Title

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Differences in Clinical Characteristics and Outcomes Between Men and Women With Idiopathic Pulmonary Fibrosis

A Multicenter Retrospective Cohort Study

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BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a disease with a male predominance. Prior data suggest that male sex is associated with disease progression and survival. The basis for this sex difference is unknown.

RESEARCH QUESTION: Are there differences in clinical disease characteristics and outcomes between men and women with IPF?

STUDY DESIGN AND METHODS: Two tertiary care center IPF cohorts were pooled to analyze sex differences in outcomes of time to lung transplantation or death. Predictors of outcome that were analyzed included age, FVC % predicted, diffusion capacity for carbon monoxide (DLCO) % predicted, BMI, smoking history, and respiratory variables of cough, phlegm, and need for supplemental oxygen. The associations of these factors with mortality were estimated by sex and then compared using tests for interaction.

RESULTS: There were a total of 1,263 patients in the pooled cohort with follow-up data; approximately 71% of the patients were men. Male sex was independently associated with higher risk for death or lung transplantation after adjusting for age, FVC % predicted, and DLCO % predicted (hazard ratio for men, 1.4; 95% CI, 1.2-1.7; $P < .001$). Older age, lower DLCO % predicted, and presence of cough or phlegm were negatively associated with transplant-free survival in men but not in women, but only the association for cough differed statistically by sex (interaction $P = .007$).

INTERPRETATION: Male sex is associated with worse transplant-free survival in IPF. Cough may be a sex-specific predictor of survival in this population. CHEST 2020; 158(1):245-251

KEY WORDS: idiopathic pulmonary fibrosis; interstitial lung disease; sex

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive scarring disease of the lung with reported survival of 3 to 5 years after diagnosis.[1] Male predominance in IPF has been well-established across international cohorts, with men accounting for approximately 70% of all cases of IPF.[2] The basis for this

ABBREVIATIONS: DLCO = diffusion capacity of the lung for carbon monoxide; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; UCSD-SOBQ = University of California San Diego Shortness of Breath Questionnaire; UCSF = University of California San Francisco

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Take Home Point Pullout

Study Question: Are there differences in clinical disease characteristics and outcomes between men and women with idiopathic pulmonary fibrosis?

Results: Men with idiopathic pulmonary fibrosis had shorter transplant-free survival than women despite similar baseline physiology, and one predictor of survival, cough, differed by sex.

Interpretation: Men and women with idiopathic pulmonary fibrosis have differences in transplant-free survival, and further research is required to determine the cause of these differences.

male predominance is unknown, but hypotheses include disproportionate exposure among men to environmental risk factors, such as cigarette smoke or occupational particulates, and other sex-related variables (eg, sex hormones).[3,4]

Although a sex difference in terms of risk for disease has been consistently observed, whether this disease is truly sexually dimorphic (ie, whether IPF manifests distinctly in each sex) has not been described. Prior work has suggested that women may experience slower disease progression as measured by desaturation area on a 6-min walk test compared with men.[5] Other studies have suggested that men with IPF have greater risk for death than women with IPF,[6,7] but the magnitude of the difference in survival time has not previously been described. The basis for these sex-dependent differences in outcome—whether it is related to differences in risk, disease severity, different phenotypes, or something intrinsic to sex biology—remains unclear.

Furthermore, it is unknown if other characteristics (eg, respiratory symptoms such as cough and breathlessness) differ between the sexes in IPF. Understanding whether sex is associated with specific respiratory symptoms or other clinical variables may inform our understanding of IPF and the apparent discordance in prevalence and outcome based on sex. In this study, we aimed (1) to determine whether various clinical factors vary between men and women with IPF, (2) to validate that male sex is independently associated with increased risk for mortality in a large sample of patients with IPF, and (3) to analyze whether predictors of survival in IPF are sex-specific.

Methods

Study Cohorts

The sample for this study was pooled from the interstitial lung disease patient registries at two academic tertiary care centers, the University of California San Francisco (UCSF) from 2001 to 2017 and the Mayo Clinic (Rochester, MN) from 1993 to 2017. All patients with a clinical diagnosis of IPF and follow-up data in these registries were included. The diagnosis of IPF at both institutions was established by multidisciplinary evaluation according to clinical guidelines.[8] Data regarding demographics and symptoms were prospectively collected from self-administered questionnaires in the UCSF cohort and retrospectively collected from chart review in the Mayo cohort. In the UCSF cohort, symptoms of cough and phlegm were assessed as questions with binary response options (eg, Do you have cough? yes/no). BMI, lung function data of FVC % predicted and diffusion capacity for carbon monoxide (DLCO) % predicted, need for supplemental oxygen at time of diagnosis, and date of lung transplantation were extracted from the medical record. Smoking history was assessed during the routine clinical history and extracted from the medical record. For the survival analysis, time of diagnosis was set as the initial evaluation date at each site. Vital status data were attained from the Social Security Death Index or review of the medical chart.

