ERJ Express. Published on March 5, 2008 as doi: 10.1183/09031936.00165207

Gender Differences in Physiologic Progression of Idiopathic Pulmonary Fibrosis

MeiLan K. Han, MD, MS*
Susan Murray, ScD*
Charlene D. Fell, MD, MS†
Kevin R. Flaherty, MD, MS*
Galen B. Toews, MD*
Jeffery Myers, MD*
Thomas V. Colby, MD‡
William D. Travis, MD**
Ella A. Kazerooni, MD, MS*
Barry H. Gross, MD*
Fernando J. Martinez, MD, MS*

University of Michigan Health System*
Ann Arbor, MI

University of Calgary†
Calgary, Alberta, Canada

Mayo Clinic‡
Scottsdale, AZ

Memorial Sloan Kettering Cancer Center**
New York, NY

This work supported by National Institutes of Health grants # 5 P50 HL56402, U10 HL080371, 2K24HL04212, K23 HL68713 and the Alberta Heritage Medical Foundation
Corresponding Author:
MeiLan Han, MD, MS
1500 E Medical Center Drive
3916 Taubman Center
Ann Arbor, MI 48109-0360
734-763-2540
734-936-5048 (fax)
mrking@umich.edu

Body word count: 2,585
Abstract word count: 194
Running Head: Gender Differences in IPF Progression

Copyright 2008 by the European Respiratory Society.

Abstract (word count 194):

Rationale: In IPF, incidence is higher in men, and women may have better survival. We sought to determine whether the rate of increase in desaturation during serial six minute walk testing would be greater, and survival worse, for men versus women.

Methods: Serial changes in percent of maximum desaturation area over one year were estimated using mixed models in 215 patients. Desaturation area was defined as the total area above the curve created using desaturation percentage values observed during each minute of the six minute walk test. Multivariate Cox regression assessed survival differences.

Main Results: Adjusting for baseline desaturation area, six minute walk distance, change in six minute walk distance over time, and smoking history, the percent of maximum desaturation area increased an average of 2.83 per month for men and 1.37 per month for women. Women demonstrated better survival overall, which was more pronounced in patients who did not desaturate below 88% on ambulation at baseline and after additionally adjusting for six-month relative changes in desaturation area and forced vital capacity.

Conclusions: These data suggest that differences in disease progression contribute to but do not completely explain better survival of women with IPF.

Keywords: desaturation, interstitial lung disease, six minute walk test, survival

Introduction:

Idiopathic pulmonary fibrosis (IPF) is a diffuse parenchymal lung disease of unknown origin characterized by alveolar inflammation, fibrosis of the interstitial space, and pulmonary vascular disruption. Gender discrepancies in this disorder have been suggested for some time. The incidence and prevalence of disease have been reported in multiple studies to be higher in men than in women with ratios ranging from approximately 1.6:1 to 2:1 [1-3]. Prior reports have also suggested that female gender is associated with better survival [4, 5]. We hypothesized that the rate of physiologic progression of disease, as measured by serial progression in exertional oxygen desaturation, would be greater in men than women. Previously we have demonstrated that oxygen desaturation and serial increases in desaturation during six minute walk testing (6MWT) in IPF patients correlate with increased mortality [6], thus we also wanted to assess whether gender differences in survival remained after adjusting for longitudinal change in desaturation.

Materials and Methods:

Study subjects

The study utilized patients in the database of the University of Michigan Specialized Center of Research (SCOR) in the Pathobiology of Fibrotic Lung Disease. Patients in this data base were referred for enrollment in study protocols for suspected IPF based on typical symptoms, physiologic, and radiographic findings. Patients with a high resolution computed tomography (HRCT) scan showing a definite pattern of usual interstitial pneumonia (UIP) were not required to undergo a surgical lung biopsy [7-10]. Patients were treated with varied treatment regimens including no therapy; prednisone alone; prednisone with an additional

