retrospective cohort study of 2635 patients with IPF listed for lung transplantation between 1995 and 2003 at 94 transplant centers in the United States. The age-adjusted mortality rate was higher among non-Hispanic blacks [hazard ratio (HR) = 1.24, 95% confidence interval (CI) 1.06–1.45, $p = 0.009$] and Hispanics (HR = 1.29, 95% CI 1.06–1.56, $p = 0.01$) compared to non-Hispanic whites. These findings persisted after adjustment for transplantation, medical comorbidities and socioeconomic status. Worse lung function at the time of listing appeared to explain some of these differences (HR for non-Hispanic blacks after adjustment for forced vital capacity percent predicted = 1.16, 95% CI 0.98–1.36, $p = 0.09$; HR for Hispanics = 1.21, 95% CI 0.99–1.48, $p = 0.056$). In summary, black and Hispanic patients with IPF have worse survival than whites after listing for lung transplant.

Keywords

Cohort; diffuse parenchymal lung disease; forced vital capacity; interstitial lung disease; lung transplantation

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*Corresponding author: Steven M. Kawut, sk2097@columbia.edu.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by progressive scarring and destruction of the lung parenchyma recognized histopathologically as usual interstitial pneumonia. Affected patients suffer from dyspnea, cough, and impaired exercise capacity, and have a median survival of less than 3 years (1–3). With an incidence of 7–10 per 100 000 per year and no effective medical therapy, IPF is the second most common indication for lung transplantation worldwide after emphysema (4,5). Still, an inadequate donor supply and strict candidacy criteria for transplantation limit the availability of this treatment modality (5,6).

Older age at diagnosis, male gender, reduced pulmonary function and impaired exercise capacity predict a worse outcome in IPF (1,2,7–12); yet, the impact of race and ethnicity on survival in IPF is largely unknown. Two studies have not shown significant associations between race and ethnicity and survival (13,14), whereas one study found that blacks had a lower age-adjusted mortality rate attributable to pulmonary fibrosis compared to whites (15). These population-based studies certainly included patients with forms of diffuse parenchymal lung disease other than IPF (4,14,15). Nonetheless, these are landmark studies of pulmonary fibrosis which have established the epidemiology of this disease, despite their recognized limitations. We recently reported that non-Hispanic black and Hispanic patients with IPF evaluated for lung transplantation at our center had a more than 3-fold higher risk of death than non-Hispanic white patients (16). However, it is unclear whether these disparities exist at other transplant centers.

In the current work, we studied a nationwide cohort of patients classified as having IPF at the time of listing for lung transplantation with the United Network for Organ Sharing (UNOS). We hypothesized that the risk of death would be higher among non-Hispanic black and Hispanic patients compared to non-Hispanic whites even with adjustment for transplantation and other measured factors that predict mortality in this condition. These data have been previously published in abstract form (17).

Methods

We performed a retrospective cohort study of non-Hispanic black, Hispanic and non-Hispanic white adult (≥ 18 years) Americans with IPF placed on the UNOS lung transplant waiting list between 1995 and 2003. This timeframe was chosen because (1) we aimed to study the most recent cohort possible with adequate follow-up time, and (2) the data fields collected by UNOS remained constant during this period. Baseline characteristics at the time of listing and the dates and types of transplant procedures performed were obtained from a Standard Transplant Analysis and Research file based on Organ Procurement and Transplantation Network data as of July 22, 2005. Demographic and clinical data were collected by clinical staff at 94 U.S. transplant centers. The designation of IPF was determined by transplant physicians at each center and did not require lung biopsy. This approach is similar to that taken in other large epidemiologic studies of pulmonary fibrosis and outcomes in lung transplant populations (4,14,15,18). Race and ethnicity designations were supplied by each center and coded in accordance with the Office of Management and

Budget Directive (19,20). Poor performance status was defined as dependence on others for activities of daily living or hospitalization at the time of listing. Physiologic data included forced vital capacity percent predicted (FVC%), forced expiratory volume in 1 s percent predicted (FEV₁%) and pulmonary hemodynamics. UNOS recorded the distance walked in 6 min as either greater than or less than 150 ft.