Two additional data elements were available and analyzed in the UCSF cohort only: breathlessness score and presence of heartburn (assessed as a question with binary response options). Breathlessness in the UCSF cohort was assessed by use of the University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ), a validated tool to quantify breathlessness in IPF,[9] in which higher scores correspond to greater breathlessness. The presence or absence of heartburn was elicited from a prospectively collected patient questionnaire. The UCSD-SOBQ score was analyzed as a continuous variable. A preliminary analysis of data from the USCF cohort was previously presented in abstract form[10] and a subset of patients from the Mayo cohort was previously used in published survival analysis of idiopathic usual interstitial pneumonia vs connective tissue disease-related usual interstitial pneumonia.[6]

Statistical Analysis

Baseline demographics were described using means, SDs, and proportions, as appropriate, and then compared by sex using *t* and χ^2 tests. For the survival analysis, the outcome was a composite of death or lung transplant (ie, transplant-free survival); patients were censored at last known follow-up. We estimated the associations of sex and clinical variables selected a priori with transplant-free survival using Cox proportional hazards models adjusted for age, FVC % predicted, and DLCO % predicted, and site cohort. All of these associations were estimated first overall and then among men and women separately. In a final step, the sex-specific estimates were compared using interaction terms. We also performed a sensitivity analysis using death as the primary outcome, censoring at lung transplant. Associations between cough and other clinical variables of breathlessness and heartburn in the UCSF cohort were analyzed using logistic regression.

Results

Baseline Characteristics

There was a total of 1,284 patients with a diagnosis of IPF between the two registries, of whom 21 were excluded because of lack of follow-up data. Of the remaining 1,263 patients, 652 were in the UCSF cohort and 611 were in the Mayo cohort. The baseline characteristics of the study cohort are summarized in Table 1. The median follow-up time was 3.0 years (interquartile range, 1.4-6.3) in the UCSF cohort and 3.2 years (interquartile range, 1.3-6.7) in the Mayo cohort (between-cohort difference $P = .41$). The UCSF cohort had a greater proportion of men, higher mean age at time of diagnosis, and a greater proportion of ever smokers compared with the Mayo cohort. The UCSF cohort also had a higher baseline FVC % predicted value and more frequently reported symptoms of cough and phlegm. The Mayo cohort had higher supplemental oxygen use at baseline.

The sex-stratified characteristics of the pooled cohort are summarized in Table 2. Men comprised approximately 71% of the total cohort. Overall, men were older and more frequently reported a history of smoking than women. Women had a higher baseline BMI. Physiological variables, including FVC % predicted, DLCO % predicted, and need for supplemental oxygen, and the presence of respiratory symptoms of cough and phlegm were similar between the sexes at baseline.

Combined Survival Analysis

The median survival time in the pooled cohort was 3.1 years. There were 679 composite events among men and 255 among women. Each of the a priori covariates of age, male sex, FVC % predicted, and DLCO % predicted were independently associated with death or transplant; the covariate of cohort was not associated with outcome. Male sex was associated with higher risk for death or transplant with an adjusted hazard ratio (HR) of 1.42 (95% CI, 1.21-1.67). Unadjusted Kaplan-Meier survival curves are shown by sex in Figure 1 and indicate a median survival of 3.9 years for women and 2.8 years for men ($P < .001$ by the log-rank test).

Each of the respiratory variables of cough (HR, 1.21; 95% CI, 1.02-1.45), phlegm (HR, 1.19; 95% CI, 1.02-1.39), and need for supplemental oxygen (HR, 1.35; 95% CI, 1.14-1.60) were significantly associated with greater risk of death or transplant when adjusting for sex, age, FVC % predicted, DLCO % predicted, and cohort. BMI and smoking history were not independently associated with survival. The direction and magnitude of these pooled observations were consistent when analyzing the cohorts individually (data not shown).