immunosuppressive agent including azathioprine, cyclophosphamide, methotrexate, or myocophenolate mofetil; investigational agents including bosentan, gamma interferon, GC1008, pirfenidone, tetra-thiomyolybdate, and zileuton; or miscellaneous agents including N-acetylcysteine and colchicine (Table 1). Therapy decisions were made by the treating clinician. The lack of a prospectively defined treatment regimen, varying lengths of therapy, and the overlap of treatment regimens precluded our ability to evaluate the effect of treatment on serial change in pulmonary function, 6MWT, or survival; we have little evidence to date that any of these treatments were effective in improving outcomes. Ten of these patients (nine men and one woman) eventually underwent lung transplantation. We excluded patients with underlying connective tissue disease, obvious occupational exposure, or a histopathologic pattern other than UIP. Approval for the use of these data was obtained from the Institutional Review Board of the University of Michigan. A subgroup of these patients has been previously described [6, 7, 10-14].

Study Design

This study consisted of a mixed models analysis to determine whether exertional hypoxemia in IPF deteriorates more rapidly in men than women, adjusting for baseline DA, baseline 6MWT distance (6MWD), change in 6MWD over time, and smoking history. Several survival models were also constructed initially adjusting for age, smoking history, baseline DA, and DL_{CO} (carbon monoxide diffusing capacity) % predicted. In a subset of physiologically milder patients who did not desaturate below 88% predicted during the baseline 6MWT, we also included a 6-month relative change in both DA and FVC (forced vital capacity) % predicted as well.

Methods

Desaturation area (DA) was defined as the total area above the curve created using desaturation percentage values observed during each minute of the 6MWT, thereby summing up the differences between an oxygen saturation (SaO_2) of 100% and the patient's SaO_2 at each minute (Figure 1) [6]. For example, a patient with a SaO_2 of 98% at each minute during the 6MWT would have a DA of 12 (100-98 = 2 x 6 minutes = 12). For safety, we stopped the 6MWT when patients reached a SaO_2 of 86% and a desaturation score of 14% was assigned for that minute and all subsequent minutes of the 6MWT; thus the maximum possible DA score for an individual is 14 x 6=84. A higher DA indicates higher overall quantity of desaturation during the 6MWT.

Statistical Analysis

All analyses used SAS 9.1 statistical software. Baseline characteristics were compared using a two-sample Student's t-test. The mixed models analysis was performed using PROC MIXED, which adjusts appropriately for missing data due to attrition. In this mixed model all DA values were divided by 84 (maximal possible value for DA) and multiplied by 100, so that parameters estimate change in the percent of the maximal DA score. In order to assess survival differences between men and women, multivariate Cox regression models were used. Follow-up time was based on date of diagnosis, either open lung biopsy or diagnostic HRCT. An initial survival analysis adjusting for gender, age, baseline DA, DL_{CO}% predicted, and smoking status was performed in patients with available data (n=179). Additional analyses were then performed on the group of patients who did not desaturate below 88% on the baseline 6MWT (n=103). Next we examined a subset of those patients in whom serial 6MWT data was available (n=72). For each of these patients, a 6-month predicted DA value was obtained from individual regression lines, provided that each patient was able to perform at least two 6MWT within the first 12

months of follow-up and was still alive at the 6-month time mark. Relative change in DA was calculated by subtracting the baseline value from the 6-month predicted value and dividing by the baseline value, with follow-up commencing at the moment a patient trajectory became available for analysis. This method was also used to calculate 6-month relative change in FVC % predicted. Gender-specific survival curves were constructed adjusting for the average values of 6-month relative change in DA, baseline DA, age, smoking history, DL_{CO} % predicted, FVC % predicted, and 6-month relative change in FVC % predicted. In all of the survival analyses, two mortality endpoints were considered: (1) death following diagnosis, regardless of transplant status and (2) death following diagnosis with censoring at time of transplant.

Results:

Baseline Characteristics

Baseline demographic data on all 215 patients are presented in Table 2. There was no significant difference in most baseline variables except the percent of men versus women who were former or current smokers. Because of this, the rest of the analyses were adjusted for smoking history.