We obtained the median family income and the percentage of adults who completed high school and college in each patient's residence zip code from the 2000 U.S. Census database (21), reflecting neighborhood-level socioeconomic status. Mortality was determined using a Social Security Death Index file generated on July 8, 2005 and the UNOS file. These are both validated indices (22). Subjects not reported as dead in either index were censored on the latest date reported to UNOS. The Columbia University Medical Center Institutional Review Board approved the study.

Statistical analysis

Continuous variables were summarized by mean $\pm$ standard deviation or median [interquartile range (IQR)]. Categorical variables were summarized by frequency and percentage. We used analysis of variance and *t*-tests with the Bonferroni correction to compare normally distributed continuous variables and Kruskal–Wallis and Wilcoxon rank sum tests to compare variables that did not meet this assumption. Categorical variables were compared using chi-squared tests.

The primary endpoint was time from the date of listing for transplantation to the date of death. We used Cox proportional hazards models to estimate the risks of death of non-Hispanic blacks and Hispanics compared to non-Hispanic whites. We built nested models with terms for race and ethnicity forced into the models. We used purposeful selection of covariates to identify factors that may have confounded or mediated observed associations between race/ethnicity and survival time. Covariates that changed the coefficients of race/ethnicity by >20% after inclusion were considered strong confounders. p-Value-based variable selection techniques were not performed. Time-varying covariates for transplantation status and for the first 30-day post-transplant period (a period characterized by a high mortality rate during which the assumption of proportional hazards may not be met) were employed (23–26). p-Values <0.05 were considered statistically significant. SAS 9.1 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

There were 3195 non-Hispanic black ('black'), Hispanic or non-Hispanic white ('white') patients with IPF listed for lung transplantation between 1995 and 2003. We excluded those who underwent heart–lung transplantation (*n* = 32) or living donor lung transplantation (*n* = 6) as well as those with implausible dates (*n* = 4), leaving 3154 patients. We also excluded those with missing data for FVC% (*n* = 151), height or weight (*n* = 29), tobacco use (*n* = 105), performance status (*n* = 79), steroid use (*n* = 112), diabetes (*n* = 61) or hypertension (*n* = 116). Subjects with a missing zip code or a zip code that was not included in the year 2000 U.S. Census Summary File 3B were also excluded (*n* = 99). In total, 519 (16%) subjects were excluded for missing data, leaving a final cohort of 2635 subjects. Race and ethnicity

did not differ between those excluded for missing data and those included in the analysis (11% black, 7% Hispanic and 82% white in both groups, $p = 0.80$). Subjects excluded due to missing data were also similar to those with complete data in terms of age ($p = 0.41$), gender ($p = 0.42$), FVC% ($p = 0.37$) and medical comorbidities (all $p > 0.40$). Subjects with missing data were somewhat less likely than those with complete data to undergo transplantation (38% vs. 46%, respectively, $p < 0.01$) and were slightly more likely to die during the study period (69% vs. 60%, respectively, $p < 0.01$).

Population

Characteristics of the final cohort at the time of listing are shown in Table 1. Eleven percent of the patients were black ($n = 299$), 7% were Hispanic ($n = 173$) and 82% were white ($n = 2163$). Black and Hispanic patients were younger and more likely to be female than white patients. Black and Hispanic patients also had more medical comorbidities than whites, with higher frequencies of diabetes and poor performance status, but were less likely to have been smokers. Black patients were more likely to have treated hypertension than Hispanic or white patients. White patients were more likely to have private medical insurance or a college education and lived in higher income neighborhoods of higher educational attainment more often than blacks and Hispanics. Minority patients had a somewhat lower FVC% (44%, 45% and 51% for blacks, Hispanics and whites, respectively) and slightly higher pulmonary artery pressure at the time of listing (30 mmHg, 28 mmHg and 25 mmHg, respectively). Pulmonary capillary wedge pressure and cardiac index did not differ between groups. Hispanics (but not blacks) were more likely than whites to have a 6-min walk distance less than 150 ft.

