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# Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry

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## Abstract

**Background:** The INSIGHTS-IPF registry provides one of the largest data sets of clinical data and self-reported patient related outcomes including health related quality of life (QoL) on patients with idiopathic pulmonary fibrosis (IPF). We aimed to describe associations of various QoL instruments between each other and with patient characteristics at baseline.

**Methods:** Six hundred twenty-three IPF patients with available QoL data (St George's Respiratory Questionnaire SGRQ, UCSD Shortness-of-Breath Questionnaire SoB, EuroQol visual analogue scale and index EQ-5D, Well-being Index WHO-5) were analysed. Mean age was  $69.6 \pm 8.7$  years, 77% were males, mean disease duration  $2.0 \pm 3.3$  years, FVC pred was  $67.5 \pm 17.8\%$ , DL<sub>CO</sub> pred  $35.6 \pm 17\%$ .

**Results:** Mean points were SGRQ total 48.3, UCSD SoB 47.8, EQ-5D VAS 66.8, and WHO-5 13.9. These instruments had a high or very high correlation (exception WHO-5 to EQ-5D VAS with moderate correlation). On bivariate analysis, QoL by SGRQ total was statistically significantly associated with clinical symptoms (NYHA;  $p < 0.001$ ), number of comorbidities ( $p < 0.05$ ), hospitalisation rate ( $p < 0.01$ ) and disease severity (as measured by GAP score, CPI, FVC and 6-min walk test;  $p < 0.05$  each). Multivariate analyses showed a significant association between QoL (by SGRQ total) and IPF duration, FVC, age, NYHA class and indication for long-term oxygen treatment.

**Conclusions:** Overall, IPF patients under real-life conditions have lower QoL compared to those in clinical studies. There is a meaningful relationship between QoL and various patient characteristics.

**Trial registration:** The INSIGHTS-IPF registry is registered at Clinicaltrials.gov (NCT01695408).

**Keywords:** Patient related outcomes, Psychometrics, Idiopathic pulmonary fibrosis, Cohort study

## Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial lung disease associated with a high symptom burden, significant comorbidities and early death [1–3]. Median survival is 3–5-years, shorter than for many malignancies [4]. The antifibrotic drugs, pirfenidone

and nintedanib, slow lung function decline but have not been convincingly shown to improve survival or quality of life (QoL) [5, 6]. Beside prolonging survival, major aims for IPF therapy include improving symptoms and QoL domains like physical functioning, social participation and emotional well-being [7].

A number of patient-reported outcome (PRO) measures have been used in IPF research [8]. However, the majority of PRO data were generated in single-center cohorts or controlled clinical trials, and there are very limited QoL response data from IPF patients collected under

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real-world conditions. Such data could be used to improve understanding of disease burden at the individual and group levels, to better discern response to therapeutic interventions and to plan for trials of novel therapies.

In the present study, we aimed to summarize QoL data collected in a nationwide, “real-world”, observational registry of patients with IPF and to examine associations between QoL and several other clinical variables.

## Methods

INSIGHTS-IPF (“Investigating significant health trends in idiopathic pulmonary fibrosis”) is an investigator-initiated, multicenter (19 centers from all parts of Germany), observational registry study of data collected, within the confines of routine clinical care, from patients with IPF since November 2012. The study materials were approved by the Ethics Committee of the Medical Faculty, Technical University of Dresden, and by further local ethic committees as per local requirements. INSIGHTS-IPF is registered at Clinicaltrials.gov (NCT01695408). The protocol [9, 10] and a detailed description of the baseline characteristics of the cohort [1] have been previously published. In brief, patients are eligible for enrolment if they are at least 18 years old, have IPF (definite, probable or possible, applying the 2011 IPF guideline [11]) based on physician diagnosis, and have provided written informed consent. There are no explicit exclusion criteria. Clinical data are collected at enrolment and thereafter at 6-month intervals. At follow-up visits, events such as hospitalization and acute exacerbation (as judged by the treating physician) are recorded. Data are reported via a secure internet based data collection form.

