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The St. George's Respiratory Questionnaire as a prognostic factor in IPF

Taiki Furukawa¹, Hiroyuki Taniguchi^{1*}, Masahiko Ando², Yasuhiro Kondoh¹, Kensuke Kataoka¹, Osamu Nishiyama³, Takeshi Johkoh⁴, Junya Fukuoka⁵, Koji Sakamoto⁶ and Yoshinori Hasegawa⁶

Abstract

Background: It is unclear whether health related quality of life (HRQL) may have a predictive value for mortality in idiopathic pulmonary fibrosis (IPF).

We investigated the relationship between HRQL assessed using the St. George's Respiratory Questionnaire (SGRQ) and survival time in patients with IPF, and tried to determine a clinical meaningful cut off value to predict poorer survival rates.

Methods: We retrospectively analyzed consecutive patients with IPF who underwent an initial evaluation from May 2007 to December 2012. The diagnosis of IPF was made according to the 2011 international consensus guidelines. We used Cox proportional hazard models to identify independent predictors for mortality rate in patients with IPF.

Results: We examined 182 eligible cases, average age was 66 years old, and 86% were male. Mean levels of percent predicted FVC, DLco, six-minute-walk test distance, and the SGRQ total score were around 80%, 58%, 580 m, and 34 points. On multivariate analysis, the SGRQ total score (hazard ratio [HR], 1.012; 95% confidence interval [CI] 1.001–1.023; $P = .029$) and percent predicted FVC (HR, 0.957; 95% CI 0.944–0.971, $P < .001$) were independent predictors for mortality rate. Moreover, a score higher than 30 points in the SGRQ total score showed higher mortality rate (HR, 2.047; 95% CI, 1.329–3.153; $P = .001$).

Conclusions: The SGRQ total score was one of independent prognostic factors in patients with IPF. Total scores higher than 30 points were associated with higher mortality rates.

Trial registration: This study was retrospective, observational study, so it is not applicable.

Keywords: Health related QoL, Idiopathic pulmonary fibrosis, Prognostic factors, The St. George's Respiratory Questionnaire

Background

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease characterized by chronic, progressive fibrosing interstitial pneumonia of unknown etiology [1]. As the disease condition progresses, dyspnoea on exertion becomes severe and health-related quality of life (HRQL) seriously deteriorates [2].

HRQL is a subjective and multidimensional appraisal that focuses on the impact of illness and treatment on physical, emotional, and social well-being [3]. HRQL tools can thus capture various information that physiologic or

radiologic measures cannot. Therefore, it has been considered to be one of the most important endpoints in pharmacological trials and rehabilitation for IPF [4, 5].

The St. George's Respiratory Questionnaire (SGRQ) is the most frequently used tool to measure HRQL. It was developed as a standardized, self-administered, disease-specific health status evaluation scale for patients with chronic obstructive disease [6]. The questionnaire consists of 50 items with 76 weighted responses that produce scores in three domains and one total score. The domains are symptoms (breathlessness, cough, and wheeze), activities (that are limited by the symptoms), and impacts (social and psychologic effect of the respiratory diseases). The score for each domain is calculated

* Correspondence: taniguchi@tosei.or.jp

¹Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan

Full list of author information is available at the end of the article



from 0 to 100, with higher scores corresponding to worse HRQL.

In patients with COPD, the SGRQ was shown to be a significant predictor of mortality [7, 8]. However, in patients with IPF, the relationship between HRQL assessed using the SGRQ and mortality has not fully been studied.

The aim of the present study was to investigate whether the SGRQ has a predictive value for mortality in IPF, including various dimensional clinical factors previously reported as prognostic factors, namely MMRC [9], % predicted FVC, % predicted DLco [1, 10–15], 6MWD, desaturation during 6MWT [13, 16–18], and BMI [19]. We also sought a clinically meaningful cut off value to predict poorer mortality rate.

Methods

Study subjects

Two-hundred and five consecutive patients with IPF, who underwent systemic initial evaluation from May 2007 to December 2012 at a center for respiratory diseases (Aichi, Japan), were identified from their medical records. The diagnosis of IPF was made according to the 2011 international consensus guidelines, and since 2011 the accuracy of the diagnosis has been confirmed by multidisciplinary discussion (MDD); however, some of the patients who initially presented before 2010 had been diagnosed based on different guidelines. The diagnosis for these patients was therefore confirmed according to the 2011 guidelines and MDD before May 2015 [1]. A thoracic radiologist with 27 years of experience re-read the chest high-resolution CT (HRCT) that had been obtained at the initial evaluation. This thoracic radiologist was blind to the clinical course and examination data for each patient.

Patients were excluded from the present study if there was clinical evidence of other known conditions, such as connective tissue disease, left heart failure, an occupational or environmental exposure that may result in interstitial lung disease, or a history of ingestion of an agent known to cause interstitial lung disease. Moreover, patients who had been prescribed medication for IPF (i.e. anti-fibrotic drug, corticosteroid, immunosuppressant), or who had undergone long-term oxygen therapy before initial evaluation at a center for respiratory diseases (Aichi, Japan) were also excluded. Finally, we examined 182 patients with IPF who were newly diagnosed. Of them, 55 patients who were in a clinical trial were enrolled. The present study was approved by a local institutional review board (IRB No. 509).