Transplantation

During the study period, 39% of blacks, 47% of Hispanics and 46% of whites underwent lung transplantation ($p = 0.07$). Among those who were transplanted, the median time from listing to lung transplantation did not differ between groups [250 days (IQR 99 to 494 days) for blacks; 225 days (IQR 110 to 533 days) for Hispanics and 215 days (IQR 86 to 455 days) for whites, $p = 0.39$]. Blacks and Hispanics were more likely to undergo double lung transplantation than were whites (37% and 39% vs. 26%, respectively for those transplanted, $p = 0.001$).

Survival

There were 1594 deaths during the study period. The median survival of the cohort was 1.7 years (IQR 7 months to 3.4 years). The age-adjusted mortality rate was higher for blacks and Hispanics compared to whites [Figure 1; Table 2; hazard ratio (HR) for blacks = 1.24, 95% confidence interval (CI) 1.06–1.45, $p = 0.009$; HR for Hispanics = 1.29, 95% CI 1.06–1.56, $p = 0.01$]. Differential timing or probability of lung transplantation did not explain the results, as adjustment for this factor did not change these effect estimates (Table 2, Model 2). Categorizing the transplant procedure as single or double did not influence the hazard ratios (data not shown).

Next, we adjusted for potentially important clinical covariates (gender, body mass index, diabetes, hypertension, steroid use, smoking status, year of listing and performance status)

(Table 2, Model 3). Hispanic ethnicity and black race were still independently associated with an increased mortality rate after inclusion of these factors in the model. Further adjustment for type of health insurance and group-level socioeconomic indicators (median family income and community educational attainment) did not materially alter these findings (Table 2, Model 4). Additional adjustment for individual-level educational status resulted in similar findings for Hispanics but reduced the magnitude of the association for blacks ($n = 2\,208$; HR for blacks = 1.17, 95% CI 0.98–1.41, $p = 0.09$; HR for Hispanics = 1.34, 95% CI 1.08–1.67, $p = 0.007$).

We then examined the role of differences in severity of lung disease and exercise tolerance at the time of listing. Inclusion of FVC% in the model reduced the associations between race and ethnicity and mortality, suggesting that differences in pulmonary function explained some of the disparities in outcome in the fully adjusted model (Table 2, Model 5). However, even in the FVC%-adjusted model, it appeared that minority patients may have had increased mortality rates compared to whites of borderline statistical significance ($p = 0.09$ for blacks and $p = 0.056$ for Hispanics).

Inclusion of pulmonary artery pressure instead of FVC% in Model 5 reduced the differences in risk for blacks compared to whites, albeit with a smaller sample size due to missing data ($n = 2\,009$; HR for blacks = 1.17, 95% CI 0.96–1.41, $p = 0.12$; HR for Hispanics = 1.26, 95% CI 0.99–1.60, $p = 0.06$). Alternatively, adjustment for 6-min walk distance did not substantially change the effect estimates for race/ethnicity ($n = 2\,419$; HR for blacks = 1.26, 95% CI 1.06–1.50, $p = 0.01$; HR for Hispanics = 1.23, 95% CI 0.99–1.52, $p = 0.06$). Minimal changes in the effect estimates after adjustment for these variables suggest a lack of confounding by these factors; however, missing data limited these analyses and resulted in widened 95% CIs.

The exclusion of patients with missing data from the final cohort could have affected the results. To address this, we examined the association of race and ethnicity status with the risk of death after including those with missing data. Age, gender and transplantation status were available for all 3154 subjects in this analysis. Black race and Hispanic ethnicity remained significantly associated with the age, gender and transplant-adjusted risk of death in the entire cohort of patients listed for lung transplantation ($n = 3154$; HR for blacks = 1.16, 95% CI 1.01–1.3, $p = 0.04$; HR for Hispanics = 1.24, 95% CI 1.04–1.5, $p = 0.02$).

