A New Tool to Assess Quality of life in Patients with Idiopathic Pulmonary Fibrosis or Non-Specific Interstitial Pneumonia *

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Abstract

Background: Quality of life (QoL) is significantly impaired in patients with pulmonary fibrosis, however reliable tools to assess QoL are still missing. We thus aimed to develop a new questionnaire called QPF to measure QoL in patients with fibrotic idiopathic interstitial pneumonias (IIP).

Methods: As part of a multi-center validation study in a pre-post design, 200 patients with idiopathic pulmonary fibrosis (IPF) or idiopathic non-specific interstitial pneumonia (iNSIP) filled in the questionnaire at 2 measurement time points with an interval of 6 months. Cross-validation was carried out with the St. Georges Respiratory Questionnaire (SGRQ).

Results: The alpha of the QPF-total score and its subscales range from .858 to .616 and can be rated as good. In contrast to the SGRQ, the QPF was able to detect a change in the patient's mood ("Condition" scale) in the course of treatment. This could be due to the SGRQ being a condition specific measure but also due to the greater amount of items, especially those with a job-related theme, which are not relevant for the sample examined. The questionnaire can be used to evaluate treatment response more appropriately, by collecting data on physical performance and general behaviour.

Conclusion: This newly developed questionnaire maps the special needs of the patients well and is superior to the SGRQ. The QPF is suitable for screening as well as for supplementing the medical history and for monitoring the course of disease in fibrotic IIPs.

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown etiology. IPF affects elderly, predominantly male ex-smokers [1, 2]. Precise information on the prevalence and incidence of IPF is limited. Estimates of the prevalence of IPF range from 2 to approx. 29 cases per 100,000, the incidence approx. 10 per 100,000 in the general population [3]. The prevalence of IPF is increasing, whereby it is unclear whether this increase is influenced by geographical, ethnic or cultural factors, or whether improved diagnosis and demographic change play a role.

Despite the improved situation due to the therapeutic options with pirfenidone and nintedanib for IPF or other new drug developments [4], the therapeutic options for chronically progressive pulmonary fibrosis, especially for IPF, are still limited [5, 6, 7]. While in the case of IPF antifibrotic therapy halts disease progression and may positively impact survival [3] prognosis still remains poor and the burden of disease is still high. As the disease progresses, the patient's activities become more restricted due to increasing breathing difficulties. These significant limitations inevitably affect quality of life [8–15]. In addition, there is evidence of associations between pulmonary fibrosis and depressive mood and a perceived impairment in independence [10,11]. Nishiyama et al. [16,17] identify dyspnea as the most important prognostic factor for assessing the quality of life. Using focus groups, Swigris and colleagues [18] identified the factors that had the greatest impact on the quality of life from a patient's perspective:

symptoms, therapy procedures, sleep, exhaustion, future thoughts, employment, finances, dependency, family, sexuality, social involvement, mental and spiritual wellbeing and mortality.

To date, existing instruments for assessing the quality of life do not seem to be able to map the specific problems comprehensively [18, 19]. Currently available questionnaires assess more generally, non-disease-specific aspects of quality of life. For example, the 15-item K-BILD questionnaire [20] covers quality of life-specific factors in a very general way. In the course of the item reduction from 71 originally to 15, essential aspects were excluded, such as coughing, medication, sleep and sexuality; according to the authors, this elimination inevitably led to a loss of information in favour of a low number of items. The diseasespecific LQ questionnaires Chronic Respiratory Questionnaire (CRQ) [21] and St. George's Respiratory Questionnaire (SGRQ) [22] were both originally developed for patients with obstructive pulmonary diseases [9, 10, 11, 23, 24, 25] and not for pulmonary fibrosis. However, fibrosing lung diseases cover a different range of symptoms; associated with thoracic tightness, shortness of breath and non-productive cough. Berry et al. [26] compared patients with COPD and with pulmonary fibrosis and showed that despite comparable physiological condition or symptom severity, patients with pulmonary fibrosis showed significantly poorer quality of life values than patients with COPD (measured with SGRQ and SF-12).

We thus aimed to create a novel QoL measure to better reflect specific aspects in patients with fibrotic idiopathic interstitial pneumonias (IPF and NSIP).