Repeated Measures Analysis

Male gender was associated with a more rapid increase in DA over time as compared to women, with the percentage of the maximum DA (% of Max DA) increasing by 2.83 per month for men versus 1.37 per month for women. Thus after the course of one year, the gender difference in % of Max DA is 17.5 ($p=0.01$). This indicates that the progression of exertional hypoxemia is more rapid in men (See Table 3).

Survival Analysis

A multivariate Cox regression model evaluating gender differences adjusted for age, smoking history, DL_{CO} % predicted, and DA demonstrated a statistically significant survival advantage for women (HR 0.63; 95% CI 0.41-0.97; p=0.04) (Table 4). When FVC % predicted was included in the multivariate model it was found to be a non-significant predictor of survival and the corresponding gender HR continued to favor women (p=0.048). Censoring these patients at the time of transplant did not substantially change the results (HR 0.61; 95% CI 0.39-0.94, p=0.03).

We next examined the impact of gender on patients with less severe disease because it is in these patients that there would be the most opportunity for exertional hypoxemia to change over time and subsequently influence survival. Therefore we performed a survival analysis only on patients who did not desaturate below 88% during their first 6MWT (n=103). In this analysis, the better survival for women was even more pronounced than in the overall patient population (HR 0.48; 95% CI 0.26-0.89; p=0.02; see Table 5) and remained marginally significant at the same order of clinical significance when censoring patients at time of transplant (HR 0.57; 95% CI 0.31-1.05; p=0.07).

Next we added 6-month relative change in DA, baseline FVC % predicted and 6-month relative change in FVC % predicted to the model (n=72; Table 6), as we have previously demonstrated increase in DA and decrease in FVC to be predictive of survival in IPF [6]. In this model, female gender was still associated with better survival (HR 0.38; 95% CI 0.15, 0.95; p=0.04). Baseline DA, 6-month relative change in DA, and 6-month relative change in FVC were also significant independent predictors of survival in this model. Adjusted survival curves are presented in Figure 2. These curves plot survival for men and women adjusted for the

following average parameters of patients: age = 62.85 years, baseline DA = 47.52 or 56.57 % of maximum DA, 6 month relative change in % of maximum DA = -.72, probability of smoking history = 77%, average FVC% predicted 71%, 6 month relative change in FVC% predicted 5%. Of note only one patient in this group underwent transplant during the follow-up period and censoring that patient at the time of transplant did not substantially change the results of the analysis.

Discussion:

Gender discrepancies in IPF have been suggested by several investigators. These differences include a higher prevalence of disease and higher mortality in men. As several groups, including ours, have suggested that serial measures of pulmonary physiology, particularly exertional desaturation, strongly influence survival in IPF, we hypothesized that the rate of physiologic progression of disease would be greater in men than women. In this study we have made several important observations, including: 1) men with IPF demonstrate more rapid deterioration in exertional desaturation over time as compared to women; 2) survival is worse in men compared to women; and 3) better survival for women persists after additionally adjusting for relative change in exertional desaturation and FVC % predicted.

The importance of longitudinal change in FVC, DL_{CO} and 6MWT has been confirmed by several groups [6, 15, 16], but gender differences in longitudinal change in physiologic parameters have not been formerly reported. As such we explored and documented a gender difference in the rate of deterioration in exertional desaturation. While it could be argued that the difference in physiologic trajectories was due to systematic differences in disease stage, there was no significant difference in baseline pulmonary function measurements or DA between

genders and the change in DA over time was adjusted for age, smoking history, DLCO% predicted, and baseline DA. The etiology of the gender specific difference in disease progression, however, is not readily obvious.

We also demonstrate better survival for women with IPF compared to men, after adjusting for age, smoking history, DL_{CO} % predicted, and DA. This is in contrast to a lesser powered retrospective analysis of 99 patients with IPF where gender was not detected to be a significant predictor of survival in a multivariate analysis adjusted for measures of lung function, age, and smoking history [17]. In the older literature, several papers suggest a survival advantage [3, 18] for women and several do not [19, 20], but this may be due to lack of power and a mixture of diagnoses prior to the development of the clinical-radiologic-pathologic diagnostic methods now in place. However most recent reports suggest a survival advantage for women with relative risks of death for men compared to women ranging from 1.4 to 2.3 [4, 5].