When we censored at transplantation, the effect estimates were virtually identical with wider 95% CIs (due to the elimination of post-transplantation deaths from the analysis) ($n = 2635$; age- and gender-adjusted HR for blacks = 1.15, 95% CI 0.94–1.40, $p = 0.16$; HR for Hispanics = 1.33, 95% CI 1.04–1.69, $p = 0.02$). The race and ethnicity variables met the assumption of proportional hazards. Exclusion of potentially influential subjects from the models only increased the magnitude of the associations between black race and Hispanic ethnicity and the risk of death.

Discussion

We found that black and Hispanic patients classified as having IPF who were listed for lung transplantation in the United States during the study period had higher mortality rates than whites independent of age, gender, medical comorbidities, insurance status, transplantation and socioeconomic status. These disparities in survival were attributable in part to worse lung function among both blacks and Hispanics compared to whites at the time of listing for lung transplantation. Although not surprising that lung function played some role in determining worse outcomes, this is the first demonstration that minority patients are more likely to have reduced lung function at the time of listing, disproportionately affecting their survival compared to whites. These findings are particularly disconcerting in light of all patients in this study having been listed for transplantation, therefore undergoing care and monitoring by transplant center physician and nursing staffs accustomed to treating patients with severe IPF. Lastly, receiving lung transplantation did not affect these findings, suggesting both pre- and post-transplant contributors to these disparities.

These results confirm and extend our previous report of increased mortality among minority IPF patients (16). IPF therefore joins the growing list of pulmonary diseases in which outcomes differ by race and ethnicity, such as asthma (27), lung cancer (20,28) and pulmonary arterial hypertension (29). While it is likely that not all patients in this cohort had IPF as it is currently defined, our classification is similar to the specificity of other large landmark epidemiologic studies (4,14,15).

Differences in pre-referral medical care, timing of referral and disease phenotype may have contributed to the disparities in disease severity and survival by race and ethnicity. There are currently no known medical therapies that improve survival in IPF. However, lower vaccination rates, poorly managed medical comorbidities, overuse of corticosteroids, underuse of supplemental oxygen and less access to pulmonary rehabilitation could explain the worse lung function and outcomes seen in minority patients in this study.

Barriers to obtaining high-quality medical care faced by minority patients and the physicians who serve them could lead to later referral and could account for our findings. It is well established that physicians who care for minority patients report less access to advanced imaging and specialist consultation despite similar insurance coverage (30). The probability of lung transplantation does not account for these findings, since our results did not change after adjustment for transplantation. The effects of pre-referral care and timing of referral may therefore adversely affect outcomes in minority patients even after undergoing this life-saving procedure. As the new lung allocation system in the United States prioritizes those patients having more severe disease, observed differences in survival may be affected, even though our findings were independent of the timing of transplantation.

Finally, race may serve as a surrogate for a genetic profile which produces a distinct disease phenotype. Indeed, the frequencies of key 'overexpressing' gene polymorphisms which drive inflammation and fibrosis vary by racial and ethnic groups (31–33). On the other hand, complex diseases such as IPF are characterized by complicated gene-environment interactions, so that variability in a single locus is unlikely to explain our results. In addition,

it is implausible that one or several 'high-risk' genetic profiles cause similarly poor outcomes in the diversity of conditions which manifest racial disparities (e.g., coronary heart disease, lung cancer, asthma, pulmonary hypertension and now IPF). Independent of the quality of care or biologic differences, timely diagnosis or referral, specific cultural belief systems may also have contributed to differences in disease outcomes (28). In any case, the Department of Health and Human Services has targeted such differences in disease outcomes based on race and ethnicity whatever the mechanism (34). This study therefore identifies a new focus for future basic scientific and public health initiatives.

While it is widely accepted that IPF is typically diagnosed after the age of 50 and is more common among men than women (35), blacks and Hispanics in our study tended to be younger and were more likely to be female than whites in our study. Since the manifestations of pulmonary fibrosis in minority populations have not been previously described, these differences may represent a novel finding of a different demographic distribution of IPF among minorities compared to whites. Inclusion of patients with lung disease due to connective tissue disease preferentially in the minority groups might be an alternate explanation for the age and gender differences between groups. Even so, recent studies have found similar outcomes both before and after lung transplantation between patients with connective tissue disease-related lung disease and idiopathic interstitial pneumonia (36,37), lessening the impact of such misclassification on our findings.