Data collection

Clinical data were retrospectively collected from a medical chart review. The eligible patients had undergone all of

the tests and assessments that were physical examination and assessment of physiological function, dyspnoea (modified Medical Research Council (MMRC) scale and Baseline Dyspnoea Index (BDI) score), exercise capacity (6-minute-walk test (6MWT) and desaturation during 6MWT), and HRQL, which was assessed using the SGRQ [6] at the initial evaluation. The Japanese version of the SGRQ has been previously validated [20].

All patients completed pulmonary function tests (PFTs) by spirometry (CHESTAC-55 V; Chest, Tokyo, Japan), according to the ATS/ERS criteria [21]. Diffusion capacity for carbon monoxide (DLco) was also measured (CHESTAC-55 V). The values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and DLco were measured according to the American Thoracic Society/European Respiratory Society recommendation [22]. The 6MWT was performed according to the ATS/ERS criteria [23]. The duration from initial evaluation to the last attendance or death was recorded. We analyzed censored cases by calling them to confirm their life-or-death status.

Statistical analysis

We performed all analyses by using SPSS (version 22; Chicago, IL, USA). Clinical variables were used as continuous variables, except that the categorical variables of gender, smoking status, and a history of surgical lung biopsy were coded as one or zero for the analyses. Continuous variables were presented as mean \pm standard deviation unless otherwise stated. Categorical variables were reported as counts and percentages. The survival time was calculated with the life table method. We performed univariate and multivariate Cox proportional hazards analyses to investigate the relationships between clinical variables and mortality rate with adjustment for age and gender. Results of Cox proportional hazards analyses were presented in terms of estimated hazard ratios (HRs) with corresponding 95% confidence intervals (CI); *p* values of less than 0.05 were considered to be statistically significant. In order to select final prognostic predictors in multivariate analysis, all candidate predictors for which the *p*-value was < 0.1 on univariate analysis were included in a forward selection method, with a *p*-value of 0.05 used for final entry or removal. To avoid multicollinearity, some of the highly correlated variables were excluded on multivariate analysis if they had Pearson's correlation coefficients higher than 0.7. We performed a receiver operating characteristic (ROC) curve analysis to find an optimized cutoff value for 3-year survival prediction. Survival curves were estimated using the Kaplan–Meier method, and compared using the log-rank test across the higher and lower groups of the SGRQ total score.

Results

Patient characteristics

The characteristics of the study population are shown in Table 1. Average age was 65.6 years old, and 85.2% of the patients were male. Surgical lung biopsy was performed to diagnose IPF in 97 patients (53.3%). Median follow-up time was 36.1 months (interquartile range, 19.3 to 48.6 months), 12 cases were lost to follow-up, and 94 patients (51.6%) died within the follow-up times. MST was 48.3 months (95% CI, 43.5 to 53.1 months).

Baseline levels of clinical indices

Table 1 shows all variables we collected in the present study: mean levels of PaO₂, the pulmonary function test, exercise capacity, dyspnoea scale and HRQL score. Mean percent predicted FVC was 79.7%, mean percent predicted DLco was 58.2%. Mean score on the SGRQ total domain was 34.5 points and its distribution is shown in Fig. 1. The relationship between SGRQ and baseline physiological measures is shown in Additional file 1: Table S1. Comorbidities, especially diabetes and orthopedic disease, were

Table 1 Baseline characteristics of study population^a (N = 182)

Characteristic	
Age, y	65.6 ± 8.0
Male gender, N (%)	155 (85.2)
BMI, kg/m ²	24.0 ± 3.4
Ever smoking, N (%)	147 (81.9)
Surgical Lung Biopsy, N (%)	97 (53.3)
Arterial blood gas analysis	
PaO ₂ , mmHg	82.0 ± 11.6
Pulmonary function	
FVC, % predicted	79.7 ± 19.1
FEV ₁ / FVC	85.2 ± 7.5
DLco, % predicted (N = 179)	58.2 ± 20.1
Dyspnoea index	
MMRC (0/1/2/3/4)	51 / 74 / 41 / 15 / 1
BDI (N = 180)	8.9 ± 2.4
6MWT (N = 181)	
6MWD, m	580 ± 136
SpO ₂ nadir, %	82.8 ± 9.1
SGRQ score	
Symptom	44.2 ± 22.6
Activity	40.0 ± 26.1
Impact	27.7 ± 19.8
Total	34.5 ± 20.2

^aBMI body mass index, FVC % predicted percent predicted forced vital capacity; FEV₁ forced expiratory volume in the first second, DL_{CO} % predicted percent predicted diffusion capacity for carbon monoxide, PaO₂ partial pressure for oxygen, 6MWD 6-min walk distance, SpO₂ oxygen saturation by pulse oximetry
^aPlus-minus values are means ± SD