Vital statistics in the U.S. indicate that the unadjusted average life expectancy for men is 74.7 years and for women is 80 years [21]. In this study, we controlled for physiologic parameters known to influence survival in IPF and still saw significant differences in survival between men and women, well beyond the magnitude of survival differences seen in the general population. Interestingly, in our subjects who did not desaturate below 88% on the baseline 6MWT, the survival advantage for women was even more pronounced. Our data are also strengthened by the rigorous definition of UIP using a clinical-radiographic-pathological format.

As DA trajectory and survival both differed between genders, we also tested the hypothesis that relative change in DA may influence survival and help to explain gender differences. As such, we focused on those patients with oxygen saturation above 88% during their baseline 6MWT and in whom serial 6MWT data were available. We chose to specifically

examine this group because they have less severe disease and thus theoretically more room to deteriorate during the observation period of this study thus allowing us to better evaluate how change in physiology impacts survival. In this survival analysis we also included FVC % predicted and 6-month relative change in FVC % predicted in the model as we have previously shown change in FVC to be a significant predictor of survival [6]. Other predictors included gender, age, smoking history, and DL_{CO} % predicted. The survival advantage for women became even more pronounced (HR 0.38; 95% CI 0.15-0.95; p=0.04). Consequently these data suggest that while differences in disease progression likely contribute to better survival for women, female gender is still associated with enhanced survival independent of relative change in DA and FVC. A smaller series of IPF patients did not suggest that gender impacted on the predictive value of longitudinal change in exertional desaturation on survival [22]. Differences may reflect the reduced power due to sample size or methodology used to define six minute walk desaturation. Additional prospective data collection is required to better define these differences.

Importantly, IPF is not the only fibrotic disorder where gender dimorphism has been noted. Women are relatively protected from fibrotic diseases involving the liver and kidney. Men with chronic renal disease progress more rapidly than women to end-stage renal failure [23]. Population data also suggest end stage liver disease in the form of cirrhosis is much more common in men than women (2.3 to 2.6:1) [24]. In both end-stage renal and hepatic disease, a potential role for estrogen has been proposed and in animal models appears to be protective [25-27]. The average age of women in this study was 64.2 years suggesting the majority of women would have been post-menopausal when estrogen levels are low. To the contrary, a prior report of bleomycin-induced pulmonary fibrosis in rats demonstrated diminished fibrosis in female ovariectomized rats; the fibrotic response was restored with estradiol replacement [28]. Thus an

exact explanatory mechanism for our data is not readily obvious, and the role of estrogen on the fibrotic process must be further clarified. Better understanding gender differences in disease progression may offer further insight into the pathogenesis of the disease.

There are limitations to this study. The data are retrospective and potentially subject to several types of bias. Treatments were not systematically assigned. One gender versus the other may tend to present at different stages of the disease, although this was not readily apparent in our cohort based on predictors studied as part of Table 2. While women tend to be more frequent seekers of health care in general, they are also less likely to receive subspecialty referrals [29]. Furthermore, the survival data may be biased by a differential presence of comorbidities such as cardiovascular disease. We did not prospectively assess the development of pulmonary vasculopathy, which may be important as desaturation has been suggested to be associated with a greater prevalence of pulmonary hypertension in IPF patients [30]. A strength of this study, however, is that the longitudinal analysis of DA was adjusted for factors that could potentially bias the results including baseline DA, distance walked, change in distance walked over time, age and smoking status. Furthermore, patient diagnosis was assigned based on the current standard of care, a multidisciplinary clinical-radiologic-pathologic process. In summary we have determined that while differences in the rate of physiologic progression likely contribute to survival differences between men and women, there may be other uncharacterized gender-related influences on survival. Prospective validation of the data is required to define potential therapeutic implications of these data.