### Patient-reported outcome measures

Enrollees complete PROs at enrolment and yearly thereafter. PROs include the University of California San Diego Shortness of Breath Questionnaire (UCSD SOB), the St. George’s Respiratory Questionnaire (SGRQ), World Health Organization-5 Well-Being Index (WHO-5) and the EuroQol five-dimensional questionnaire (EQ-5D).

#### UCSD SOB

This questionnaire includes 24 items, each with a response scale 0 (Not at all) to 5 (Maximally or Unable to do because of breathlessness). The total score ranges from 0 to 120, with a higher score indicating more severe dyspnea [12, 13].

#### SGRQ

The SGRQ was originally developed for patients with chronic obstructive pulmonary disease or asthma [14], however, as a respiratory disease-specific instrument, it has frequently been used in IPF [15]. There are 50 items

divided into three components (symptoms, activity, and impacts). Scores for each component and a total score range from 0 (highest QoL) to 100 (poorest QoL).

#### WHO-5

The 5 items of the questionnaire tap mood, vitality, and general health. Each item is scored 0 to 5. The total ranges from 0 to 25, with higher scores connoting better well-being.

#### EQ-5D

The EQ-5D taps 5 domains (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and is commonly used in cost-utility evaluation. Based on domain scores, a sum utility score is calculated ranging from negative values (−0.59 worse than death) to 1 (perfect state). Respondents also rate their current health on a 20-cm vertical visual analogue scale (VAS) scored from 0 to 100 [16].

### Data collection and statistical analysis

Data were collected using an internet-based case report form (eCRF) with automated plausibility checks. On-site monitoring, with source data verification, was performed in the majority of centers (currently 70%).

Summary statistics were generated for baseline data. Pearson product-moment correlation coefficients and univariate linear regression were used to examine associations between variables. Backward selection was used to generate multivariable models using the following candidate variable: disease duration, long-term oxygen therapy, physician’s judgment on IPF behavior (stable, slowly or rapidly progressing), NYHA stage, duration since first symptoms in years, GAP index [17], number and type of comorbidities (left heart insufficiency, coronary heart disease (CHD), carotid stenosis, stroke, peripheral arterial disease, atrial fibrillation, deep venous thrombosis (DVT), pulmonary arterial embolism, pulmonary hypertension, arterial hypertension, reflux, diabetes mellitus, emphysema, lung cancer, obstructive sleep apnea, depression/depressive disorder, anxiety), 6-min walk distance, gender, hospitalization in last 12 months, pulmonary rehabilitation, and CPI. Standard errors and confidence intervals were estimated by the Huber White sandwich estimator to account for the clustering of patients within the study centers. Data were analyzed with STATA 12.1 (StataCorp LP. Stata Statistical Software: Release 12. College Station, TX, USA).

## Results

### Baseline characteristics

Data for QoL were available for 623 of a total of 737 patients (84.5%). Baseline characteristics are presented in Table 1. Patients mean age was  $69.6 \pm 8.7$  years, 77.2%

**Table 1** Baseline characteristics

Characteristic	Value
Male sex	481 (77.2%)
Age, years	69.6 ± 8.7
Body mass index, kg/m <sup>2</sup>	27.5 ± 4.1
Underweight	4 (0.6%)
Normal weight	167 (26.8%)
Overweight	305 (49.0%)
Obesity	147 (23.6%)
Age at first symptom onset, years	65.8 ± 10.1
Age at IPF diagnosis, years	67.6 ± 9.6
Duration since first symptoms, years	3.6 ± 4.0
Disease duration, years	2.0 ± 3.3
Disease duration of less than 6 months	242 (38.8%)
Smoking status	
Never	237 (38.0%)
Former	376 (60.4%)
Current	10 (1.6%)
Gastro-oesophageal reflux	192 (30.8%)
Emphysema	55 (8.8%)
Genetic predisposition	31 (5.0%)
Six-minute walk distance, meters	272.4 ± 196.1
% FVC	67.5 (±17.8)
% FEV <sub>1</sub>	75.3 (±19.4)
% DL <sub>CO</sub>	35.6 (±17.0)
Long term oxygen use	201 (32.3%)
GAP index	
Stage I	87 (20.2%)
Stage II	238 (55.2%)
Stage III	106 (24.6%)

Based on sample of patients with HrQoL data (n = 623). Values are n (%) or mean ± standard deviation

GAP Gender, Age, Physiology index

were male; all but one were Caucasian (99.7%). Their mean FVC was 67.5 ± 17.8% predicted and DLCO 35.6 ± 17% predicted. A comparison of baseline characteristics of the 623 patients with and 114 patients without available QoL data can be found in Additional file 1: Table S1.

