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Gender influences health-related Quality of Life in IPF

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Summary

Background: HRQL in IPF patients is impaired. Data from other respiratory diseases led us to hypothesize that significant gender differences in HRQL in IPF also exist.

Methods: Data were drawn from the NIH-sponsored Lung Tissue Research Consortium (LTRC). Demographic and pulmonary physiology data along with MMRC, SF-12, and SGRQ scores from women vs. men were compared with two-sample *t*-tests. Multivariate linear regression was used to examine the association between SF-12 component scores and gender while adjusting for other relevant variables.

Results: The study sample consisted of 147 men and 74 women. Among several baseline variables, only DL_{CO}% predicted differed between women and men, (43.7 vs. 38.0, *p* = 0.03). In

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity for carbon monoxide; FVC, forced vital capacity; HRQL, health-related Quality of Life; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LTRC, Lung Tissue Research Consortium; MMRC, Modified Medical Research Council; SCOR, Specialized Center of Research; SF-12, short form 12 questionnaire; SF-36, short form 36 questionnaire; SGRQ, St. George's Respiratory Questionnaire; QOL, Quality of Life; UMHS, University of Michigan Health System.

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general, men exhibited lower (better) MMRC scores (1.7 vs. 2.4, $p = 0.02$), particularly those with milder disease as measured by $DL_{CO}\%$ predicted. In an adjusted analysis, SF-12 PCS scores in men were lower (worse) than women ($p = 0.01$), an effect that was more pronounced in men with greater dyspnea scores. In a similar analysis, SF-12 MCS scores in women were lower than men (worse) (48.3 vs. 54.4, $p = 0.0004$), an effect that was more pronounced in women with greater dyspnea scores.

Conclusions: Significant gender differences in HRQL exist in IPF. As compared to women, men reported less severe dyspnea, had worse SF-12 PCS scores, but better SF-12 MCS scores. Dyspnea appears to have a greater impact on the physical HRQL of men and the emotional HRQL of women. An improved understanding of the mechanism behind these differences is needed to better target interventions.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia.¹ In fact, prevalence estimates are on the rise and are predicted to continue to increase.² The clinical course of IPF tends to be progressive and mortality is high. Consequently, IPF patients, like many others with other debilitating, life-shortening diseases, have impaired Quality of Life (QOL). Because there is no effective pharmacologic therapy proven to slow decline in pulmonary function or reduce mortality, IPF patients (and the practitioners caring for them) often focus on attempting to maintain or improve their QOL. IPF profoundly impairs a patient's sense of well-being, but relatively few studies have examined QOL or health-related QOL (HRQL) – defined here as an individual's perception of the impact of health on his or her QOL – in this patient population. A recent systematic review of HRQL in IPF found only seven studies (with a total of 512 patients) meeting rigorous inclusion criteria.³ Only a few studies have examined longitudinal changes in HRQL in IPF, but each reports worsening HRQL over time.^{4,5} No studies have examined differences in HRQL or symptoms between male and female patients with IPF.

In chronic obstructive pulmonary disease (COPD), it is clear that men and women differ in a number of aspects.^{6,7} Female COPD patients are more likely than males to report severe dyspnea, and on balance, females have worse HRQL than men.⁸ Female COPD patients suffer higher levels of anxiety and depression than their male counterparts which could contribute to HRQL discrepancies.^{9,10} Finally, disease status does not predict the presence or intensity of symptoms in females with COPD as well as it does in males.¹¹ Only recently have investigators begun to systematically explore differences in disease behavior between female and male IPF patients. It is well-established that women are less prone to develop IPF than men (although the number of women with IPF appears to be rising at a steeper rate than men,² but the observations that women have better survival and experience less rapid progression of disease than men are new.¹² In this study, we aimed to further examine differences between female and male IPF by focusing on HRQL and dyspnea. We hypothesized that HRQL would be more impaired and dyspnea would be more severe among women than men.