References

1. Carrington CB, Gaensler EA, Coutu RE, FitzGerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978: 298(15): 801-809.
2. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006: 174(7): 810-816.
3. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. *Thorax* 1980: 35(3): 171-180.
4. Mannino DM, Etzel RA, Parrish RG. Pulmonary fibrosis deaths in the United States, 1979-1991. An analysis of multiple-cause mortality data. *Am J Respir Crit Care Med* 1996: 153(5): 1548-1552.
5. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006: 61(11): 980-985.
6. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB, Martinez FJ. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six minute hallwalk. *Am J Respir Crit Care Med* 2006.
7. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD, Flint A, Toews GB, Lynch JP, 3rd, Martinez FJ. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003: 168(5): 543-548.
8. Hunninghake GW, Lynch DA, Galvin JR, Gross BH, Muller N, Schwartz DA, King TE, Jr., Lynch JP, 3rd, Hegele R, Waldron J, Colby TV, Hogg JC. Radiologic findings are

strongly associated with a pathologic diagnosis of usual interstitial pneumonia. *Chest* 2003: 124(4): 1215-1223.

9. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000: 161(2 Pt 1): 646-664.

10. Flaherty KR, King TE, Jr., Raghu G, Lynch JP, 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004: 170(8): 904-910.

11. Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA, Gross BH, Jain A, Strawderman RL, 3rd, Paine R, Flint A, Lynch JP, 3rd, Martinez FJ. Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Respir J* 2002: 19(2): 275-283.

12. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP, 3rd, Martinez FJ. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003: 168(9): 1084-1090.

13. Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, Travis WD, Mumford JA, Murray S, Flint A, Lynch JP, 3rd, Martinez FJ. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003: 58(2): 143-148.

14. Flaherty KR, Travis WD, Colby TV, Toews GB, Kazerooni EA, Gross BH, Jain A, Strawderman RL, Flint A, Lynch JP, Martinez FJ. Histopathologic variability in usual

and nonspecific interstitial pneumonias. *American journal of respiratory and critical care medicine* 2001: 164(9): 1722-1727.

15. Collard HR, King TE, Jr., Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003: 168(5): 538-542.

16. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD, Kitaichi M, Colby TV. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005: 171(6): 639-644.

17. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? *Chest* 1997: 111(1): 51-57.

18. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, Burmeister LF, Hunninghake GW. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994: 149(2 Pt 1): 450-454.

19. Tukiainen P, Taskinen E, Holsti P, Korhola O, Valle M. Prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1983: 38(5): 349-355.

20. Stack BH, Choo-Kang YF, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1972: 27(5): 535-542.

21. National Center for Health Statistics. United States Life Tables, 2003. *National Vital Statistics Report* 2006: 54(14): 1-40.

22. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2005: 25(1): 96-103.

23. Silbiger SR, Neugarten J. The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 1995: 25(4): 515-533.

24. Dai WJ, Jiang HC. Advances in gene therapy of liver cirrhosis: a review. *World J Gastroenterol* 2001: 7(1): 1-8.

25. Blush J, Lei J, Ju W, Silbiger S, Pullman J, Neugarten J. Estradiol reverses renal injury in Alb/TGF-beta1 transgenic mice. *Kidney Int* 2004: 66(6): 2148-2154.

26. Xu JW, Gong J, Chang XM, Luo JY, Dong L, Hao ZM, Jia A, Xu GP. Estrogen reduces CCL4- induced liver fibrosis in rats. *World J Gastroenterol* 2002: 8(5): 883-887.

27. Yasuda M, Shimizu I, Shiba M, Ito S. Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. *Hepatology* 1999: 29(3): 719-727.

28. Gharaee-Kermani M, Hatano K, Nozaki Y, Phan SH. Gender-based differences in bleomycin-induced pulmonary fibrosis. *Am J Pathol* 2005: 166(6): 1593-1606.

29. Franks P, Clancy CM, Naumburg EH. Sex, access, and excess. *Ann Intern Med* 1995: 123(7): 548-550.

30. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006: 129(3): 746-752.

Figure 1. Schematic for Calculation of Desaturation Area. With permission from Flaherty, et al [6].

