Validation of the Cough Quality-of-Life Questionnaire in Patients With Idiopathic Pulmonary Fibrosis

Noah Lechtzin, MD, MHS, FCCP; Marisa E. Hilliard, PhD; and Maureen R. Horton, MD

Background: Cough is a pervasive and disabling symptom of idiopathic pulmonary fibrosis (IPF) and is an independent predictor of disease progression. The Cough Quality-of-Life Questionnaire (CQLQ) is a validated measure of cough-specific quality of life that could be used as an outcome measure in therapeutic trials for IPF. This study aimed to assess the reliability and validity of the CQLQ in individuals with IPF.

Methods: The CQLQ was administered as an outcome within a previously published 27-week, placebo-controlled, crossover trial of thalidomide for cough in IPF. Participants were adults with IPF and chronic cough. A cough visual analog scale (VAS) and the St. George's Respiratory Questionnaire (SGRQ) were administered to establish concurrent validity of the CQLQ.

Results: Internal consistency was high (Cronbach $\alpha > .70$) for the CQLQ total and four of six subscale scores. The CQLQ total score demonstrated concurrent validity through significant correlations with scores on the cough VAS and SGRQ total and subscale scores (r range, 0.63-0.81; $P < .05$). The intraclass correlation coefficient for the CQLQ completed at baseline and after a therapeutic washout period at week 15 was 0.87, indicating very good test-retest reliability.

Conclusions: This study supports the use of the CQLQ as a valid and reliable instrument in IPF and should be used to assess cough-specific quality of life in therapeutic trials.

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Abbreviations: CQLQ = Cough Quality-of-Life Questionnaire; ICC = intraclass correlation coefficient; IPF = idiopathic pulmonary fibrosis; MID = minimally important difference; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale

Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal, fibrotic lung disorder of unknown etiology with no proven pharmacologic therapy.¹ IPF is the most common idiopathic interstitial pneumonia, accounting for >60% of cases, but it is also the least treatable and has the worst prognosis.¹⁻³ The majority of patients with IPF die within 3 to 5 years of diagnosis.^{1,3}

Cough is frequently a debilitating symptom in patients with IPF^{4,5} and is an independent predictor of disease progression.⁶ Clinical trials in IPF have traditionally focused on outcomes such as pulmonary function and

survival, but recently, more emphasis has been placed on assessing patient-reported outcomes, such as health-related quality of life.^{7,8} The Cough Quality-of-Life Questionnaire (CQLQ) is a well-established instrument that measures the impact of cough-specific quality of life.⁹ The CQLQ was developed and validated in people with chronic and acute cough not associated with underlying lung disease. We aimed to determine the validity and reliability of the CQLQ in a population with IPF.

MATERIALS AND METHODS

This study was performed within the context of a randomized clinical trial of thalidomide to treat cough in IPF.¹⁰ It was

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Affiliations: From the Johns Hopkins University School of Medicine, Baltimore, MD.

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Correspondence to: Noah Lechtzin, MD, MHS, FCCP, Johns Hopkins University School of Medicine, 1830 E Monument St, 5th Floor, Baltimore, MD 21205; e-mail: nlechtz@jhmi.edu

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approved by the Johns Hopkins Medicine Institutional Review Board (Approval # NA 00007590). The trial was a double-blinded, two-treatment, two-period crossover study with two 12-week treatment periods separated by a 2-week drug-free washout period. Participants were recruited between February 2008 and March 2011. All participants provided written informed consent.

Setting and Participants

Eligibility criteria were age > 50 years and a clinical history consistent with IPF (≥ 3 months and ≤ 5 years) and chronic cough, defined as cough > 8 weeks duration that adversely affected quality of life and was not due to other identifiable causes. All participants had high-resolution chest CT scans results consistent with IPF or a surgical lung biopsy specimen demonstrating usual interstitial pneumonitis, an FVC $\geq 40\%$ and $\leq 90\%$ predicted, a total lung capacity of $\geq 40\%$ and $\leq 80\%$ predicted, and a diffusing capacity of lung for carbon monoxide of $\geq 30\%$ and $\leq 90\%$ predicted at screening. The main exclusion criteria were pregnancy, women with child-bearing potential, toxic or environmental exposure to respiratory irritants, collagen vascular disease, airflow obstruction, active narcotic antitussive use, peripheral vascular disease or neuropathy, inability to give informed consent, allergy or intolerance to thalidomide, or a life expectancy < 6 months in the opinion of the investigators.