We included post-transplantation time in our adjusted survival models with a simple yet powerful methodology which is the standard for studies of transplantation (23–26). Whereas censoring observations at the time of transplantation would be an alternative, such an approach neglects what is most important to patients, families, physicians and policy-makers, i.e. overall survival. The lifespan of a patient with IPF does not end at transplant, and the sequelae of IPF and pre-transplant management may affect post-transplant functional status and long-term outcome. For these reasons, post-transplant survival is important to include in studies of long-term outcomes of progressive and incurable lung diseases. Nevertheless, our findings were similar when we censored patient-time at transplantation.

There were several limitations. First, this study was retrospective and therefore suffers from the usual issues with this design. Second, some patients in our study may not have had IPF as it is currently defined, especially since the UNOS database preceded the release of the current diagnostic guidelines (38). There are no data to suggest that misclassification of IPF diagnosis would occur differentially by race. Therefore, the differences in outcome between groups may be even larger than those shown. In addition, the demonstration of such robust differences in outcome without knowledge of the histopathology and potential inciting factors increases the generalizability of the results. Most other large epidemiological studies of IPF have used similar methodology for defining IPF (4,14,15). Third, the UNOS database receives non-standardized race and ethnicity information when patients are listed, possibly resulting in misclassification. Fourth, although we adjusted for a variety of individual- and group-level covariates, residual or unmeasured confounding may be present. For example, we did not have access to the absolute values of forced vital capacity or to the various reference values (which may or may not have accounted for race) used by each center,

possibly resulting in inadequate adjustment for lung function. Fifth, we excluded patients with missing data for certain variables. While the final cohort may have been somewhat healthier than the full cohort, race and ethnicity in the included and excluded groups were similar, and analysis of the full cohort showed identical results. Missing pulmonary artery pressure data for 24% of the final cohort may have limited our ability to detect an even stronger role of pulmonary hypertension in explaining the disparate outcomes, since pulmonary hypertension is an important predictor of survival in IPF (39–41).

Lastly, patients with IPF who are listed for transplantation are clearly highly selected. Referral to a tertiary-care lung transplant center and the stringent vetting process for listing for transplantation (including screening for adequate health care coverage, social and family support, self-care and compliance with a complicated medical regimen) would be expected to homogenize patient groups, tending to minimize differences between minority and white patients. Considering this selection process, the strength and consistency of our findings is therefore even more remarkable, as we would expect even greater differences in an unselected patient population with IPF. This is also the largest cohort study of IPF ever published to our knowledge, bolstering its generalizability.

In conclusion, we found an increased mortality rate among Hispanic and black patients with IPF listed for lung transplantation compared to whites after adjustment for a variety of factors and due, at least in part, to more severe disease at the time of listing. This study confirms our previous work showing that minority patients with IPF not only are more severely ill at the time of evaluation for lung transplantation, but also have a higher risk of death once listed. Our findings add IPF to the growing list of pulmonary diseases that have a disproportionate effect on black and Hispanic Americans. Future research should focus on elucidating the mechanisms of these disparities, with the ultimate goal of alleviating differences in survival. In the meantime, educational efforts should be targeted to physicians who care for minority patients with IPF encouraging early referral for subspecialist care and transplantation evaluation.

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Figure 1.
Age-adjusted survival curves.