Methods

On the basis of a literature research on the subject of quality of life in patients with interstitial pulmonary diseases (see literature), an expert group from the German Society of Pulmonary Diseases (DGP) with support of patients suffering from pulmonary fibrosis (organized in the Lung fibrosis e.V., Essen) an item pool was created. This version of the questionnaire was initially presented to 52 patients with idiopathic pulmonary fibrosis or idiopathic NSIP as part of primary care. After returning and reviewing these questionnaires, an item and a factor analysis were carried out. In addition, the criticisms and improvements in the item formulations provided by patients and treating physicians were taken into account. As a result, the questionnaire on quality of life in patients with idiopathic pulmonary fibrosis and NSIP (QPF) comprises at first 6 question complexes with 41 items, an additional files shows this in more detail (see additional file 1). As part of a multicenter validation study in a one-group pre-post design, the questionnaire was filled in by n = 200 patients at 2 time points at an interval of 6 months. The questionnaire was validated linguistically by back and forth translation into German and English (Kirsten et al., accepted for publication in Pneumologie).

Recruitment

Data collection took place from February 2017 to December 2018 in seven tertiary care centers for ILD. Consecutive patients were recruited prospectively after giving written informed consent. The

questionnaires were issued at the baseline (t1) during initial contact and six months later (t2) during a re-appointment in the same center. Questionnaires were filled out in a quiet room without distraction.

Inclusion criteria:

- Idiopathic pulmonary fibrosis or idiopathic non-specific interstitial pulmonary fibrosis (iNISP) according to diagnostic criteria of the ATS / ERS (2011 for IPF and 2013 for NSIP)
- sufficient knowledge of German, reading and writing skills, which make it possible to fill out the questionnaires

Exclusion criteria:

- Significant respiratory infection in the past 4 weeks
- Significant comorbidity (e.g. severe CAD, heart failure) impeding QoL
- cognitive or linguistic restrictions that hinder the completion of the questionnaires

Instruments

The sociodemographic and medical data of the patients including age, gender, body weight and other chronic diseases were recorded using a self-developed questionnaire. As an external criterion, the patient's self-assessed state of health and the degree of stress on their patient were recorded on the basis of a visual analogue scale, and the patient's prognosis with a doctor's assessment.

The quality of life was recorded using the newly developed questionnaire on the quality of life in fibrosing lung diseases (QPF). This comprises 42 items (final form 5 subscales, 23 items) with the 6 subscales:

1. Condition
2. Impairments
3. Problems
4. Shortness of breath
5. Cough
6. Health status

There is a 6-step answer format for items on scales 1 and 2, items on scales 3–5 are answered dichotomously (yes / no). In the "Problems" scale, weight loss < 3 kg is rated with 1,> 3 kg with 0 points. In the "shortness of breath" scale, the question "How many minutes do you need after a strenuous activity to come back to rest?" <5 min with 1 point, > 5 min with 0 points.

In the “cough” scale, the “occasional” intake of cough suppressants is rated with 1, the “constant” intake with 0 points. With the item "How many good days without significant cough and shortness of breath did you have in the last week?" 0 points are awarded for "no day" (1 day: 1 point, 3 days: 2 points, 7 days: 3 points).

Health status (scale 6) is assessed using a visual analogous scale. This is 10 cm long, 10 points are awarded per centimeter, i.e. "My state of health is very good." gives 100 points, "My state of health is very bad." results in 0 points. The final calculation is carried out by adding up the raw values to a total value (0-198 points). A higher score representing a better quality of life.

The Saint George Respiratory Questionnaire (SGRQ, [22]) containing 50 items, was used to cross-validate the QPF. The SGRQ has been developed as a multidimensional survey tool for assessing the impairment of disease-specific quality of life in adult patients with chronic obstructive pulmonary diseases. The operationalization of the disease-specific quality of life in chronic respiratory diseases takes place on the basis of three impairment areas, which are summarized on the scales symptoms (frequency and form of clinical symptoms), activity (everyday activities) and stress (due to illness and medication). A weighted scale value is determined for each of the three subscales and for the entire test, which indicates the degree of impairment of the disease-specific quality of life in a value range from “0” - no impairment to “100” - maximum impairment.