Figure 2. Comparison of survival between men and women who did not desaturate below 88% on baseline six minute walk test, adjusted for the following average parameters of patients: age 62.85 years, 77% probability of prior or current smoking history, DL_{CO}% predicted 48.3, baseline desaturation area 47.52, 6-month relative change in desaturation area -0.72, baseline FVC 71% predicted and change in FVC% predicted 5% (n=72).

Table 1. Treatments administered to 215 patients*

	Men 142 n (% of total men)	Women 73 n (% of total women)	P-value
None	23 (16.2%)	12 (16.4%)	0.96
Prednisone alone	10 (7.0%)	8 (11.0%)	0.33
Prednisone + cytotoxic agent[α]	64 (45.1%)	26 (35.6%)	0.18
Cytotoxic agent alone[α]	5 (3.5%)	1 (1.4%)	0.36
Investigational agent[β]	43 (30.3%)	23 (31.5%)	0.85
Miscellaneous[δ]	31 (21.8%)	15 (20.5%)	0.75

*Some patients received more than one treatment regimen, thus gender percents total greater than 100%.

[α]azathioprine, cyclophosphamide, methotrexate, or mycophenolate mofetil

[β] bosentan, gamma interferon, GC1008 anti-TGFβ antibody, pirfenidone, tetra-thiomyolybdate, or zileuton

[δ]N-acetylcysteine or colchicine

Table 2. Baseline characteristics by gender for 215 patients with Idiopathic Pulmonary Fibrosis

	Men n=142	Women n=73	P-value
Age in Years	63.0	64.2	0.39
Baseline Desaturation Area (% of Max DA*)	59.0 (70.2% of Max DA)	60.1 (71.5% of Max DA)	0.81
Percent of Patients Whose Baseline 6MWT Demonstrated Desaturation Below 88%	37.3	35.6	0.68
FVC % Predicted	64.7	65.8	0.68
DL_{CO} % Predicted	44.0	44.9	0.73
pH	7.42	7.43	0.64
$paCO_2$	38.8	38.6	0.79
paO_2	75.1	73.5	0.17
Resting O_2 Saturation	94.3	94.5	0.81
Distance Walked in Feet	902.6	787.8	0.18
Percent Former or Current Smokers	82.4	63.0	0.002

* % of Max DA derived by dividing DA by 84 (maximal possible value for DA) and multiplying by 100; 6MWT = six minute walk test

Table 3. Mixed models analysis for predictors of change in % of maximum desaturation area (DA) over time. DA was converted to a percent of maximum possible DA (% of Max DA) to make the parameters more interpretable. For example, a DA of 12 would be divided by 84 (maximum possible DA) and multiplied by 100 = 14.3%. Thus for continuous predictors, a one unit change in the predictor results in a corresponding change in the % of Max DA (n=215).

Predictor Variable	Change in % of Max DA	P-value
Time in Months if Male	2.83	<0.0001
Time in Months if Female	1.37	0.01
Female	-1.25	0.14*
Baseline % of Max DA	0.86	<0.0001
Distance Walked (feet)	-0.005	<0.0001
Distance Walked by Month Interaction (feet-month)	-0.002	<0.0001
Former or Current Smoker versus Nonsmoker	0.49	0.59

*Note that no significant difference was seen in DA between genders at baseline (p=0.14); it is the rate of change in DA over time that significantly differed between genders. Men increased their % of Max DA an average of 2.82 per month; women increased their % of Max DA an average of 1.37 per month.

Table 4. Multivariate survival model examining the impact of gender, adjusted for age, DL_{CO}% predicted, desaturation area, and smoking history (n=179).

Variable	Hazard Ratio	95% CI	P-value
Female	0.63	0.41, 0.97	0.04
Age in Years	1.00	1.00, 1.05	0.04
DL_{CO} % Predicted	0.18	0.04, 0.82	0.03
Desaturation Area	1.02	1.00, 1.03	0.009
Former or Current Smoker	1.06	0.68, 1.65	0.80

Table 5. Multivariate survival model examining the impact of gender in patients who did not desaturate below 88% during their baseline six minute walk test, adjusted for age, DL_{CO}% predicted, desaturation area, and smoking history (n=103).