Methods

The study sample was identified through the multi-center Lung Tissue Research Consortium (LTRC) (<http://www.ltrcpublic.com>). The LTRC is a tissue bank sponsored by the National Heart Lung and Blood Institute that began sample collection in 2003. The two primary groups of patients on whom the LTRC collects data include COPD and interstitial lung disease (ILD); the majority of data are from patients with IPF. Prior to specimen procurement, all LTRC subjects undergo an extensive, standardized, pre-operative phenotypic evaluation which includes demographics, detailed occupational history, complete pulmonary function testing and a standardized chest CT scan. A final clinical diagnosis of IPF was assigned based on currently accepted international consensus guidelines.¹³ All subjects with a final clinical diagnosis of IPF at the time of data query were included in this analysis (221 of the 1400 enrolled at the time of data query in February 2009). Each subject included in this analysis underwent diagnostic surgical lung biopsy or lung transplant as part of their clinical care for IPF. Subjects with an alternative diagnosis on pathological evaluation were excluded. All subjects provided written informed consent, and the institutional review board at each institution approved the study.

Clinical assessment

Demographic data, smoking and medical history, along with dyspnea and HRQL assessments were collected via self-administered questionnaires prior to biopsy or transplant. Dyspnea was quantified using the modified Medical Research Council dyspnea scale (MMRC)¹⁴ which is a five-point scale that asks respondents to rate dyspnea from 0 (absent) to 4 (dyspnea when dressing/undressing). The MMRC has previously been used to evaluate dyspnea in IPF patients; its scores correlate with HRQL¹⁵ and predict survival.¹⁶ General HRQL was assessed with the SF-12 version 2[®]. The SF-12 taps the same eight domains as the SF-36 and like the SF-36, it also has two psychometrically-derived primary subscales, the physical and mental health composite scores (PCS and MCS). Scores from the SF-12 and each primary subscale range from 0-100, with higher scores indicating better HRQL. The SF-12 is a shorter alternative to the SF-36 which has accepted validity in IPF.^{4,17} Multiple

studies, however, have documented the comparability of the SF-12 to the SF-36 in different diseases.^{18,19} For each domain and summary component, we used scoring algorithms to generate linear T-score transformations to place scores on scales with mean scores equal to 50 and standard deviations of 10. Saint George's Respiratory Questionnaire (SGRQ) is an obstructive lung disease-specific questionnaire, with three domains, all scored from 0 to 100. Higher scores correspond to worse HRQL.²⁰ The SGRQ appears to possess longitudinal validity in IPF.¹⁷

Physiologic testing

Spirometry before and after the administration of albuterol and DL_{CO} were measured according to American Thoracic Society guidelines. The 6-min walk test was completed using a modification of a previously published protocol.²¹ The average length of time between clinical assessment and physiologic testing was approximately 1 day.

Statistical analysis

All analyses were completed by using SAS statistical software, version 9.1 (SAS Inc., Cary, NC). Baseline characteristics, SGRQ, and SF-12 data were compared between genders by using two-sample Student's *t*-tests. Because the MMRC data were skewed, a Wilcoxon rank sum test was used to compare MMRC scores between genders. Multivariate linear regression was used to examine the association between gender (independent variable) and either HRQL or MMRC scores (dependent variables) while adjusting for age, FVC and DL_{CO}% predicted, body mass index (BMI), and smoking. Because each of these candidate variables could potentially confound the association between gender and HRQL or MMRC scores, we elected not to perform univariate analyses and included all of them in each multivariate model. No adjustment was made for multiple comparisons, thus it is possible that one in 20 comparisons based on a cutoff of $p < 0.05$ may be spuriously statistically significant.

Results

The study sample consisted of 147 men and 75 women. Demographics are outlined in Table 1. Men and women were of similar average age (63.3 years for men vs. 62.3 years for women, $p = 0.44$). There was no significant difference between men and women in baseline FVC%

Table 1 Demographics by gender.