Statistics

The Sample size was determined on the basis of the planned statistical methods with G * Power [two-sided testing, $\alpha = .05$, Power $1- \beta = .95$]. Assuming a conservative estimate of the effect size of .5, the sample size thus determined is n = 42. The pre-test showed that the patient group surveyed is very heterogeneous with regard to the quality of life and also achieved extreme test values. In order to ensure a normal distribution and thus the representativeness of the data, the planned sample size was increased to n = 70. Considering a high drop-out and lost-to-follow-up rate, especially due to expected mortality, a sample size of n = 200 patients was calculated.

Item analyses were carried out as a procedure for test validation of the QPF. Differences in mean values were tested for significance using one-factor analysis of variance with repeated measurements. For construct validation, correlation effects between the individual QPF and SGRQ measurement methods were calculated using Pearson correlation coefficients. An error probability of < 5% is determined on both sides. The statistical evaluation was carried out with the statistics program IBM SPSS Statistics 22.

Results

219 patients were recruited. 10 patients died during the 6-month period, 9 patients were lost to follow up. Accordingly, data from 200 patients at t1 and t2 were collected. The mean age of the patients was 70.97 years (50–90 years), 82.5% were male. Comorbidities (self-reported by the patients) were frequent (36% of patients) (Table 1).

Table 1
Comorbidities

	n	Percent
Diabetes	22	11.0
Arthrosis	8	4.0
Coronary Artery Disease	8	4.0
Hypertension	7	3.5
Asthma	5	2.5
Hypothyroidism	4	2.0
Rheumatism	3	1.5
Hay fever	2	1.0
Lung cancer	2	1.0
Cluster headache	1	.5
COPD	1	.5
Depression	1	.5
Epilepsy	1	.5
Glaucoma	1	.5
Congestive heart disease	1	.5
Heart failure	1	.5
Ankylosing spondilitis	1	.5
Prostata hyperplasia	1	.5
GERD	1	.5
Sleep apnea syndrome	1	.5
total	72	100.0

Table 1.

Item analysis

The reliability according to Cronbach (homogeneity index) results in an alpha of .827 (unstandardized) for the QPF-scale “condition” (7 items in total, n = 200). The alpha of this scale can be considered satisfactory. The selectivity indices range from .146 to .800. According to common criteria (selectivity = at least .3), however, the indices of the item "Condition_7" (selectivity = .146) must be rated as insufficient.

The alpha of this scale to .858 increased by eliminating this item, which seems possible without losing information (Table 2).

Table 2
Indices of the QPF “Condition” scale

In the past two weeks	Selectivity	Cronbach`s Alpha if item is deleted
… I was happy and in a good mood	.800	.766
… I felt calm and relaxed	.783	.764
… I felt energetic and active	.715	.773
… I felt fresh and rested when I woke up	.633	.788
… my everyday life was full of things that interest me	.695	.779
… I was very afraid of how my illness would progress	.303	.848
… my family / friends was a big help	.146	.858

Table 2

The QPF scale "impairment" has an alpha of .882 (6 items, n = 200). This value can be considered sufficient. The selectivity is between .539 and .777. There is no reason to eliminate any item (Table 3).

Table 3
Selectivity indices of the QPF impairment scale

In the past six months I felt restricted …	Selectivity	Cronbach`s Alpha if item is deleted
… in my everyday activities, e.g. gardening, household	.733	.857
… in my family life	.716	.860
… when participating in public events, e.g. cinema, club	.777	.849
… on vacation trips	.683	.865
… through my tools, e.g. stair lift, oxygen device	.719	.859
… through my medication	.539	.886

Table 3.

The analyses of the QPF revealed some problematic items. The discriminatory power of the seventh item on the QPF-scale “Condition” ("In the last two weeks my family / friends was a big help.") had to be rated as insufficient (discriminative power = .146). This item has thus been eliminated because the low

selectivity does not allow an assessment of how well it distinguishes between people with low and high burden of disease.