Sex-Stratified Survival Analysis

The Results of the sex-stratified analysis of predictors of death or transplant are summarized in Figure 2. Lower FVC % predicted and the need for supplemental oxygen was associated with greater risk for death or transplant in both sexes. Older age and lower DLCO % predicted were associated with death or transplant in men but not women, but tests for interaction were not statistically significant. Neither BMI nor smoking history was associated with transplant-free survival for either sex. Cough and phlegm were each independently associated

TABLE 1] Baseline Characteristics of the Cohort

Characteristic	Pooled Cohort (N = 1,263)	UCSF (n = 652)	Mayo Clinic (n = 611)	*P* Value
Men	901 (71)	493 (76)	408 (67)	.001
Age, y	68 ± 8.9	70 ± 8.6	66 ± 8.9	< .001
BMI, kg/m^2	29 ± 5.5	28 ± 5.0	30 ± 5.6	< .001
Ever smokers	840 (67)	459 (70)	381 (64)	.01
FVC % predicted	66 (17.5)	69 (17.6)	64 (16.9)	< .001
DLCO % predicted	46 (15.5)	46 (17.0)	46 (15.5)	.82
Cough	984 (78)	565 (87)	419 (69)	< .001
Phlegm	527 (42)	379 (59)	148 (24)	< .001
Supplemental oxygen use	599 (52)	195 (35)	404 (66)	< .001
Heartburn	n/a	264 (39)	n/a	n/a
UCSD-SOBQ score, median (IQR)	n/a	38 (18-67)	n/a	n/a

Values are No. (%), mean ± SD, or as otherwise indicated.
DLCO = diffusion capacity for carbon monoxide; IQR = interquartile range; n/a = not applicable; UCSD-SOBQ = University of California San Diego Shortness of Breath Questionnaire; UCSF = University of California San Francisco.

TABLE 2] Sex-Stratified Characteristics of the Pooled Cohort

Characteristic	Women (n = 362)	Men (n = 901)	*P* Value
Age, y	67 ± 8.8	69 ± 9.0	< .001
BMI, kg/m^2	30 ± 6.2	29 ± 5.1	< .001
Ever smoker	187 (52)	653 (73)	< .001
FVC % predicted	67 ± 18.1	66 ± 17.2	.56
Dlco % predicted	47 ± 16.8	46 ± 16.2	.75
Cough	295 (81)	689 (77)	.06
Phlegm	138 (38)	389 (44)	.10
Supplemental oxygen use	174 (50)	425 (52)	.59
Heartburn	175 (35)	98 (55)	< .001
UCSD-SOBQ score, median (IQR)	49 (27-74)	35 (16-64)	.003

Values are No. (%), mean ± SD, or as otherwise indicated. See Table 1 legend for expansion of abbreviations.

with worse transplant-free survival in men only; however, tests for interaction were only significant for cough ($P = .007$). The need for supplemental oxygen use was associated with worse transplant-free survival in both sexes. We performed a sensitivity analysis using death as the primary outcome, which did not change the magnitude or direction of these observed associations (data not shown).

Differential Predictors of Respiratory Symptoms in Men and Women

To further investigate the differential relationship between cough and transplant-free survival between the sexes, we performed an exploratory analysis of association between cough and other variables clinically related to cough, namely heartburn and dyspnea score. Men were more likely to report heartburn than women (54% vs 35%, respectively; $P < .01$). The UCSD-SOBQ score was higher for women than men. Cough was associated with heartburn in women (OR, 4.11; 95% CI, 1.27-13.36) but not men (OR, 0.97; 95% CI, 0.57-1.64). Breathlessness as assessed by UCSD-SOBQ, however, was associated with cough in men (OR, 1.02; 95% CI, 1.01-1.04) but not in women (OR, 1.02; 95% CI, 0.99-1.04).

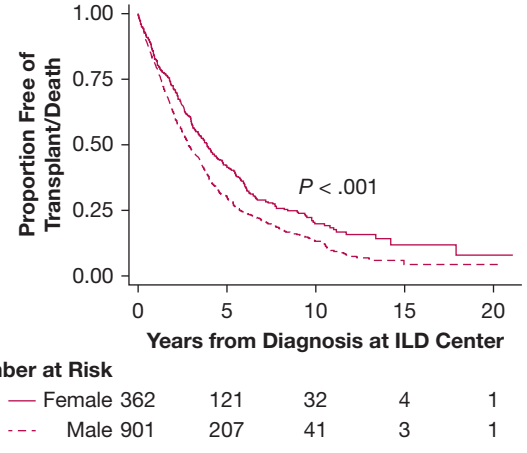

Figure 1 – *Kaplan-Meier survival estimates by sex. ILD = interstitial lung disease.*

Discussion

This is the largest study of survival in a well-characterized pooled cohort of patients with IPF. Our Results confirm prior reports of a male disadvantage in survival in IPF.[6,7] In the pooled cohort, men had a 40% greater risk for transplant or death over women, and crude survival estimates indicate a difference of approximately 13 months in median transplant-free survival between the sexes.