Patients were treated with antifibrotic therapies (49.5%), oral glucocorticoids (23.7%); N-acetylcysteine (33.7%), and long-term O<sub>2</sub> therapy (32.3%). Most (90.0%) had definite IPF, 5% probable IPF, and 5% possible IPF. At enrolment, treating physicians rated IPF as stable in 36.3%, slowly progressing in 30.9% and rapidly progressing in 11.2%.

**PRO scores and their inter-correlations at enrolment**

Baseline values for PROs and their inter-correlations are shown in Table 2. According to the SGRQ, the greatest

impairment was in the activity component. Based on the WHO-5 index, 46.4% of the patients showed depressive symptoms.

**Associations between PRO scores and clinical variables at enrolment**

For the SGRQ, associations with various demographic and clinical characteristics of patients at baseline are shown in Fig. 1. Statistically significantly higher total SGRQ score (indicating reduced QoL) were associated with lower age (51.8 for patients ≤60 years versus 46.9 for patients >65 years), female gender (46.9 for male versus 53 for female), higher NYHA classes (compared to NYHA class I), longer duration of symptoms, higher CPI, lower %FVC, and higher GAP stage (Fig. 1). Correlations between QoL and %DLCO (EQ-5D: 0.28, *p* < 0.001; SGRQ: -0.26, *p* < 0.001; UCSD: -0.22, *p* < 0.001) or %FVC (EQ-5D: 0.33, *p* < 0.001; SGRQ: -0.40, *p* < 0.001; UCSD: -0.43, *p* < 0.001) were moderately strong. Patients without comorbidity had a mean SGRQ total score of 44; those with 2 comorbidities 47; and those with ≥4 comorbidities 59 (ANOVA, *p* < 0.001 for difference between groups) (Table 3). QoL was also significantly associated with some types of pharmacological and non-pharmacological therapies of patients with IPF (Table 4).

In multivariate models (Table 5), LTOT, GAP index (stage III), physician’s judgement (rapid progression), and NYHA class were independent predictors of EQ-5D VAS. The same variables (except for the GAP index) were associated with SGRQ total score.

Both the EQ-5D index and the EQ-5D TTO were statistically significantly associated with LOT, the 6-MWD and the NYHA functional class (II, III, and IV). The WHO-5 was associated with LOT, and NYHA class III and IV. Finally, the UCSD SoB was associated with LOT, and NYHA class and %FVC.