	Men <i>n</i> = 147 (SD)	Women <i>n</i> = 74 (SD)	<i>p</i> -value
Age in years	63.3 (8.2)	62.3 (9.9)	0.44
FVC% predicted	62.1 (16.8)	64.4 (18.7)	0.36
DL _{CO} % predicted	38.0 (14.8)	43.7 (17.9)	0.03
BMI	29.6 (5.1)	30.8 (5.3)	0.14
Cigarette pack years	23.3 (13.3)	22.2 (11.3)	0.65
Walk distance (meters)	365.8 (136.2)	347.9 (109.1)	0.34

Table 2 Comparison of mean SF-12, MMRC, SGRQ scores.

	Men (SD)	Women (SD)	<i>p</i> -value
MMRC (median)	2	3	0.02
SF-12 PCS	35.6 (12.5)	37.7 (9.9)	0.21
Physical functioning	34.1 (12.2)	32.7 (10.8)	0.40
Role-physical	37.7 (13.0)	36.8 (12.6)	0.62
Bodily pain	49.2 (11.8)	49.0 (10.4)	0.88
General health	39.4 (13.3)	42.2 (11.7)	0.13
SF-12 MCS	54.4 (9.7)	48.3 (12.2)	0.0004
Vitality	45.9 (11.6)	44.6 (11.1)	0.42
Social functioning	47.6 (11.3)	43.9 (12.8)	0.05
Role-emotional	48.1 (11.4)	41.9 (14.1)	0.002
Mental health	53.0 (8.9)	47.8 (10.8)	0.0007
Total SGRQ score	44.6 (23.6)	48.2 (20.1)	0.27
Activity subscore	57.7 (30.3)	75.3 (24.3)	0.05
Impacts subscore	35.2 (22.7)	37.6 (21.9)	0.39
Symptoms subscore	49.7 (25.0)	48.9 (20.3)	0.81

predicted (62.1 men vs. 64.4 women, $p = 0.36$), but women had slightly higher DL_{CO}% predicted than men (38.0 men vs. 43.7 women, $p = 0.03$). No significant difference was observed in 6-min walk distance between genders (mean 365.8 m men vs. 347.9 m women, $p = 0.34$), and there was no significant difference between genders in BMI or cigarette pack years.

Results for between gender comparisons for MMRC, SF-12 and SGRQ are displayed in Table 2. MMRC scores were significantly better (lower) in men vs. women median score 2 for men and 3 for women ($p = 0.02$). Because of differences in DL_{CO}% predicted between groups, the possibility of a gender-DL_{CO} interaction was explored in multivariate models for MMRC. Figure 1 shows the relationship between DL_{CO}% and gender for the MMRC outcome ($p = 0.02$ for gender-DL_{CO} interaction). No significant difference in unadjusted SF-12 PCS scores were observed between genders; however, the SF-12 MCS score was significantly better (higher) in men than women (54.4 men vs. 48.3 women, $p = 0.0004$). Social functioning, role-emotional, and mental health domain scores were also better for men than women while the other MCS and PCS subdomains

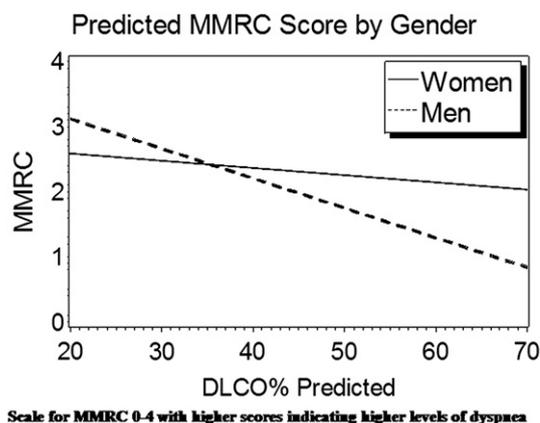


Figure 1 Graphical relationship between DL_{CO}% predicted and MMRC demonstrating more dyspnea in women than men at higher levels of DL_{CO}% predicted.