Randomization and Interventions

All participants were randomized to begin the study with either thalidomide ($n = 12$) or placebo ($n = 12$). Participants received each treatment for 12 weeks in a crossover design, with a 2-week washout period between treatments.

The CQLQ,⁹ the St. George's Respiratory Questionnaire (SGRQ),¹¹ and a 10-cm visual analog scale (VAS) were completed at study entry, after the first 12 weeks of the study, after the 2-week washout period, and after the second 12-week treatment period. A physician asked participants whether their cough had worsened, improved, or was unchanged at each study visit. This value obtained at week 12 and week 27 was used to calculate the minimally important difference (MID) score for the CQLQ.

The CQLQ comprises 28 questions about cough and its effects and is scored with a 4-point Likert scale, with lower scores indicating less impact of cough on health-related quality of life.⁹ The CQLQ total score can range from 28 to 112. The mean CQLQ total score in people with chronic cough is 65.4 ± 14.6 ,⁹ with estimated MID scores between 10.58 and 21.89.¹² The following six CQLQ subscales have been developed and validated in people with chronic cough⁹: physical complaints, psychosocial issues, functional abilities, emotional well-being, extreme physical complaints, and personal safety fears. The CQLQ demonstrates excellent psychometric properties in chronic cough, but it has yet to be validated, and an MID score has yet to be calculated for individuals with IPF.

The SGRQ is a disease-specific measure of the impact of respiratory disease on overall health, daily life, and perceived well-being. The questionnaire comprises 50 (76 responses) items that produce three domain scores and one overall score. The SGRQ domains are symptoms (frequency and severity), activities (those that cause or are limited by breathlessness), and impacts (social functioning and psychologic disturbances resulting from airways disease). The SGRQ is widely used in clinical trials of IPF and has been demonstrated to be a valid tool for differentiating changes in IPF.¹³⁻¹⁵

On a 10-cm VAS, participants were asked to mark their answer to the following question: "Considering all the ways your cough affects you, on the average, how have you been doing in the past week?" The anchors of the VAS were no cough and worst cough.

Analyses

Baseline characteristics were summarized and are presented as mean $\pm$ SD or median with range, as appropriate. The Shapiro-Wilk's test was used to test for normality of distribution.¹⁶ The CQLQ values were normally distributed at every study visit.

Cronbach α ¹⁷ was used to determine internal consistency for the CQLQ subscales at baseline. Test-retest reliability of the total CQLQ score measured at baseline and after a therapeutic washout period at week 15 was determined by calculating the intraclass correlation coefficient (ICC) by a one-way random-effects model.¹⁸ These two study visits reflect time points when the participants were not taking study drugs. To establish concurrent and convergent validity, Pearson correlation coefficient (r) was used to compare the baseline CQLQ total score and subscales to the baseline cough VAS (concurrent) and the SGRQ total and subscale scores (convergent).

The MID is the smallest change in a quality-of-life measure's score at which quality-of-life change as measured by the instrument is clinically meaningful.¹⁹ In the present study, the MID was determined by two different methods. The first compared change in CQLQ to participants' subjective responses to a question about whether their cough had worsened, stayed the same, or improved after treatment at weeks 12 and 27 of the study. Cough was categorized into one of five categories: much worse, slightly worse, unchanged, slightly better, or much better. These categories were further dichotomized into no change or worsened vs improved. We used the ROCMIC command of STATA, release 12 (StataCorp LP) statistical software, which computed a receiver operating characteristic curve for CQLQ and the dichotomous subjective change in cough and found the cut point corresponding to a 45° tangent line intersection; this is mathematically equivalent to the point at which the sensitivity and specificity are closest together.²⁰ The second method was a distribution-based approach commonly called 1 SEM, which used the following equation:

$$\text{SEM} = \text{baseline SD} \sqrt{1 - \alpha}$$

where α is Cronbach α for the change from baseline to 12 weeks and from week 12 to week 27.^{21,22} $P < .05$ was considered significant for all analyses. All statistical analyses were performed with STATA, release 12 (StataCorp LP) software.