**Discussion**

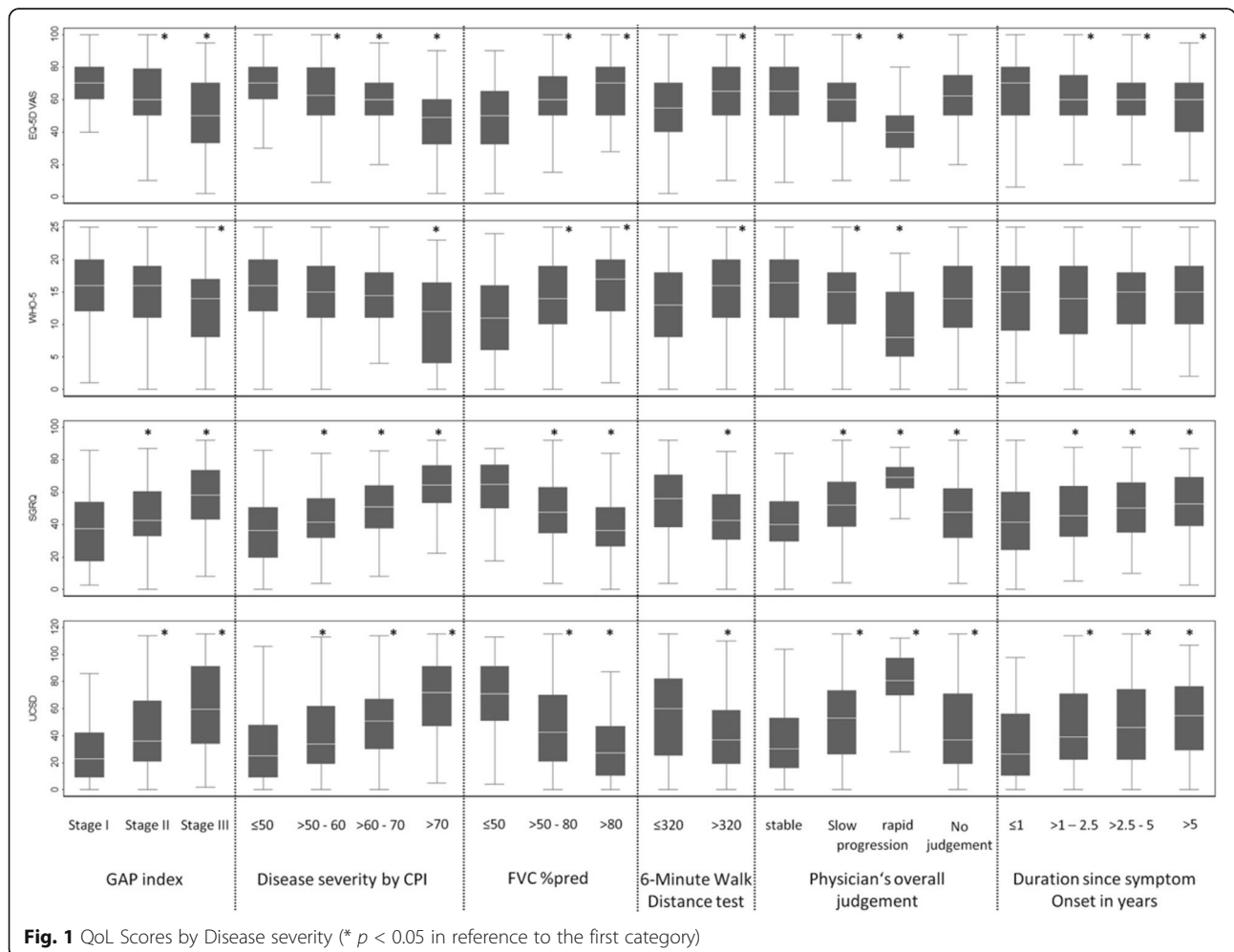
Idiopathic pulmonary fibrosis (IPF) is not only a severe life-shortening disease; it also significantly impairs patients’ quality of life. In this study, we present data from a large cohort of IPF patients. To our knowledge, this is one of the first-presentations of such data collected under real-world conditions. Overall, impairment in QoL and symptom burden were immense.

Compared to a very recent report from the Australian IPF registry, QoL impairment was very similar with a SGRQ total score of 46.6 (and 48.3 in our registry). Similarly, to the data presented here, an association between QoL and dyspnoea and physiological data were reported. Yet, in contrast to our analyses also cough and depression were major contributors to diminished QoL – reasons for this may be explained by different tools used to assess depression (HADS) and a structured

**Table 2** Correlations between different measures of QoL at baseline

	mean (SD)	EQ-5D VAS	EQ-5D Index	WHO-5	SGRQ total	SGRQ symptoms	SGRQ activity	SGRQ impacts	UCSD Shortness of breath
EQ5D VAS	60.0 (19.7)	1	0.62	0.56	-0.67	-0.51	-0.62	-0.63	-0.69
EQ5D Index	66.8 (21.3)		1	0.66	-0.70	-0.45	-0.65	-0.69	-0.73
WHO-5	13.9 (6.0)			1	-0.67	-0.47	-0.57	-0.67	-0.67
SGRQ	48.3 (20.7)				1	0.77	0.91	0.96	0.88
SGRQ symptoms	57.2 (21.2)					1	0.60	0.68	0.64
SGRQ activity	62.3 (24.2)						1	0.79	0.85
SGRQ impacts	37.9 (21.8)							1	0.83
UCSD Shortness of breath	47.8 (31.2)								1

Green fields highlight very strong ( $r \geq 0.80$ ) or strong ( $r \geq 0.60-0.79$ ) correlations, yellow fields moderate ( $r = 0.30-0.59$ ) correlation