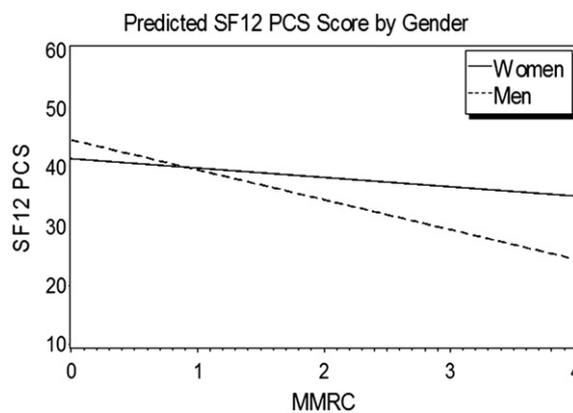
showed no significant gender difference. No significant difference in total SGRQ score was seen, although the activity score was better (lower) for men than women (57.7 men vs. 75.3 women, $p = 0.05$).

Results of multivariate analyses for predicting SF-12 PCS scores are shown in Table 3. After correcting for lung function, functional capacity (as measured by 6MWD), and other important potential predictors, female gender was associated with higher (better) scores ($p = 0.01$). Longer 6MWD ($p = 0.002$) and lower MMRC score ($p = 0.04$) were also associated with higher SF-12 PCS scores. For the PCS outcome variable, a significant MMRC-gender interaction was detected ($p = 0.009$) that is graphically displayed in Figure 2.

Results of multivariate analyses for predicting SF-12 MCS scores are also shown in Table 3. Here, after correcting for lung function, functional capacity (as measured by 6MWD), and other important potential predictors, female gender was associated with lower (worse) MCS scores ($p = 0.008$). Higher BMI and lower MMRC were also associated with better MCS scores ($p = 0.04$ and $p = 0.05$, respectively). A significant MMRC-gender interaction was also detected for SF-12 MCS ($p = 0.004$), graphically displayed in Figure 3. No significant gender differences were observed in multivariate analyses (adjusted for the same predictors as SF-12 analyses) for SGRQ total or subscores (data not shown).

Discussion

Prior data suggest that HRQL in IPF patients as assessed by the SF-36 (similar to the SF-12), SGRQ and other instruments is impaired in multiple domains, but particularly domains tapping physical functioning, symptoms, and level of independence.³ Work by others also suggests that dyspnea, as measured by the MMRC or other scales, correlates



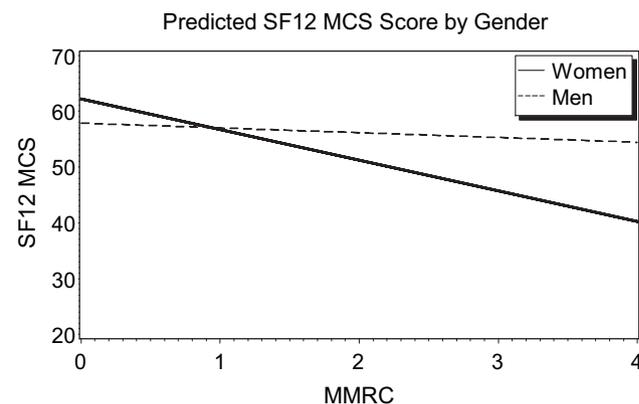
Scale for MMRC 0-4 with higher scores indicating higher levels of dyspnea; scale for PCS 0-100 with higher scores indicating better health status

Figure 2 Graphical relationship between SF-12 PCS score and MMRC demonstrating worse PCS scores in men than women with greater dyspnea.

strongly with HRQL scores in IPF.^{15,22} In COPD men and women differ in their symptom intensity and degree of HRQL impairment.^{6,7} Although very recent research has shown improved survival and less rapid physiologic progression for women with IPF as compared with men,¹² no study has examined whether these differences between genders extend to HRQL or dyspnea in IPF.³ In the current study, we observed significant differences in HRQL scores between men and women. Data from U.S. general population norms show men score approximately 2.5 points higher on the SF-12 PCS and just under 2 points higher on the MCS compared with women.²³ In contrast, in the current study, in analyses adjusted for a number of clinically important potential confounders, we observed that *female* gender was associated with a higher PCS score (by 5 points). Furthermore, as expected, females had lower MCS scores than males, but in an adjusted analysis, the difference we observed was over three times greater than expected (6.6 points compared with just under 2 points for population norms).