Variable	Hazard Ratio	95% CI	P-value
Female	0.48	0.26, 0.89	0.02
Age in Years	1.03	0.99, 1.06	0.11
DL_{CO} % Predicted	0.20	0.03, 1.26	0.09
Desaturation Area	1.03	1.01, 1.04	0.001
Former or Current Smoker	1.02	0.57, 1.82	0.95

Table 6. Multivariate survival model examining the impact of gender in patients who did not desaturate below 88% during baseline 6MWT and in whom 6MWT trajectory data were available. Analysis ddjusted for age, DL_{CO} % predicted, desaturation area (DA), 6-month relative change in DA, smoking history, FVC% predicted, and 6-month relative change in FVC (n=72).

Variable	Hazard Ratio	95% CI	P-value
Female	0.38	0.15, 0.95	0.04
Age	1.02	1.02, 0.99	0.23
DL_{CO} % predicted	2.93	0.20, 41.9	0.43
Desaturation Area	1.05	1.02, 1.08	0.0006
6-Month Relative Change in DA	2.91	1.51, 5.60	0.001
Former or Current smoker	0.71	0.28, 1.79	0.43
FVC % predicted	0.35	0.05, 2.53	0.30
6-Month Relative Change in FVC	1.57	1.15, 2.13	0.004

6MWT = six minute walk test

Figure 1.