**Table 3** Association of QoL and comorbidities

N (%)	EQ-5D VAS		WHO-5		SGRQ total		UCSD	
	mean (SD)	Delta 95% CI p value	mean (SD)	Delta 95% CI p value	mean (SD)	Delta 95% CI p value	mean (SD)	Delta 95% CI p value
No comorbidity	151 (20.5%)	65.6 (20.0) (ref)	15.1 (5.6)	(ref)	44.1 (22.0)	(ref)	55.5 (21.7)	(ref)
One comorbidity disease	196 (26.6%)	61.5 (20.2) -4.05 (-8.65; 0.56) 0.085	14.5 (6.3)	-0.60 (-1.98; 0.78) 0.393	46.1 (21.1)	2.03 (-3.05; 7.11) 0.433	56.0 (21.6)	3.79 (-4.39; 11.96) 0.363
Two comorbidity diseases	184 (25.0%)	60.0 (19.1) -5.54 (-10.09; -0.99) 0.017	14.4 (5.5)	-0.70 (-2.02; 0.63) 0.305	46.8 (19.4)	2.78 (-2.18; 7.74) 0.271	55.8 (20.7)	9.08 (0.62; 17.54) 0.036
Three comorbidity diseases	116 (15.7%)	56.0 (17.9) -9.53 (-14.51; -4.55) <0.001	12.5 (6.1)	-2.61 (-4.23; -0.99) 0.002	52.9 (19.5)	8.80 (3.17; 14.44) 0.002	60.9 (21.7)	19.73 (10.59; 28.87) <0.001
≥Four comorbidity diseases	90 (12.2%)	50.9 (18.3) -14.66 (-20.18; -9.14) <0.001	10.6 (6.0)	-4.54 (-6.26; -2.82) <0.001	59.1 (16.7)	15.03 (9.40; 20.65) <0.001	61.4 (19.5)	31.36 (20.16; 42.57) <0.001
List of significant comorbidities		Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Atrial fibrillation, Pulmonary arterial embolism, Pulmonary hypertension, Arterial hypertension, Diabetes mellitus, Emphysema, Lung cancer, Depression, Anxiety	Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Atrial fibrillation, Pulmonary arterial embolism, Pulmonary hypertension, Arterial hypertension, Diabetes mellitus, Depression, Anxiety	Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Atrial fibrillation, Pulmonary arterial embolism, Pulmonary hypertension, Arterial hypertension, Diabetes mellitus, Depression, Anxiety	Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Pulmonary hypertension, Lung cancer, Depression, Anxiety	Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Pulmonary hypertension, Lung cancer, Depression, Anxiety	Left heart insufficiency, Coronary heart disease, Carotid stenosis/ Stroke, Pulmonary hypertension, Lung cancer, Depression, Anxiety	

95% CI 95% confidence interval, delta mean difference between the groups, ref. reference group, SD standard deviation