Table 3 Multivariate model SF-12.

PCS	Parameter	95% CI	p-value
Intercept	44.54	25.54, 63.56	<0.0001
Female gender	5.17	1.23, 9.10	0.01
Age in years	-0.07	-0.25, 0.12	0.48
FVC%	-3.80	-17.03, 9.44	0.57
DL _{CO} %	-2.52	-17.09, 12.04	0.73
Cigarette pack years	-0.07	-0.20, 0.05	0.25
BMI	-0.06	-0.42, 0.31	0.77
Walk distance in meters	0.03	0.01, 0.04	0.002
MMRC	-4.39	-5.84, -2.94	0.04
MCS			
Intercept	51.37	28.41, 74.32	<0.0001
Female gender	-6.61	-1.80, -11.42	0.008
Age in years	0.07	-0.15, 0.29	0.53
FVC%	4.31	-20.51, 11.87	0.60
DL _{CO} %	-5.23	-23.05, 12.59	0.56
Cigarette pack years	-0.13	-0.28, 0.03	0.10
BMI	0.57	0.02, 0.92	0.04
Walk distance in meters	-0.006	-0.03, 0.01	0.52
MMRC	-1.79	-3.56, -0.008	0.05



Scale for MMRC 0-4 with higher scores indicating higher levels of dyspnea; scale for PCS 0-100 with higher scores indicating better health status.

Figure 3 Graphical relationship between SF-12 MCS score and MMRC demonstrating worse MCS scores in women than men with greater dyspnea.

Another finding from this study was the observation that in the case of milder IPF as defined by higher $DL_{CO\%}$ predicted, there was discordant dyspnea perception between genders. On balance, women reported more severe dyspnea than men. However, at lower levels of lung function (as assessed by $DL_{CO\%}$), the gender gap closed. Between genders, discordant dyspnea, as measured by the MMRC, has also been reported in COPD.⁷ Neurobiological studies demonstrate that women have a higher intrinsic sensitivity than men to noxious somatic sensations, including dyspnea.^{24,25} Thus, it is possible that women are inherently more keen to sense (and report) dyspnea at earlier stages of IPF. An alternative explanation is that the female subjects in this study were more physically fit and active than the male subjects. Data required to examine this possibility were not collected as part of this study, but the absence of significant differences between genders in BMI and 6MWD argue against this hypothesis. Regardless, as IPF progresses and lung function becomes increasingly impaired, both men and women will sense significant dyspnea.

We also observed that, even after accounting for differences in age, pulmonary physiology, functional capacity, and other important predictors, there were differences between genders in HRQL: males had more impaired HRQL in physical health domains but less impaired HRQL in mental health domains than females. Gender differences in social roles could explain some of these differences. Considering women frequently regard themselves as caregivers, it is possible that the emotional impact of this disease may be different for them than for men. Another possibility is that women may view the social stigma of the disease, such as needing to wear supplemental oxygen, as more bothersome. Differences between how men and women cope with chronic illness could influence the emotional impact of a disease. Men tend to be more proactive in trying to modify their environment when confronted with significant challenges, such as health problems; this could prove advantageous when dealing with a disease such as IPF.²⁶ Differences in socioeconomic or the presence or type of comorbid conditions at the time of diagnosis may also influence gender differences in HRQL. We believe these possibilities merit further investigation.