Table 4

Table 4
QPF “Problems” selectivity indices

	Selectivity	Cronbach`s Alpha if item is deleted
Have you noticed a “drop in performance” in the past six months?	.266	.406
Did you lose weight unintentionally?	.184	.431
Do you suffer from new night sweats?	.152	.442
Did you lose your appetite?	.323	.396
Are you tired unusually often?	.277	.392
Do you fall asleep unintentionally during the day?	.190	.431
Do you suffer from heartburn?	.089	.457
Did you notice that your fingernails / toenails have changed?	.044	.507
Do your fingers change color when it is cold?	.149	.442
Do you have swollen ankles in the evening?	.188	.433
Do you suffer from joint problems?	.212	.423

The QPF “Cough” scale shows an alpha of .608. The selectivity indices are .136 to .469. The items "Do you mainly cough in the morning?", "Do you have coughing attacks until you pass out?" And "Do you need a cough suppressant?" have selectivity below .30 and therefore are insufficient (Table 5).

Table 5
Selectivity indices of the QPF “Cough” scale

	Selectivity	Cronbach`s Alpha if item is deleted
Do you suffer from irritable cough?	.444	.524
Do you cough after exertion?	.469	.514
Do you cough at night?	.309	.575
Do you cough mainly in the morning?	**.226**	.607
Do you have coughing attacks until you pass out?	**.136**	.616
Do you need a cough suppressant?	**.234**	.599
Do you have sputum?	.423	.532

Table 5.

The QPF scale "shortness of breath" also has a low internal consistency with alpha = .301. The items "I have no shortness of breath.", "I have shortness of breath when I exercise hard, e.g. in sports.” and “I have shortness of breath at rest.” have a selectivity below .30. Leaving out the item "I don't have difficulty breathing." would increase the alpha to .536 (Table 6).

Table 6
Selectivity indices of the QPF “Shortness of breath” scale

	Selectivity	Cronbach`s Alpha if item is deleted
I don't have difficulty breathing.	**– .515**	.536
I have difficulty breathing when I exert myself, e.g. during sports.	**.090**	.294
I have difficulty breathing with little effort, e.g. when climbing stairs.	.302	.107
I have shortness of breath at the slightest strain, e.g. when I dress or undress.	.319	.080
I have shortness of breath at rest.	**.251**	.226
Has your breathlessness worsened in the past 3 months?	.315	.077

Table 6.

The “Shortness of breath” scale turns out to be problematic, the patients often answered implausible not matching the rest of the answers. Many patients answer "yes", i.e. the double negation was obviously misunderstood. Some patients also crossed out that "don´t" in the question "I don’t have difficulty breathing."

Scale mean values QPF and SGRQ

Table 7 shows the mean scores of the QPF and SGRQ. The results of the one-factor analysis of variance with repeated measurements showed no significant changes in the point values at the level of the overall scores in the 6 months of observation in either method. However, one can see a small numerical decrease in the overall score in the QPF in the sense of a deterioration in the quality of life. The SGRQ total score increased over time, also indicating a deterioration in the quality of life. At the scale level, there were significant differences in terms of a deterioration or improvement in the QPF-condition and QPF-breathlessness scales and also in the SGRQ activity scale (see Table 7, bolded cells).

Table 7
Scale differences of the QPF and SGRQ at t1 and t2

	Mean t1	Mean t2	P value
QPF-scales (range)			
Total score (0-198)	97.11	95.36	.400
Condition (0–35)	23.22	21.94	**.044**
Impairment (0–30)	9.25	10.43	.086
Problems (0–12)	3.71	3.75	.880
Shortness of breath (0–7)	2.88	3.18	**.032**
Cough (0–14)	4.23	4.13	.476
Health status (0-100)	53.8	51.95	.398
SGRQ-Scales (range)			
Total score (0-100)	38.80	41.70	.138
Symptoms (0-100)	41.82	40.84	.683
Activity (0-100)	53.55	59.43	**.019**
Burden (0-100)	38.80	31.63	.256

Table 7.