Because there was no difference in baseline physiology between the sexes as determined by FVC % predicted, Dlco % predicted, or need for supplemental oxygen, the difference in survival time does not appear to be caused by differences in disease severity at baseline. In this population, Dlco % predicted was not associated with outcome in women as it was in men; this may primarily reflect the differences in the numbers of events in each group, but could also suggest divergent contributors to impaired diffusion between the sexes, such as the presence of emphysema or pulmonary hypertension.

Senescence on both the organismal and cellular levels is understood to play an important role in the pathobiology of IPF.[11,12] In a mouse model of pulmonary fibrosis, not only did male mice exhibit a more profound fibrotic response to bleomycin, but the fibrotic response was also exacerbated by age in male

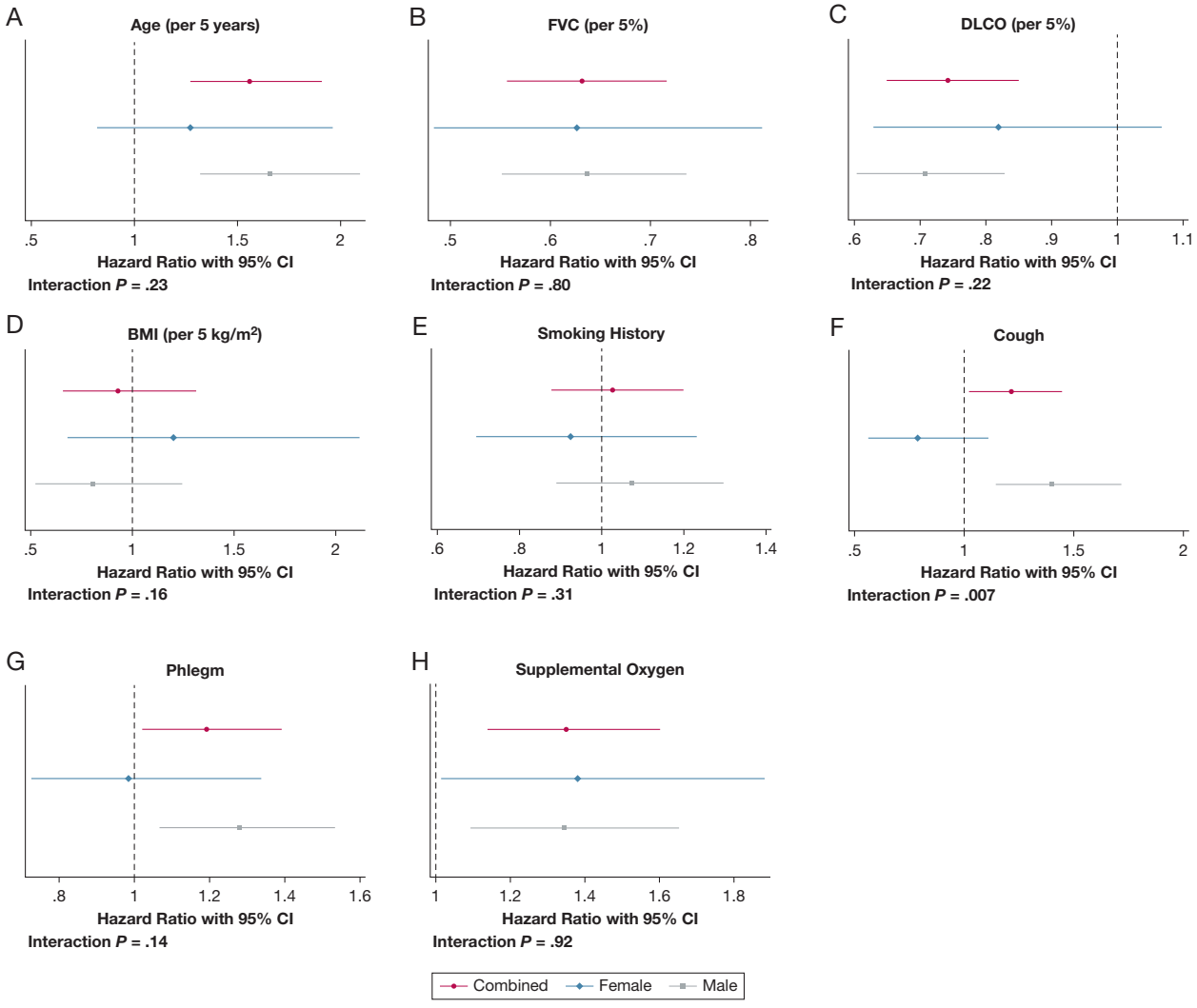

Figure 2 – *A-H, Forest plots show adjusted hazard ratio (HR) and 95% CI for each of the stated variables for the overall sample, women, and men. All models were adjusted for age, FVC % predicted, DLCO % predicted, and cohort. A, Age was associated with transplant-free survival in both sexes. B, FVC % predicted was associated with transplant-free survival in both sexes. C, DLCO % predicted was associated with transplant-free survival in both sexes. D, BMI was not significantly associated with transplant-free survival for either sex. E, Smoking history was not significantly associated with transplant-free survival for either sex. F, Cough was associated with worse transplant-free survival in men (HR, 1.40; 95% CI. 1.14-1.72) but not women (HR, 0.79; 95% CI, 0.56-1.11; interaction P = .007). G, Phlegm may be differentially associated with worse transplant-free survival in men (HR, 1.28; 95% CI, 1.07-1.53) and women (interaction P = .14). H, Supplemental oxygen need was similarly associated with worse transplant-free survival in men (HR, 1.34; 95% CI, 1.09-1.65; P = .005) and women (HR, 1.38; 95% CI, 1.02-1.88; P = .04). DLCO = diffusion capacity of the lung for carbon monoxide.*

mice only.[13] Our data suggest that senescence may be similarly related to survival between the sexes.

Our findings build on a previous study demonstrating that the symptom of cough was independently associated with disease progression.[14] In that study, cough did not meet statistical significance as an independent predictor for transplant-free survival, perhaps because of the smaller sample size and fewer events. In our study, although there was no difference in the frequency of reported cough between the sexes, the presence of cough was negatively associated with survival in men only; more importantly, the sex-specific HRs differed both qualitatively and statistically.

Cough is multifactorial with potential etiologies including laryngopharyngeal reflux of nasal and gastroesophageal fluids, underlying airways disease and emphysema, and lung parenchymal fibrosis. The disparate findings regarding association between cough and transplant-free survival in IPF may be a consequence of differing etiologies of cough in men and women. For example, men were more likely to report a history of smoking in this cohort and may therefore

