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INTERSTITIAL LUNG DISEASE

Health-Related Quality of Life in Patients with Idiopathic Pulmonary Fibrosis

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Abstract
Purpose Idiopathic pulmonary fibrosis (IPF) produces symptoms and activity limitations that impair health-related quality of life (HRQOL). The Patient-Reported Outcomes Measurement Information System® (PROMIS®) includes measures of self-reported health and HRQOL for a range of conditions. This study evaluated the HRQOL of individuals with IPF using PROMIS measures and examined associations between HRQOL and key symptoms or supplemental oxygen need.
Methods Individuals who reported being told by a doctor that they have IPF completed an online battery of measures at baseline and 7–10 days later (for test–retest reliability). Measures included a brief survey of demographic and health-related questions, the PROMIS-29 profile, the Modified Medical Research Council Dyspnea Scale (MMRC), PROMIS dyspnea severity short form, A Tool to Assess Quality of life in IPF (ATAQ-IPF) and one cough item from the Functional Assessment of Chronic Illness Therapy (FACIT).
Results 220 individuals were included in the final sample. Except for sleep disturbance, all PROMIS domain scores significantly ($p < .01$) differed by MMRC level. Supplemental oxygen users were more impaired than non-users in fatigue, physical function, and social role participation ($p < 0.01$). The test–retest reliability was acceptable to excellent (>0.7) for all scales, but was lower for sleep disturbance (0.64).
Conclusions People with IPF report substantial deficits in HRQOL across a range of PROMIS domains, and deficits vary by dyspnea and cough severity. These deficits warrant monitoring in clinical practice and consideration when investigating new therapies. Further research is required to further evaluate the psychometric performance of the PROMIS-29 in IPF.

Keywords Health-related quality of life · Idiopathic pulmonary fibrosis · PROMIS

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia, with a prevalence of 14–63 cases per 100,000 people in the US [1, 2]. Among those over age 65, IPF affected as many as 495 individuals per 100,000 in 2011 [3]. IPF is a devastating, progressive disease characterized physiologically by declining lung function [4]. Median survival ranges from 3 to 5 years post-diagnosis [5–7]. Key symptoms of IPF include dyspnea, cough, and fatigue. Exacerbations—acute and clinically significant deteriorations that occur without warning and without a known cause—make the clinical course of the disease less predictable [4, 8]. As IPF progresses, dyspnea leads to severe limitations in activity, and IPF patients experience significant negative impacts on their social roles and emotional well-being [9]. Despite the significant toll of IPF on patients' health-related quality of life (HRQOL), there is limited research on the HRQOL experiences of IPF patients [10].

The Patient-Reported Outcomes Measurement Information System® (PROMIS®) is an NIH Roadmap/Common Fund initiative that has advanced the use of a common set of patient-reported outcome (PRO) tools. PROMIS aims to develop ways to measure patient-reported symptoms, such as pain and fatigue, and aspects of HRQOL across a wide variety of chronic diseases and conditions [11]. The PROMIS network has developed item banks and short forms in multiple health domains for adults and children as well as a set of global health items and profile measures of varying lengths.

The objective of this study was to obtain PROMIS scores for patients with IPF on eight health domains (depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation, sleep disturbance, and dyspnea severity), with broad goals of augmenting the existing knowledge base about the HRQOL of individuals with IPF, enabling comparisons between IPF patients and people in the general U.S. population, and examining associations between key symptoms and HRQOL in IPF.

Methods

Study Design and Participants

Individuals with IPF were identified by an internet research panel company, which invited a sample of 300 IPF patients for the baseline survey. In addition to their existing internet research panel, the company partnered with patient advocacy organizations to reach greater numbers of IPF patients in their recruitment efforts. Participants were eligible if they self-identified as having been told by a doctor that they have IPF. Eligible patients who completed the baseline assessment (Time 1) were subsequently invited to participate in the test–retest assessment 7–10 days later (Time 2). The Northwestern University Institutional Review Board determined that the study qualified for Exemption under United States Department of Health and Human Services CFR 46.101(b).