**Table 4** Association of QoL and therapy for IPF

	N (%)	mean (SD)	Delta 95% CI	p value	mean (SD)	Delta 95% CI	p value	mean (SD)	Delta 95% CI	p value	mean (SD)	Delta 95% CI	p value
<b>Antiinflammatory therapy<sup>a</sup></b>													
No	426 (57.8%)	63.6 (19.0)	(ref)		14.9 (5.9)	(ref)		43.9 (19.9)	(ref)		40.0 (27.9)	(ref)	
Yes	311 (42.2%)	55.4 (19.7)	-8.25 (-11.35; -5.15)	<0.001	12.6 (6.0)	-2.22 (-3.18; -1.25)	<0.001	53.7 (20.4)	9.84 (6.54; 13.13)	<0.001	57.6 (32.3)	17.55 (11.47; 23.62)	<0.001
<b>Antifibrotic therapy</b>													
No	372 (50.5%)	59.7 (20.9)	(ref)		14.0 (5.9)	(ref)		46.8 (21.7)	(ref)		46.2 (32.0)	(ref)	
Yes	365 (49.5%)	60.3 (18.4)	0.63 (-2.48; 3.74)	0.691	13.8 (6.2)	-0.19 (-1.17; 0.78)	0.698	49.9 (19.4)	3.05 (-0.29; 6.38)	0.074	49.4 (30.3)	3.13 (-3.04; 9.31)	0.319
<b>Long-term oxygen therapy</b>													
No	503 (68.3%)	65.8 (17.9)	(ref)		15.2 (5.7)	(ref)		42.0 (19.2)	(ref)		36.4 (27.3)	(ref)	
Yes	234 (31.8%)	47.8 (17.9)	-17.93 (-20.96; -14.90)	<0.001	11.1 (5.7)	-4.15 (-5.14; -3.17)	<0.001	61.2 (17.3)	19.18 (16.08; 22.28)	<0.001	71.2 (24.9)	34.83 (29.40; 40.25)	<0.001
<b>Other non-pharmacological therapy<sup>b</sup></b>													
No	721 (97.8%)	60.3 (19.7)	(ref)		14.0 (6.0)	(ref)		48.1 (20.6)	(ref)		47.5 (31.1)	(ref)	
Yes	16 (2.2%)	49.4 (19.1)	-10.86 (-20.35; -1.37)	0.025	10.3 (6.4)	-3.71 (-6.87; -0.54)	0.022	56.3 (23.0)	8.24 (-3.55; 20.04)	0.17	66.4 (30.5)	18.98 (-2.30; 40.25)	0.08
<b>Pulmonary rehabilitation</b>													
Unknown	219 (30.3%)	57.7 (20.5)	-4.04 (-7.57; -0.50)	0.025	13.5 (6.3)	-0.69 (-1.80; 0.42)	0.222	50.8 (21.2)	4.56 (0.78; 8.34)	0.018	52.8 (34.0)	8.32 (1.01; 15.63)	0.026
No	464 (64.3%)	61.8 (19.2)	(ref)		14.2 (6.0)	(ref)		46.3 (20.4)	(ref)		44.5 (29.7)	(ref)	
Yes	39 (5.4%)	51.5 (19.4)	-10.24 (-17.14; -3.33)	0.004	11.9 (5.3)	-2.25 (-4.20; -0.31)	0.023	60.7 (17.1)	14.42 (8.20; 20.64)	<0.001	67.2 (27.6)	22.63 (10.20; 35.06)	<0.001
<b>Reflux therapy</b>													
No	510 (69.2%)	61.8 (19.7)	(ref)		14.3 (6.0)	(ref)		46.4 (20.3)	(ref)		44.5 (30.2)	(ref)	
Yes	227 (30.8%)	56.1 (19.3)	-5.67 (-8.99; -2.34)	0.001	12.8 (5.9)	-1.53 (-2.57; -0.48)	0.004	52.7 (20.8)	6.31 (2.67; 9.94)	0.001	54.7 (32.1)	10.13 (3.45; 16.80)	0.003

<sup>a</sup>Daily oral glucocorticoids; 95% CI 95% confidence interval, delta mean difference between the groups, ref. reference group, SD standard deviation

<sup>b</sup>Other non-pharmacological therapy includes: flutter, physiotherapy, yoga, inhalation furosenid, breathing therapy, spinal exercise, tai chi, cardiac pacemaker

**Table 5** Predictors of QoL in stepwise multivariable linear regression analyses

	EQ-5D VAS		WHO-5		SGRQ		UCSD				
	Beta	95% CI p value	Beta	95% CI p value	Beta	95% CI p value	Beta	95% CI p value			
Age					0.28	0.05; 0.52	0.018				
Disease duration in months					0.07	0.02; 0.12	0.010				
GAP index											
Stage I	(ref)										
Stage II	-5.02	-10.78; 0.74	0.087								
Stage III	-12.24	-19.71; -4.78	0.001								
Physician's overall judgment											
Stable disease	(ref)		(ref)		(ref)						
Slow progression	-5.46	-12.48; 1.55	0.126	-0.42	-1.61; 0.76	0.484	2.59	-3.36; 8.54	0.392		
Rapid progression	-15.28	-25.42; -5.14	0.003	-2.74	-4.73; -0.75	0.007	9.06	1.35; 16.76	0.021		
No judgement possible	-5.43	-12.72; 1.86	0.144	-0.43	-1.68; 0.81	0.495	2.40	-3.98; 8.77	0.460		
Long-term oxygen therapy	-14.31	-20.66; -7.95	<0.001	-3.20	-4.32; -2.08	<0.001	7.42	1.74; 13.10	0.011		
NYHA functional class											
I	(ref)				(ref)		(ref)				
II	-8.52	-15.67; -1.37	0.020		12.85	5.76; 19.94	<0.001	15.78	7.55; 24.01	<0.001	
III	-7.40	-15.36; 0.55	0.068		21.05	13.06; 29.04	<0.001	28.96	18.96; 38.95	<0.001	
IV	-24.87	-37.41; -12.32	<0.001		29.63	19.32; 39.94	<0.001	38.49	22.48; 54.51	<0.001	
FVC %pred			0.04	0.01; 0.07	0.006	-0.21	-0.36; -0.06	0.005	-0.33	-0.57; -0.09	<0.001