have a greater burden of smoking-related airways disease or emphysema that could contribute to cough. Furthermore, cough was associated with breathlessness in men but not women, suggesting that cough in men may be reflective of disease severity that is not captured by typical physiological variables. On the other hand, we observed point estimates for cough in women that showed a trend toward cough being protective. Our data demonstrate that cough in women was more likely to be associated with the presence of heartburn than in men. This suggests that cough in this cohort of women may be manifestation of gastroesophageal reflux disease rather than an underlying process that also causes breathlessness.

Although the large cohort size and long duration of follow-up are particular strengths for survival analyses in this study, there are several limitations. The sample is derived from the IPF databases of two tertiary care centers, which may introduce a selection bias that limits generalization of these Results. Antifibrotic drugs were approved by the US Food and Drug Administration for the treatment of IPF in October 2014. Although pooled data from clinical trials of these medications suggest a mortality benefit,[15,16] the effect of antifibrotic therapy on FVC does not seem to differ between men and women.[17,18] Data on antifibrotic therapy was not available for our study; however, our findings regarding sex and survival were consistent when analyzed using a time-dependent indicator of pre- and postavailability of antifibrotic medications. The respiratory symptoms that we analyzed were patient-reported, by both prospective questionnaires (UCSF) and retrospective medical chart review (Mayo Clinic), with binary responses rather than quantitative assessments. We also do not have information on the presence or absence of emphysema or percent of radiographic fibrosis in this cohort. Future studies should examine radiographic features as a potential explanation for the difference in survival between men and women with IPF. Finally, given the absence of data on cause of death in this cohort, we cannot exclude the possibility that the IPF male disadvantage in survival is not caused by survival differences with respect to a comorbid disease. This requires further study.

Interpretation

Our data validate the observation of a male disadvantage in survival within a large cohort of patients with IPF and indicate that cough may be a sex-specific predictor of survival. Our findings have potential implications on the development of prognostic algorithms for IPF and our understanding of symptoms in men and women with IPF. Whether true sexual dimorphism exists in IPF, and its impact on pathophysiological and disease manifestations that may be sex-specific, requires ongoing investigation.

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Author contributions: T. Z. and J. S. L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. T. Z., E. V., and J. S. L. completed the data analysis and interpretation. T. Z. and J. S. L. wrote the manuscript. T. M., J. H. R., E. V., and H. R. C. modified the manuscript.

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