Time 1

The Time 1 survey included questions about sociodemographic characteristics (gender, age, race, ethnicity, marital status, education, and household income), health information (e.g., smoking status and whether or not they currently receive supplemental oxygen) and the PRO measures, described in more detail below. Participants were also asked whether they have ever been, or are currently, on a lung transplant waiting list or had received a lung transplant and whether they were participating in a clinical trial.

Time 2

Approximately 7–10 days after completing the initial survey, respondents were invited to complete a follow-up survey of PROMIS items. This assessment was used to evaluate test–retest reliability of the measures in the IPF population.

Measures

Dyspnea

Participants' current level of breathlessness was measured using the Modified Medical Research Council Dyspnea Scale (MMRC) [12, 13]. The scale ranges from 0 (only breathless with strenuous exercise) to 4 (too breathless to leave the house/breathless when dressing).

HRQOL

HRQOL was assessed with the PROMIS-29 profile measure [11, 14], which includes four items each from seven domains (depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation, and sleep disturbance) as well as one 11-point rating scale for pain intensity. Twenty-eight of the PROMIS-29 items apply a 5-point Likert-type scale, with the response options matched to the content of the items (e.g., frequency and severity). The one pain intensity item is an 11-point rating from 0 to 10. PROMIS measures are scored using the T-score metric, with most domains' norms based on the U.S. general population, such that a score of 50 represents

the mean of the general population (standard deviation = 10) [15]. On the anxiety, depression, fatigue, pain interference, and sleep disturbance subscales of the PROMIS-29, higher scores (>50) represent worse outcome. On the physical functioning and social role subscales of the PROMIS-29, lower scores (<50) represent worse outcome.

PROMIS dyspnea Short Form

PROMIS includes two 33-item dyspnea item banks and two 10-item short forms: one for dyspnea severity, and the other for functional limitations [16–18]. While scored using the PROMIS T-score metric, the dyspnea norms are based on a sample of individuals with chronic obstructive pulmonary disease (COPD). The PROMIS dyspnea severity short form administered in this study includes 10 common tasks (e.g., walking 50 steps on flat ground at normal speed without stopping). Respondents rate the severity of their shortness of breath when completing these tasks over the past 7 days. Shortness of breath is assessed on a 5-point scale: 0 = no shortness of breath; 1 = mildly short of breath; 2 = moderately short of breath; 3 = severely short of breath; and 4 = I did not do this in the past 7 days. If respondents indicate they did not do a task in the last 7 days, they are asked if it was attributable to dyspnea (shortness of breath) or the fact that they did not have an opportunity to do the task in the past week. If the response is because of dyspnea (i.e., "I have stopped trying, or knew I could not do this activity because of my *shortness of breath*"), the response is treated the same as the response "severely short of breath." Otherwise, the response is treated as missing (i.e., not included in score). High scores represent high levels of dyspnea severity.

Cough

Cough was measured using one item from the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system [19] ("I have been coughing"), assessed on a 0 (not at all) to 4 (very much) scale. In addition, respondents completed the 6-item A Tool to Assess Quality of life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF) cough subscale [20]. The ATAQ-IPF was developed to assess disease-specific HRQOL in patients with IPF. The full questionnaire is composed of 74 items measuring 13 domains: cough, dyspnea, forethought, sleep, mortality, exhaustion, emotional well-being, social participation, finances, independence, sexual health, relationships, and therapies. The cough subscale of the ATAQ-IPF used in the study consists of six questions about cough and its impact, with response choices ranging from 1 = strongly disagree to 5 = strongly agree. Scores are calculated as a sum of item responses, with higher scores indicating worse HRQOL.

Statistical Analyses

Sociodemographic and disease characteristics of the sample were summarized. Using the appropriate statistical test, we compared the characteristics (demographic and disease-related) of participants who completed all assessments with those who missed assessments.

Baseline and Time 2 data were used to calculate the intraclass correlation coefficient (ICC) for each PRO measure to assess the test–retest reliability in this population.