Considered variables in stepwise multivariable linear regression analyses: Disease duration, FVC %pred, Long-term oxygen therapy, Age, Physician's overall judgment, NYHA stage, Duration since first symptoms, GAP index, No. of comorbidities, 6MWD, Sex, Hospitalisation in last 12 months, Pulmonary rehabilitation, CPI

tool to assess cough severity [18]. Another, yet retrospective very recently published cohort of 182 IPF patients reported an association between the SGRQ total score and overall survival [19]. In comparison to recently-completed, randomised controlled drug trials, the patients in our registry had more severe QoL impairment and a higher symptom burden. For example, in the two INPULSIS trials of nintedanib, which together included 1066 patients, the mean total SGRQ score was 39.4–39.8 points in the various arms [20]; it was 48.3 in our registry. The same is true of other drug trials for IPF: ambrisentan (492 subjects: mean SGRQ total 40.5–44.5) [21], interferon gamma-1b (826 subjects: 41.6–42.4) [22]. Similarly, mean UCSD dyspnea score was higher in this registry (47.8) than participants in recently conducted trials (e.g., the ASCEND trial on pirfenidone, 555 patients, mean UCSD 34.0–36.6 points). [23] Such differences in symptoms and QoL are likely explained by differences in disease severity and baseline characteristics. For example, in our real world cohort, the burden of comorbidities known to portend a worse prognosis in IPF [3] was not insignificant, with 322 (51.7%) of our registry enrollees having at least two comorbid conditions [1]. These patients would have been excluded from most drug trials.

To our knowledge, this is the first time, investigators have assessed the association between the presence of

specific comorbid conditions and QoL. We observed that comorbid conditions contribute greatly to QoL impairment. However, additional research is needed to determine if therapeutic targeting comorbidities will improve QoL in these patients. Although other investigators have assessed QoL in IPF patients under real-world conditions, they found no correlation between various baseline characteristics and QoL [24]. This may stem from a lack of power. In our cohort, SGRQ total score was higher in women than men, an observation noted by other investigators [25]. The reason for this difference is unknown but merits further investigation.

Like other investigators, we found that QoL was more impaired in patients on LTOT than in those not on LTOT. In fact, LTOT was an independent predictor of QoL even with adjustment for disease severity [24, 26]. This likely stems from the real and perceived constraints LTOT places on patients [27]. QoL impairment was also greater among patients who were prescribed anti-inflammatory therapy, anti-reflux therapy and other non-pharmacological interventions. In this observational study, causation cannot be discerned, and more research is needed to improve understanding of these results.

In several studies, investigators reported correlation coefficients between the SGRQ and one or more other patient-related assessment of health related quality of life, health status or symptoms including the Borg Dyspnea Index

[26, 28], Cough Quality of Life Questionnaire [29], the Baseline Dyspnea Index [28, 30, 31], King's Brief Interstitial Lung Disease questionnaire, [32, 33] Dyspnea Score [34], Short-Form 36 Physical Component Summary [28], Dyspnea-12 [35], and UCSD SoB questionnaire [7] among others. Overall, there were moderate to strong correlation between the SGRQ total score and the total score of these instruments [15], thus supporting the validity of the SGRQ total to capture QoL in patients with IPF. It is reassuring that data from our study mirror results from these other studies. Like them, our results support the validity of the SGRQ (and the other instruments used in INSIGHTS) for use in IPF, including a large, real-world, German cohort. In future research, shorter questionnaires with longitudinal and cross-cultural validity should be developed for use in daily patient care [32, 33].