RESULTS

Ninety-eight individuals inquired about the study between February 2008 and March 2011. Of the 25 participants who signed informed consent, 24 were eligible for the trial and were randomized. Of the 24 randomized participants, 23 were treated (one left the study because of lack of interest), and 20 completed both treatment periods (three dropped out because of worsening health). The demographic characteristics of participants are shown in Table 1, and further details about the study population can be found in Horton et al.¹⁰

Table 2 shows the baseline values of CQLQ, CQLQ subscales, cough VAS, and SGRQ. The CQLQ values are similar to those reported by French et al⁹ in their original evaluation of the CQLQ in patients with acute and chronic cough. Internal consistency was high

Table 1—Patient Characteristics at Baseline

Characteristic	Value
Female sex	5 (21.7)
Age, y	67.6 ± 7.8
Race	
White	21 (91.2)
Black	1 (4.4)
Hispanic	1 (4.4)
Pulmonary function results	
FVC, % predicted	70.4 ± 13.7
FEV ₁ /FVC ratio	85.4 ± 5.4
TLC, % predicted	63.6 ± 11.4
DLCO, % predicted	57.4 ± 14.4

Data are presented as No. (%) or mean ± SD. DLCO = diffusing capacity of the lung for carbon monoxide; TLC = total lung capacity.

(Cronbach $\alpha > 0.7$) for the CQLQ total score and all subscales except extreme physical complaints and personal safety fears (Table 3). The ICC for the total CQLQ score at baseline and week 15 was 0.88 ($P < .001$), indicating good test-retest reliability.

At baseline, the CQLQ total score was significantly correlated with the cough VAS ($r = 0.63$, $P < .01$), the SGRQ total score ($r = 0.79$, $P < .01$), and all subscales of the SGRQ (r range, 0.72-0.81; $P < .05$) (Table 4). The physical complaints and functional abilities subscales of the CQLQ were significantly correlated with the cough VAS ($r = 0.63$ and 0.64 , respectively; $P < .01$), the SGRQ total score ($r = 0.77$ and 0.66 , respectively; $P < .01$), and all subscales of the SGRQ (r range, 0.50-0.72; $P < .05$). The psychologic function, emotional well-being, and extreme physical complaints subscales demonstrated significant correlations with some of these other measures (Table 4). The personal safety fears component of the CQLQ was correlated only with the SGRQ impact subscale ($r = 0.45$, $P < .05$).

At week 12, 43% of participants reported worsening of their cough symptoms, whereas 57% reported improvement. At 27 weeks, 71% of participants reported

a worsening in their cough symptoms, and 29% reported an improvement. From these ratings, the MID for the CQLQ total score was 5.0 (95% CI, 1.8-10.7). Based on the 1 SEM method, the MID for the CQLQ was 5.7 (95% CI, 4.9-6.4). In our previously published clinical trial of thalidomide for cough in IPF, we showed that the CQLQ was responsive to therapeutic interventions. Compared with placebo, the mean CQLQ score was 11.4 points lower in the treatment phase and, thus, exceeded this MID.¹⁰

DISCUSSION

Cough is a frequent, disabling symptom in patients with IPF,⁵ and it is important to be able to precisely quantify the impact of cough-specific quality of life in clinical trials and in the clinical care of patients with IPF.¹³ The current study demonstrates the validity and reliability of the CQLQ for individuals with IPF.

Construct analysis of the CQLQ showed good internal consistency for the total score and most of the subscales (Table 3). However, the extreme physical complaints and personal safety fears subscales did not perform as well as the other subscales in this sample, with substantially lower internal consistency coefficients. Test-retest reliability as indicated by the ICC was very good. Validity was assessed by comparing CQLQ scores to scores from a VAS of cough and the SGRQ. The CQLQ total score was significantly correlated with the VAS and the SGRQ scores, indicating concurrent and convergent validity, respectively.

The CQLQ personal safety fears subscale demonstrated low internal consistency (Cronbach $\alpha = 0.39$) and correlated only with the impact subscale of the SGRQ. The CQLQ was developed for patients with idiopathic cough, and the three statements that comprise the personal safety fears subscale are as follows: "I am concerned that I have cancer," "I want to be reassured that I do not have anything seriously the matter with me," and "I am concerned that I have something seriously the matter with me." These items are not relevant for patients who know they have a serious, progressive, incurable lung disease, and in the IPF

Table 2—Cough and Quality-of-Life Measures

Variable	Baseline Value
Total	60.5 ± 12.0
Physical complaints	33.8 ± 4.1
Psychologic issues	13.2 ± 3.2
Functional abilities	12.1 ± 3.6
Emotional well-being	5.1 ± 1.6
Extreme physical complaints	7.1 ± 2.0
Personal safety fears	6.5 ± 1.7
Cough VAS	64.8 ± 21.4
SGRQ total	57.4 ± 18.8
SGRQ symptoms	67.7 ± 19.7
SGRQ activity	64.3 ± 22.7
SGRQ impact	48.1 ± 20.7

Data are presented as mean ± SD. SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale.