Analysis of variance (ANOVA) was used to compare PROMIS-29 scores between dyspnea severity groups, as defined by the MMRC. PRO scores of patients on supplemental oxygen were compared to those who were not using two-sample t tests. ANOVA was also used to compare ATAQ scores between self-reported cough severity groups (using FACIT cough item).

Results

Of the 301 individuals who enrolled in the survey, 26 participants were excluded because they positively endorsed every illness on the screening question (a suspicious response pattern decided on a priori as an exclusion criterion). In addition, because participants who had received a lung transplant could potentially reflect a clinically distinct group of participants, we elected to eliminate them from the sample for analysis ($n = 28$). Finally, patients under age 50 (n = 27) were also excluded to achieve a sample that more closely reflected the age distribution of individuals with IPF. Thus, all analyses described below were conducted on a sample of 220 individuals. Characteristics of the sample are presented in Table 1.

Baseline and Time 2 PRO scores are summarized in Table 2. The test–retest reliability was acceptable to excellent for all scales but was lower for sleep disturbance (0.64). Compared to the general population (T-score = 50), PROMIS-29 scores were substantially worse in this IPF sample, with the deficits ranging from half to greater than one standard deviation across all PROMIS domains. In fact, PROMIS depression scores in this IPF sample were comparable to those in people with major depressive disorder (MDD; T-score 61.9); anxiety scores exceeded those in people with an exacerbation of COPD or MDD (T-scores 60.2 and 61.7, respectively) [21]; fatigue scores were slightly worse than in people with heart failure (T-score 58.8) [22]; and sleep disturbance scores were

Table 1 Description of sample ($n = 220$)

	Mean (SD)	Range
Age (years)	61.0 (5.6)	50–83
	N	%
Female	65	29.6
Race/ethnicity		
Hispanic	28	12.7
White	183	83.2
Black	16	7.3
American Indian/Alaska native	8	3.6
Asian	16	7.3
Other	9	4.1
Smoking history		
Current smoker	28	12.7
Previous smoker	159	72.3
Never smoked	33	15.0
Currently on supplemental oxygen	95	43.2
MMRC dyspnea grade		
0: Only breathless with strenuous exercise	11	5.0
1: Short of breath hurrying on level ground or walking up slight hill	46	20.9
2: On level ground, walk slower or have to stop for breath	122	55.4
3: Stop for breath after walking a few minutes on level ground	24	10.9
4: Too breathless to leave the house or breathless when dressing	17	7.7
Currently waiting to receive a lung transplant	33	15.0

Table 2 Patient-reported outcomes measures baseline scores and test–retest reliability coefficients

Measure	Baseline		Test–retest reliability[a]		
	N	Mean (SD)	*N*	ICC	95 % Confidence interval
PROMIS dyspnea[b]					
Dyspnea severity	220	59.2 (8.4)	160	0.98	0.97–0.98
PROMIS-29[b]					
Anxiety	220	64.4 (8.7)	160	0.89	0.86–0.92
Depression	220	62.1 (8.5)	160	0.90	0.86–0.92
Fatigue	220	60.7 (8.0)	160	0.95	0.93–0.96
Pain	220	62.9 (7.8)	160	0.92	0.90–0.94
Physical function	220	35.5 (5.3)	160	0.71	0.62–0.78
Sleep disturbance	220	56.4 (7.1)	160	0.64	0.54–0.72
Social role	220	40.9 (8.9)	160	0.85	0.79–0.89
ATAQ-IPF (6–30)	220	23.6 (5.8)	160	0.96	0.94–0.97
FACIT cough (0–4)	220	2.5 (1.2)	160	0.77	0.16–0.91

[a] Using only those with data at both Time 1 and Time 2

[b] Mean = 50, standard deviation = 10, *ATAQ-IPF* A Tool to Assess Quality of life in Idiopathic Pulmonary Fibrosis, *FACIT* Functional Assessment of Chronic Illness Therapy

nearly comparable to people with obstructive sleep apnea (T-score 51.8) [23]. ATAQ-IPF cough subscale scores were also a full standard deviation worse than those seen in the sample of IPF patients used to develop and validate the ATAQ-IPF [20]. In addition, PROMIS dyspnea severity scores for this IPF sample were worse than the COPD reference population by nearly a full SD (T-score 50) [17, 24] and worse than a sample of patients with systemic sclerosis (T-score 40.5) [25].