The final novel observation from this study was that among men, dyspnea appears to have a greater association with physical HRQL domains than mental HRQL domains, while among women, the impact of dyspnea is greater on mental HRQL domains than physical HRQL domains. The experience of dyspnea has sensory and affective dimensions. It is associated not only with lung dysfunction, but also with emotional responses to sensations, and higher-order interpretations of these experiences (e.g., meaning) which influence not only self-reports of dyspnea intensity per se, but also the impact of dyspnea on patient physical and emotional functioning. The greater impact of dyspnea on emotional HRQL in women in our data is consistent with findings from other studies in which investigators observed greater emotional burden of chronic disease on women than men. For example, women with COPD are more likely to suffer from anxiety and depressive disorders.⁶ Clear neurobiologic differences exist between men and women both in their sensitivity and processing of noxious somatic

sensations but also in the higher level processing and interpretation of that information.²⁷ Brain regions associated with the affective dimension of dyspnea have been identified, but gender differences have not yet been examined.

The average SGRQ activity score in "healthy" men has been reported to be 12.17 vs. 14.58 for women.²⁸ We observed a much greater difference of approximately 18 points, although the difference was absent when we adjusted for potential confounders. This is in contrast to COPD where female patients have worse (higher) SGRQ scores than males.⁸ As opposed to the SF-12, however, the SGRQ is an obstructive disease-specific instrument that may lack the sensitivity to capture gender differences in IPF. This is a subject worthy of further investigation.

There are limitations to our study. While on average, male and female subjects were similar and we adjusted for multiple possible confounders including lung function and 6 min walk distance, we acknowledge that physiologic measures of disease status are not the only significant contributors to HRQL. We do not have data on length of time since IPF diagnosis or any data on treatment. Differing disease duration could influence dyspnea, one of the main drivers of HRQL in IPF.^{3,22} Medications, such as oral glucocorticoids in particular²⁹ or immune suppressing agents, sometimes prescribed for patients with ILD, may cause adverse effects that impact HRQL. Also lacking in our dataset are other potentially meaningful variables that could influence HRQL, including socioeconomic status and comorbid physical or mental conditions. Finally, a question that often arises in studies of HRQL is whether the selected instruments are appropriate for assessing the population under study. To our knowledge, the psychometric properties of the SF-12 have never been systematically examined in IPF, but investigators of several recent studies have reported that the SF-36 and SGRQ possess reasonable reliability and both cross-sectional and longitudinal validity in IPF.^{4,17} All SF-12 items are in the SF-36, and numerous studies have demonstrated their comparability, hence it can be reasonably assumed the SF-12 would perform similar to the SF-36 in IPF as well. A strength of this study is the very well-characterized patient population in which IPF was diagnosed rigorously by multidisciplinary clinical, radiological and pathological assessments.^{30,31} Furthermore, the large variety of patients, ranging from those diagnosed with surgical biopsy (milder disease) and those undergoing lung transplantation (severe disease), provides a wide snapshot of the IPF population.

In conclusion, it appears as though men with IPF have less dyspnea, worse physical HRQL, but better emotional HRQL than women with IPF. However, dyspnea more profoundly impacts the physical HRQL of men and the emotional HRQL of women. IPF differs from other chronic respiratory diseases, particularly COPD, where women have worse physical and worse mental HRQL than men, whether assessed by the SF-36 or SGRQ.^{8,32} Up until recently, women were frequently excluded from clinical research, particularly therapeutic trials. The realization that men and women might differ from biologic, social and psychologic perspectives and that this could influence disease presentation and progression has only of late become a topic of discussion within the academic community. Future research

will need to incorporate gender differences in a way that has previously not been explored, in IPF or otherwise. Based on the analyses we present here, clinical trials in IPF that seek to assess change in HRQL will need to take into account the expected numbers of men and women to be randomized and baseline differences that exist. Further longitudinal data will be needed to determine whether change in HRQL differs by gender so that these data can be incorporated into clinical trial design as well. From the standpoint of developing and testing therapies in IPF, our data suggest drugs intended to improve exercise capacity or dyspnea might impact HRQL in men and women differently. Finally, our data suggest that if we seek to improve HRQL in IPF, particularly in patients with severe disease, that men may be in greater need of interventions that target physical domains and women interventions that emotional domains of HRQL.

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Conflict of interest statement

None declared.

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