Table 3—CQLQ Internal Consistencies

CQLQ Scale	Cronbach α	No. Items
Total	0.89	28
Physical complaints	0.81	9
Psychosocial issues	0.78	5
Functional abilities	0.85	5
Emotional well-being	0.72	4
Extreme physical complaints	0.51	4
Personal safety fears	0.39	3

CQLQ = Cough Quality-of-Life Questionnaire.

Table 4—Correlations Among CQLQ, VAS, and SGRQ

CQLQ Scale	Comparison Measure				
	VAS	SGRQ Total	SGRQ Symptom	SGRQ Activity	SGRQ Impact
Total	0.63 ^a	0.79 ^b	0.72 ^c	0.72 ^b	0.81 ^b
Physical complaints	0.63 ^a	0.77 ^b	0.50 ^c	0.72 ^b	0.71 ^b
Psychologic issues	0.39	0.54 ^c	0.29	0.40	0.62 ^a
Functional ability	0.64 ^a	0.66 ^a	0.53 ^c	0.54 ^c	0.66 ^a
Emotional well-being	0.31	0.50 ^c	0.19	0.42	0.57 ^a
Extreme physical complaints	0.54 ^c	0.54 ^c	0.38	0.34	0.63 ^a
Personal safety fears	−0.09	0.34	0.05	0.23	0.45 ^c

See Table 2 and 3 legends for expansion of abbreviations.

^a $P < .01$.

^b $P < .001$.

^c $P < .05$.

population, they probably do not add to the discriminative capacity of the CQLQ. The extreme physical complaints subscale comprises four items about complications of cough, such as posttussive emesis and cough-induced incontinence. There may be unique characteristics of the cough associated with IPF that make these extreme physical complaints less problematic, or perhaps patients with IPF are less bothered by them than patients with idiopathic cough. Therefore, although the CQLQ total score and three of the subscales perform well in patients with IPF, the use of the personal safety fears and extreme physical complaints subscales should be used with caution in this population.

The limitations of this study are largely because of the study sample. This small study recruited patients with IPF who were troubled by cough and who joined an experimental drug trial for cough. Typically, validation studies are done in much larger populations, and a small sample size results in less confidence in the values of some results, such as the MID. Thus, the present findings may have limited generalizability because of the small size and single-center design. Ideally, these analyses should be reproduced in other, larger groups with interstitial lung disease. Additionally, we would recommend that others perform similar studies of the CQLQ and other quality-of-life measures to help us to better understand the utility of patient-reported outcomes in various populations.

The CQLQ scores in the present study population are comparable to patients who present solely for the evaluation of chronic cough and, therefore, may not be representative of all patients with IPF. Despite of this, we show the CQLQ to have a high degree of internal consistency, evidence of criterion validity, and good test-retest reliability. The MID of 5 is considerably smaller than the effect we demonstrated in our previously published clinical trial of thalidomide for IPF, which was 11.4 (95% CI, 7.0-15.7).¹⁰ The calculation of the MID in the current study verifies that the observed quality-of-life improvement in our previous publica-

tion was clinically meaningful. This value can be used in other clinical trials for IPF to evaluate the degree to which treatments have a meaningful impact on patient quality of life. The CQLQ had good test-retest reliability, although this was examined on results collected 15 weeks apart and is unusually long for test-retest reliability studies; therefore, the findings should be interpreted with caution.

The results of this study support the CQLQ as a valid and reliable instrument for use in patients with IPF. It should be considered for routine use to assess and monitor quality of life in patients with IPF in clinical practice and to evaluate response to novel therapeutics in IPF clinical trials.

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Dr Lechtzin: contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and approval of the final version.

Dr Hilliard: contributed to the study conception and design; data acquisition, analysis, and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and approval of the final version.

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