We compared groups of participants who differed on three clinically related variables: MMRC category at baseline, use of supplemental oxygen at baseline, and

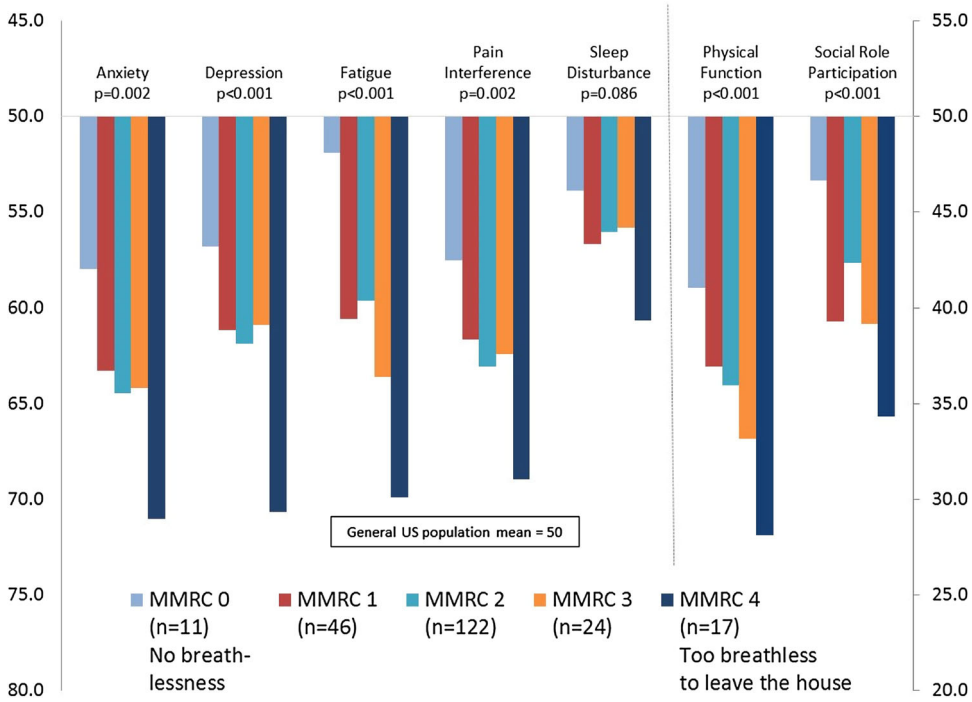

Fig. 1 Mean baseline PROMIS-29 scores by modified medical research council dyspnea scale (MMRC) category ($n = 220$)

FACIT cough item response categories. As shown in Fig. 1, dyspnea severity, as measured by the MMRC, was associated with worse mean PROMIS-29 scores. There were significant differences by MMRC category across all PROMIS-29 domains (p range <.001 to .002) except for sleep disturbance ($p = .086$).

Patients on supplemental oxygen at baseline reported worse fatigue ($p = .001$), physical function ($p = .001$), and satisfaction with social role participation ($p < .001$), with a trend toward worse dyspnea severity ($p = .074$) (see Fig. 2).

Cough severity, as measured by the FACIT cough item ("I have been coughing"), was associated with worse HRQOL measured by ATAQ-IPF (Fig. 3).

Discussion

The objective of the project was to obtain PROMIS scores across a range of relevant health domains for individuals with IPF, both for purposes of adding to the knowledge base of HRQOL in this population and for comparing with other populations, including the U.S. general population. In addition, we aimed to evaluate the association between IPF-related symptoms and use of supplemental oxygen.

The PROMIS measures, including the PROMIS-29 profile and the PROMIS dyspnea severity measure, demonstrated stability over a 7–10-day period, during which clinical change was not expected, confirming good test–retest reliability. PROMIS measures behaved as hypothesized: there were significant differences in scores from this sample compared with scores from other samples of people from the general population or with other chronic conditions. For example, HRQOL was more impaired in the study sample than the U.S. general population across all PROMIS domains, with most differences in the range of a standard deviation or more. The study sample also reported impairments in dyspnea severity, as measured by the PROMIS dyspnea, which equaled or exceeded those in samples of people with COPD or systemic sclerosis with interstitial lung disease [25].