In IPF patients, a major challenge is how to improve QoL impairment. Currently, only sildenafil, pulmonary rehabilitation or specialized, multi-modality treatment programs may have a role [36–38]. Unfortunately, the two globally-approved anti-fibrotic drugs, nintedanib and pirfenidone, have not been shown to do so. Hopefully, ongoing development and research efforts will lead to therapeutic interventions that allow IPF patients to live better with the disease.

There are limitations to our study. The QoL assessment tools we used were not originally developed for IPF, but they do have data to support their validity in this disease. Instruments such as the K-BILD [32] or A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF-cA) [39] which were developed for patients with interstitial lung disease may have reflected impairments more precisely in our cohort. However, these instruments' psychometric properties have yet to be examined in German patients. Because all registry patients were being treated in specialized ILD centers, these results may not generalize to the larger IPF population. IPF was diagnosed at the participating centers according to current guidelines without undergoing another central MDT review which may explain some differences between the results reported here and clinical trial cohorts, although recent data suggest that experienced physicians are very accurate in diagnosing IPF [40]. Further, QoL data may have been biased in the cohort reported here as incident IPF patients were slightly underrepresented compared to patients without available HrQoL data. However, a strength of the INSIGHTS-IPF registry is that enrollees were prospectively and consecutively recruited, and it employs source data verification, statistical plausibility checks and queries.

## Conclusions

Health related quality of life is substantially impaired in patients with IPF, and drivers of this impairment include symptoms, comorbidities, LOT and disease severity.

While current treatments improve the course of the disease and perhaps survival, additional investigation is needed to identify interventions that durably to improve this important outcome in IPF patients.

## Additional file

**Additional file 1: Table S1.** Comparison of baseline characteristics of patients with and without available QoL data (total enrolled patients  $n = 737$ ). (DOCX 15 kb)

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## Availability of data and materials

All data generated or analysed for this manuscript are included in this published article.

## Authors' contributions

MK, JS, SG, JK, DP and JB analysed and interpreted the data. MK, DP, AP, JK, HuWi and JB are study steering committee members. All authors were involved in collecting the data, in writing the manuscript, and approved the final manuscript.

## Ethics approval and consent to participate

The study materials were approved by the Ethics Committee of the Medical Faculty, Technical University of Dresden (EK 255082012), and by further local ethic committees as per local requirements.

## Consent for publication

Not applicable.

## Competing interests

MK reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work; AP reports grants and personal fees from Roche/InterMune, grants and personal fees from Boehringer Ingelheim, outside the submitted work; HuWi reports personal fees from Boehringer Ingelheim, personal fees from Roche, outside the submitted work; MC reports personal fees from Boehringer Ingelheim Pharma GmbH, outside the submitted work; DP reports personal fees outside the submitted work from Actelion, Bayer, Boehringer Ingelheim, GSK, Novartis, and MSD.SV reports personal fees from Boehringer Ingelheim, personal fees from Roche Pharma, personal fees from Actelion Pharma, grants and personal fees from Novartis Pharma, personal fees from Berlin Chemie, personal fees from Astra, outside the submitted work; HeWi reports personal fees from Boehringer, personal fees from Roche, during the conduct of the study; personal fees from Bayer, personal fees from Biotest, personal fees from Actelion, personal fees from GSK, personal fees from Pfizer, outside the submitted work; CN Claus Neurohr reports honoraria for lectures and serving on advisory boards from Boehringer Ingelheim and Roche Pharma. SA reports case payments from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, personal fees from Roche, outside the submitted work. TW reports grants from Boehringer, during the conduct of the study; TB reports grants from German Center for Lung Research (DZL), personal fees from Roche, outside the submitted work; JB received grants from Boehringer Ingelheim, InterMune, and Actelion and personal fees for consultation or lectures from Actelion, Bayer, Boehringer-Ingelheim, InterMune and Roche. He is member of the international IPF guideline committee. All other authors declared that they have no competing interests.



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