Construct validation of the QPF (cross validation with the SGRQ)

As shown in Table 8, some scales of the QPF correlated moderately with those of the SGRQ. The corresponding subscales also correlate with one another in a moderate significant manner. Some correlations are negative and thus indicate that there is an inverse relationship between scores of the QPF and SGRQ, which is to be assessed as a good match (high score means good QoL in QPF, bad QoL in SGRQ). The highest correlations are found between the scales "QPF_condition" and „SGRQ_total score". This could be seen as an indication that both instruments depict the construct of quality of life very

similarly. On the other hand, some correlations are positive, which means that a good QoL in the QPF is associated with a decreased QoL in the SGRQ. This could be due to the SGRQ being a condition specific measure but also due to the greater amount of items, especially those with a job-related theme, which are not relevant for the sample examined and which produced some missings.

Table 8
Intercorrelations (Pearson correlation) of the SGRQ scales with the QPF scales (t1 data, n = 200)

	SGRQ Total score	**SGRQ Symptoms**	**SGRQ Activity**	**SGRQ Burden**
QPF Total score	− .447**	− .383**	− .360**	− .437**
QPF Condition	− .593**	− .515**	− .463**	− .057
QPF Impairment	.527**	.436**	.466**	.492**
QPF Problems	.374**	.352**	.285**	.364**
QPF Shortness of breath	.571**	.399**	.540**	.534**
QPF Cough	.167*	.279**	.135	.120
QPF Health status	− .509**	− .447**	− .431**	− .483**
** =P < .01				
* = P < .05				

Table 8

Responsiveness

Global assessments (visual analogue scale) of the state of health of the patients, the degree of stress on their patient and an assessment of the progression of the disease were collected by the treating physicians. In order to check whether a (supposedly) real change in the state of health can also be represented psychometrically, groups were formed with and without a clinically significant deterioration in

the state of health (external criterion). The group with relevant changes in health status (n = 62) was formed on the basis of the following criteria:

- Deterioration of the subjectively assessed state of health at t2 by at least 50% (patient view, visual analogue scale in the QPF),
- Increase the degree of stress at t2 by at least 50% (doctor's judgment, visual analogous scale, doctor's questionnaire).

Table 9

Table 9
Differences: mean of the scale with and without the external criterion "deterioration in health status"

	Significance difference M1_M2 "No deterioration in health status" P-Values n = 138	**Significance difference M1_M2 "Deterioration in health" n = 62 P-Values**
QPF-Scales		
Total score	.868	.177
Conditions	.199	.124
Impairment	.685	**.028**
Problems	.887	.936
Shortness of breath	.831	**.002**
Cough	.603	.617
Health status	.888	**.035**

As Table 9 shows, a real deterioration in health status from the patient and doctor's perspective is shown in the subscales "impairment", "shortness of breath" and "health status" of the QPF (all shown in bold numbers).

As a further external criterion, the physicians´ assessment of the disease course at both timepoints of measurement was used. For this purpose, the attending physician reflected on the clinical status and his knowledge of the patient's lung function. At both measurement time points, 70% of the patients were classified as "stable". In 66.5% of the patients, there was no change, i.e. the patients were classified as stable or progressive at t1 and t2. In 17% of the patients there was an improvement (t1 progressive, t2 stable), in 16.5% a deterioration (t1 stable, t2 progressive) of the state of health.

Table 10 shows that the deterioration in health status (t1 stable, t2 progressive) can be shown in the subscales "impairment", "shortness of breath", "cough" and "health status" of the QPF (all shown in bold numbers).

Table 10
Differences in scale mean with and without the external criterion “forecast”

	Significance difference M1_M2 “Improvement of prognosis“ P-Values n = 34	**P value Significance difference M1_M2 Deterioration of prognosis P-Values n = 34**
QPF-scales		
Total	.847	.176
Conditions	.190	.124
Impairment	.485	**.020**
Problems	.886	.932
Shortness of breath	.832	**.001**
Cough	.604	**.017**
Health status	.877	**.022**

Table 10

Discussion

The present study was aimed to develop a disease-specific questionnaire (called QPF) for patients with IPF and idiopathic NSIP which would allow assessing particular issues on quality of life in this patient group. The Saint George Respiratory Questionnaire was used to cross-validate the QPF. The demographic features of the study population with a predominance of male sex (82.5%) and a mean age of 71 years are characteristic of this patient group. While numbers of comorbidities were also representative of this patient population, only 8 patients stated suffering on coronary heart disease and 7 had arterial hypertension and only 1 patient (.5%) stated suffering from reflux.