Reflecting the emotional burden of living with IPF, certain PROMIS-29 domain scores for the sample were comparable to—or worse than—individuals with major depressive disorder (both anxiety and depression domains), exacerbated COPD (on anxiety) [21], congestive heart failure (on fatigue) [22], and obstructive sleep apnea (on sleep disturbance) [23]. These results crystallize the debilitating impact of IPF on people's lives, overall, as well on specific areas of functioning. The study also confirms the impact of cough, one of the primary symptoms of IPF, on individuals' HRQOL.

As hypothesized, PROMIS scores differed between sample subgroups stratified on severity of IPF-related symptoms, including dyspnea and cough. On balance, respondents with greater dyspnea severity (according to the MMRC) reported greater impairment in HRQOL, as measured by the PROMIS-29 domains. This pattern held across all PROMIS-29 domains except for sleep disturbance.

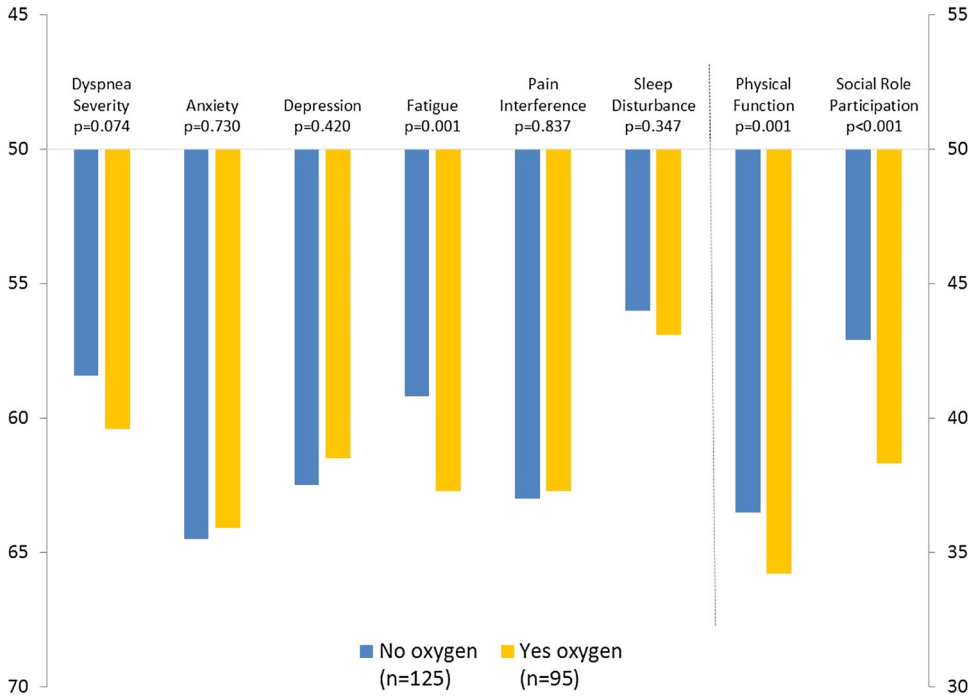

Fig. 2 Mean baseline PROMIS-29 scores by supplemental oxygen use ($n = 220$)