Table 1

Characteristics at the time of placement on the UNOS waiting list

Variable	N	Black (n = 299)	Hispanic (n = 173)	White (n = 2163)	p Value
Demographics					
Age, years	2635	46 ± 10 ^l	50 ± 10 ^l	54 ± 9	<0.0001
Female	2635	169 (57%)	85 (49%)	755 (35%)	<0.0001
Body mass index, kg/m ²	2635	29 ± 6	28 ± 5	28 ± 5	0.14
Comorbidities and functional status					
Diabetes mellitus	2635	38 (13%)	31 (18%)	224 (10%)	0.006
Drug-treated hypertension	2635	76 (25%)	22 (13%)	391 (18%)	0.001
Corticosteroid use >5mg/d	2635	175 (59%)	110 (64%)	1348 (62%)	0.41
Smoking >10 pack-years	2635	101 (34%)	61 (35%)	1051 (49%)	<0.0001
Poor performance status	2635	106 (69%)	111 (64%)	1311 (61%)	0.02
Physiologic data					
FVC%	2635	44 ± 15 ^l	45 ± 16 ^l	51 ± 17	<0.0001
FEV ₁ %	2635	45 ± 17 ^l	47 ± 17 ^l	53 ± 17	<0.0001
Mean PAP, mmHg	2009	30 ± 14 ^l	28 ± 12 ^l	25 ± 10	<0.0001
Pulmonary capillary wedge pressure, mm Hg	2049	11 ± 6	11 ± 7	10 ± 5	0.09
Cardiac index, L/min/m ²	1879	2.7 ± 0.8	2.8 ± 0.7	2.8 ± 0.8	0.22
6-Min walk distance <150 ft	2419	36 (13%)	35 (22%)	243 (12%)	0.002
Health insurance					
Private insurance	2635	203 (68%)	116 (67%)	1893 (88%)	<0.0001
Medicare	2635	57 (19%)	26 (15%)	303 (14%)	0.07
Medicaid	2635	54 (18%)	36 (21%)	93 (4%)	<0.0001
Educational status²					
Less than 9 years	2208	22 (15%)	8 (3%)	38 (2%)	<0.0001
9–12 Years		56 (37%)	114 (47%)	714 (39%)	
Some college		48 (32%)	55 (23%)	460 (25%)	
College graduate		24 (16%)	67 (27%)	602 (33%)	
Group-level socioeconomic status					

Variable	N	Black (n = 299)	Hispanic (n = 173)	White (n = 2163)	p Value
Median family income, U.S. \$	2635	45 000 (34 4000–56 000) ¹	41 100 (33 200–53 200) ¹	52 700 (42 500–67 600)	<0.0001
High school graduates, %	2635	76 (63–85) ¹	76 (69–85) ¹	85 (78–91)	<0.0001
College graduates, %	2635	16 (11–25) ¹	16 (10–27) ¹	22 (15–36)	<0.0001

Data are mean ± SD, frequency (percentage) or median (interquartile range). p Values are from ANOVA, Kruskal–Wallis or chi-squared tests, as appropriate. FVC% = forced vital capacity % predicted; FEV₁% = forced expiratory volume in 1 s % predicted; PAP = pulmonary artery pressure.

¹p < 0.05 compared to whites.

²Percentages do not add to 100% because of rounding.

Table 2

Multivariate models of the risk of death

	Hazard ratio (95% CI)	p Value
Model 1 ¹		
White	Referent group	
Black	1.24 (1.06–1.45)	0.009
Hispanic	1.29 (1.06–1.56)	0.01
Model 2 ²		
White	Referent group	
Black	1.24 (1.06–1.45)	0.008
Hispanic	1.29 (1.06–1.56)	0.01
Model 3 ³		
White	Referent group	
Black	1.28 (1.09–1.50)	0.003
Hispanic	1.31 (1.08–1.60)	0.007
Model 4 ⁴		
White	Referent group	
Black	1.24 (1.05–1.46)	0.01
Hispanic	1.28 (1.05–1.56)	0.01
Model 5 ⁵		
White	Referent group	
Black	1.16 (0.98–1.36)	0.09
Hispanic	1.21 (0.99–1.48)	0.056

n = 2 635 in each model.

¹ Model 1: Adjusted for age.

² Model 2: Adjusted for age and transplantation.

³ Model 3: Adjusted for age, transplantation, gender, body mass index, diabetes, hypertension, smoking, performance status, year of listing and steroid use.

⁴ Model 4: Adjusted for variables in Model 3 + private insurance and group-level socioeconomic status (median family income and college education).

⁵ Model 5: Adjusted for variables in Model 4 + forced vital capacity % predicted.