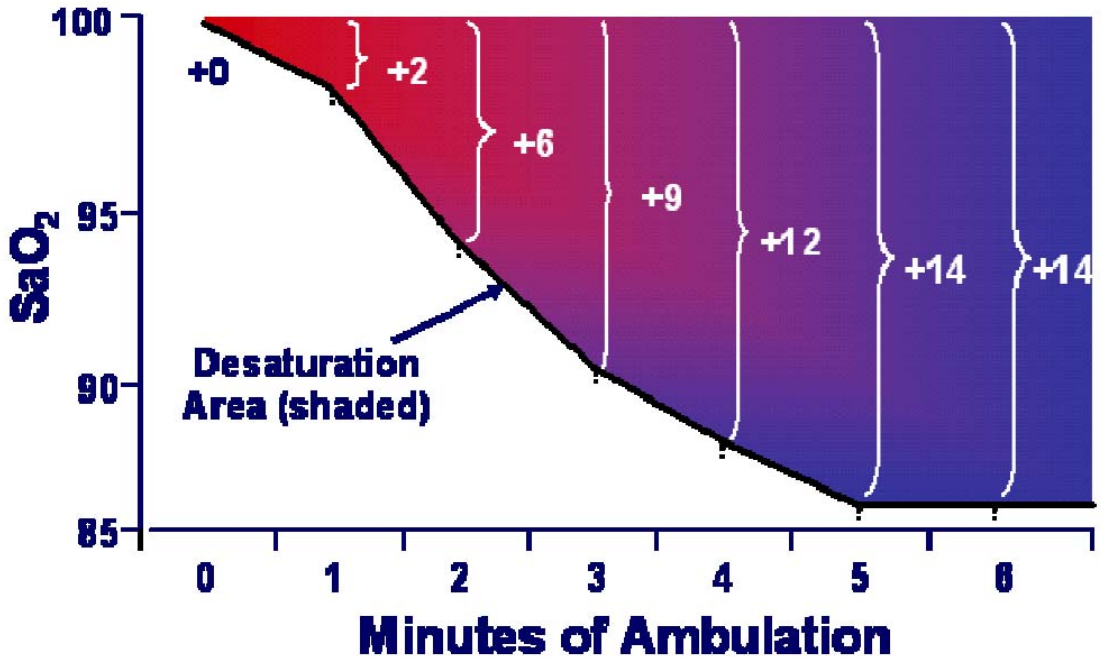
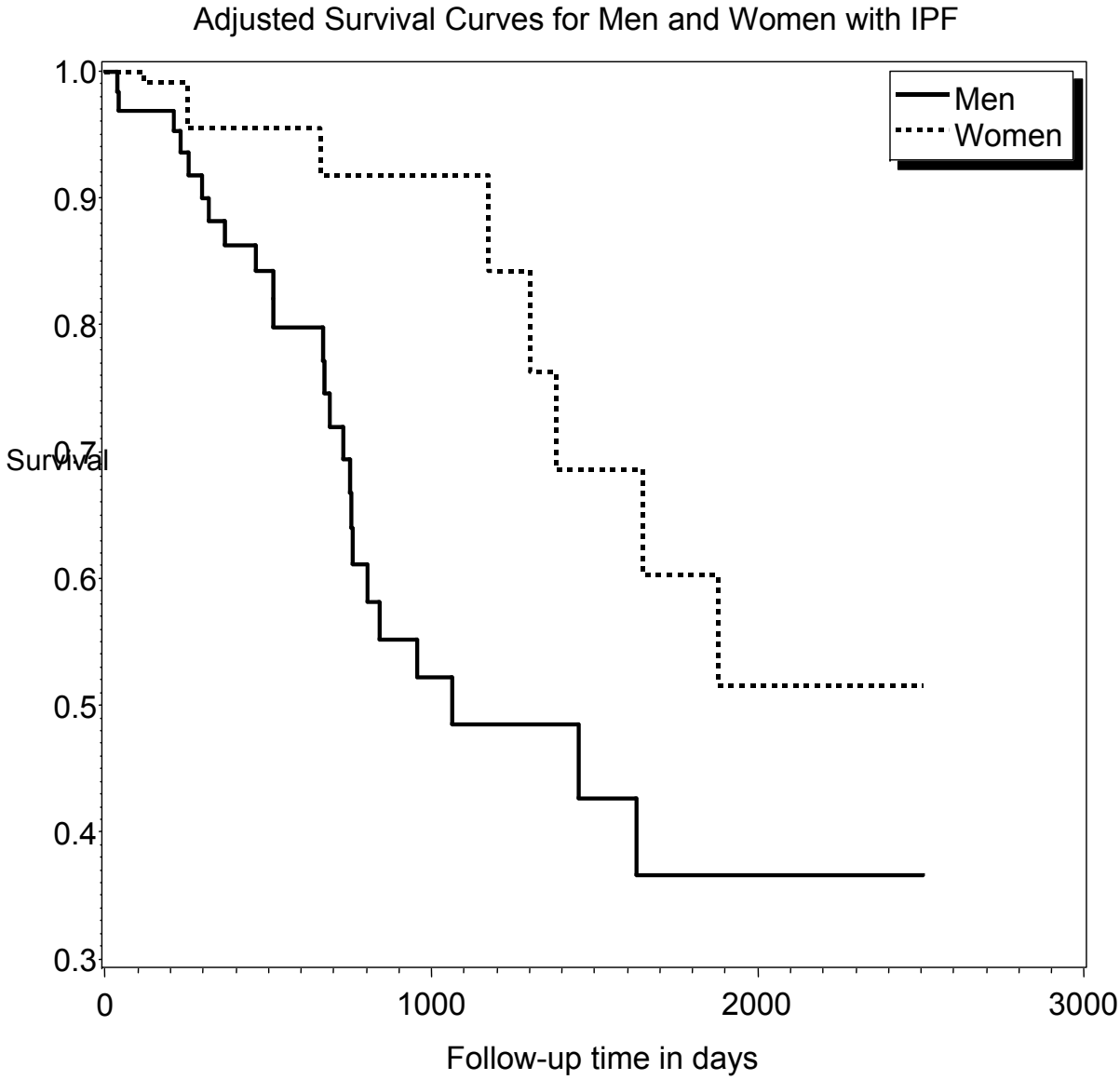

100
95
90
85
SaO_2
+0
+2
+6
+9
+12
+14
+14
Desaturation
Area (shaded)
0
1
2
3
4
5
6
Minutes of Ambulation

Figure 2.


Adjusted Survival Curves for Men and Women with IPF
Men
Women
Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
1000
2000
3000
Follow-up time in days