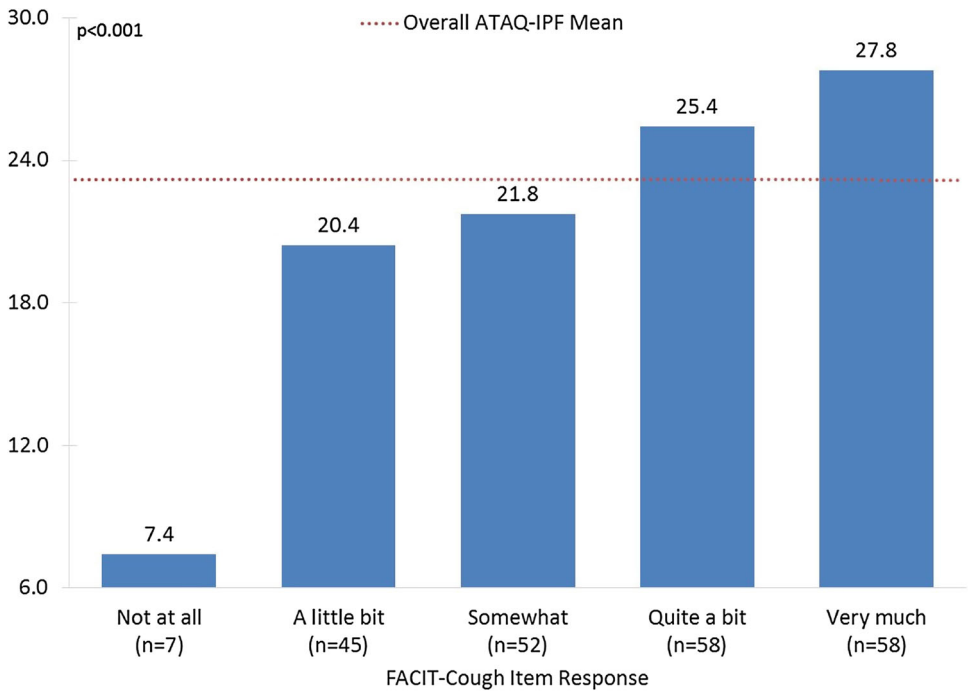

Fig. 3 ATAQ-IPF cough subscale scores by FACIT cough item responses ($n = 220$)

In addition, supplemental oxygen users (a marker of greater disease severity) reported more impairment than non-users across several of the PROMIS domains, including physical function, fatigue, and social role participation. There were no differences between oxygen users and non-users for anxiety, depression, pain interference, sleep disturbance, and dyspnea severity. Dyspnea severity showed a trend toward being significantly greater in oxygen users. Because supplemental oxygen is prescribed to, among other things, minimize dyspnea, further research is needed to more fully understand the findings with regard to supplemental oxygen use in IPF patients.

Limitations inherent in the study design warrant caution when interpreting these findings. Because we used an

internet panel for data collection, health information was based entirely on participant self-report, and eligibility was likewise based on participant report of physician-diagnosed IPF. Thus, we are unable to assess the fidelity of the IPF diagnosis or the stated presence/absences of comorbid conditions. The lack of access to clinical data reflecting IPF severity (e.g., pulmonary function tests) limited our ability to further validate the PROMIS measures in this sample using such clinical anchors. In addition, the design of this study and selection of an internet panel sample (vs. a clinic-based sample undergoing an intervention) precluded our ability to assess the responsiveness of PROMIS measures to longitudinal change in clinical status of patients with IPF. Additional research is needed to thoroughly evaluate the psychometric performance of the PROMIS-29 and PROMIS dyspnea measures in IPF.

Conclusion

This study provides preliminary evidence that the PROMIS measures are psychometrically sound and demonstrate the sensitivity to the various clinical features of IPF that result in impairment across a range of domains. Further, comparisons of PROMIS-29 data with other similarly debilitating chronic conditions shows that IPF has an equivalent detrimental impact on the HRQOL of patients' lives, especially in the areas of physical function, anxiety, pain, depression, and fatigue. All of these HRQOL deficits should be monitored in clinical practice with IPF patients and considered when investigating new therapies.

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Compliance with Ethical Standards

Conflict of Interest Shih-Yin Chen is an employee and shareholder of Biogen. David Van Brunt was an employee of Biogen when the study was conducted and is a shareholder. This manuscript relates to study of disease for which Biogen is developing treatment. However, this manuscript in no way addresses the effects, or lack thereof, of any specific compound in development. The Northwestern University investigators received payment for bona-fide services in the execution of the study, but otherwise have no conflicts of interest to declare.

Ethical Approval The Northwestern University Institutional Review Board determined that the study qualified for Exemption under United States Department of Health and Human Services CFR 46.101(b).

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