The analyses of the QPF revealed some problematic items. The discriminatory power of the seventh item on the QPF-scale “Condition” ("In the last two weeks my family / friends was a big help.") had to be rated as insufficient (discriminative power = .146). This item has thus been eliminated because the low

selectivity does not allow an assessment of how well it distinguishes between people with low and high burden of disease.

In the QPF “Cough” scale, the item “Do you have coughing attacks until you pass out?” is also characterized by a low selectivity (.136). There may be an influence here from comorbidity with obstructive respiratory diseases (n = 6). Two more items in this scale also had a low selectivity < .3. All three items were eliminated.

The QPF-scale "Problems" alpha was found to be too low at .457. The selectivity indices also did not meet the statistical requirements because they were below .3 in 10 of 11 items and thus had no discriminatory power. The following three items on the QPF “Problems” scale had a very low levels of discrimination power (< 0 15): “Have you noticed that your fingernails / toenails have changed?”, “Do your fingers change colour when it is cold?” and “ Do you have swollen ankles in the evening? ” The whole scale “Problems” was eliminated.

There were no significant results at the level of the overall scores in either the QPF or the SGRQ. The same was true for the (insignificant) reduction in the overall score in the QPF in the sense of deterioration and at the same time an increase in the overall score in the SGRQ characteristic and deterioration of quality of life.

The correlations of the QPF scales with those of the SGRQ are largely significant. The strongest correlations were found between the scales "QPF_Condition" and SGRQ_Total". This could be taken as an indication that both instruments represent the construct quality of life in a similar way.

In reality, it is usually difficult to find a suitable external criterion that tries to validate the patient's information about his or her quality of life and to explain possible changes in the questionnaire. In the present study, global assessments (visual analogue scale) of the state of health of the patients, the degree of stress on the patient and an assessment of the progression of the disease were collected by the treating physicians. Regarding the responsiveness or sensitivity of the questionnaire, two external criteria were used to check whether the QPF can reflect clinically meaningful changes in quality of life. A deterioration in health status was observed on the scales "impairment”, "shortness of breath", “cough” and "health status". This suggests that the QPF is sensitive to changes, which is particularly important for the patient group examined. It has to be taken into account that our patient group consists mainly of patients with a newly diagnosed lung disease. At this stage of the disease, it is unlikely that the health status will deteriorate within six months. At the other site there are died some patients in this time.

Conclusions

The QPF is a new questionnaire covering all important areas of quality of life in patients with IPF and idiopathic NSIP. This questionnaire is suitable for both assessment of Qol and supplementing the medical history. The questionnaire appears to be also important for monitoring the progression of

pulmonary fibrosis. In addition, the questionnaire can be used to evaluate treatment response more appropriately, by collecting data on physical performance and general behaviour.

Abbreviations

ATS
Americain Thoracic Society
COPD
Chronic Obstructive Pulmonary disease
CRQ
Chronic Respirator Questionnaire
DGP
German Society of Pneumology
ERS
European Respiratory Society
GERD
Gastro-Esophagial Reflux Disease
ILD
Interstitial Lung Diseases
IPF
Idiopathic Pulmonary Fibrosis
iNSIP
idiopathic Non-Specific Interstitial Pneumonia
SGRQ
Saint George Respiratory Questionnaire
QoL
Quality of Life

Declarations

Ethics approval and consent to participate

This study was approved by a central ethics committee (IRB 127/16 Ärztekammer Schleswig-Holstein).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the author (Dr. de Vries) on reasonable request.

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Competing interests

All authors declare that they do have no competing interests.

Authors`contributions

DK, UC, MK contributed to the conception, design, acquisition analysis, interpretation of data and drafted the manuscript. UdV contributed to the conception, design and interpretation and drafted the manuscript. FB, DKo, AG, JB, AP, MC, SS contributed to the design and acquisition of patients. JB and FB contributed to the analysis of data and contributed to the draft of the manuscript.

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