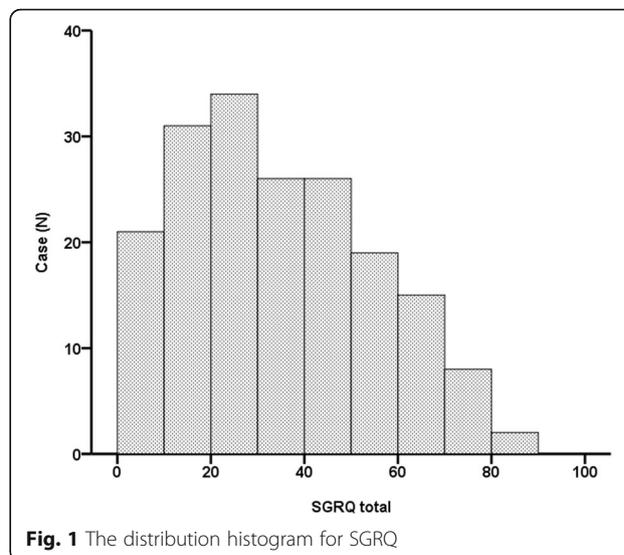


Fig. 1 The distribution histogram for SGRQ

related to SGRQ total score. However, they did not have predictive value for mortality with adjustment for age and gender (HR, 1.449; 95% CI 0.901–2.332, *P* = 0.13, HR, 0.748; 95% CI 0.325–1.720, *P* = 0.49, respectively) (Additional file 1: Table S2).

Correlation between baseline levels of clinical indices and mortality

On univariate analysis, all domain scores of the SGRQ showed significant predictive value for mortality (Table 2). Moreover, symptom, impact, and total domain showed significant predictive value for mortality with adjustment for age, gender, and %FVC model (Additional file 1: Table S3).

Table 2 Univariate Cox proportional-hazard analysis

Variables	Adjusted HRs (95% CI) ^a	<i>p</i> value
Age, y	1.005 (0.979–1.031)	0.72
Male gender	0.725 (0.394–1.334)	0.30
BMI, kg/m ²	0.882 (0.826–0.942)	<0.001
PaO ₂ , mmHg	0.978 (0.961–0.996)	0.014
FVC, % predicted	0.954 (0.941–0.967)	<0.001
DLco, % predicted	0.976 (0.964–0.989)	<0.001
MMRC	1.413 (1.14–1.753)	0.002
BDI	0.830 (0.764–0.903)	<0.001
6MWD, m	0.996 (0.994–0.998)	<0.001
SpO ₂ nadir, %	0.962 (0.944–0.98)	<0.001
SGRQ		
Symptom	1.019 (1.01–1.029)	<0.001
Activity	1.014 (1.006–1.022)	0.001
Impact	1.019 (1.009–1.029)	<0.001
Total	1.021 (1.011–1.032)	<0.001

^a; age, gender adjusted

Because the SGRQ total score included all domain scores of the SGRQ and there were high correlations between the total score and each domain score, we only used the SGRQ total score in multivariate analysis. Moreover, BDI was excluded from multivariate analysis because of its high correlation with MMRC. In multivariate analysis using a forward selection method, the SGRQ total score was an independent predictor for mortality (HR, 1.012; 95% CI, 1.001–1.023; $P = .029$), along with percent predicted FVC (HR, 0.957; 95% CI, 0.944–0.971; $P < .001$) (Table 3).

The ROC curve analysis for the 3-year mortality rate demonstrated that the most accurate and optimal cutoff value for the SGRQ total score was 30 points (area under the curve, 71.1%; 95% CI 62.8–79.4%; $P < .001$) (Fig. 2). MST was significantly shorter in patients with SGRQ total scores of over 30 points than in patients with scores under 30 points (MST, 37.7 vs 54.7 months. HR, 2.047; 95% CI, 1.329–3.153; $P = .001$) (Fig. 3).

Discussion

This is the first report to show that health status assessed using the SGRQ total score is an independent predictor of mortality in patients with IPF. Moreover, IPF patients with a SGRQ total score higher than 30 points had a higher mortality rate.

The SGRQ is widely used as an assessment tool for HRQL and is applied as one of the key endpoints in clinical trials in patients with IPF [24–29] and COPD [30–32]. However, the impact of HRQL (assessed using the SGRQ) on survival rate has not been fully studied in patients with IPF.

In the univariate analysis in this study, the SGRQ as well as various dimensional clinical factors previously reported as prognostic factors were significant predictors for mortality rate. However, the multivariate analyses showed that both the SGRQ as a patient-reported outcome and percent predicted FVC as a physiological indicator had superior capabilities as independent predictors of mortality than other widely known predictors. Baseline FVC has been reported to be a robust prognostic factor [12], and was recently included in a prognostic model [12]. The present study also shows that baseline FVC remains an important prognostic factor, and the SGRQ total score is an equally independent prognostic meaningful factor. This may be because the SGRQ is derived from multidimensional viewpoints of disease severity, and so may capture more comprehensive information than individual predictive variables.

Table 3 Multivariate Cox proportional-hazard analysis

Variables	Adjusted HRs (95% CI) ^a	p value
FVC, % predicted	0.957 (0.944–0.971)	<0.001
SGRQ total	1.012 (1.001–1.023)	0.029

^a; age, gender adjusted

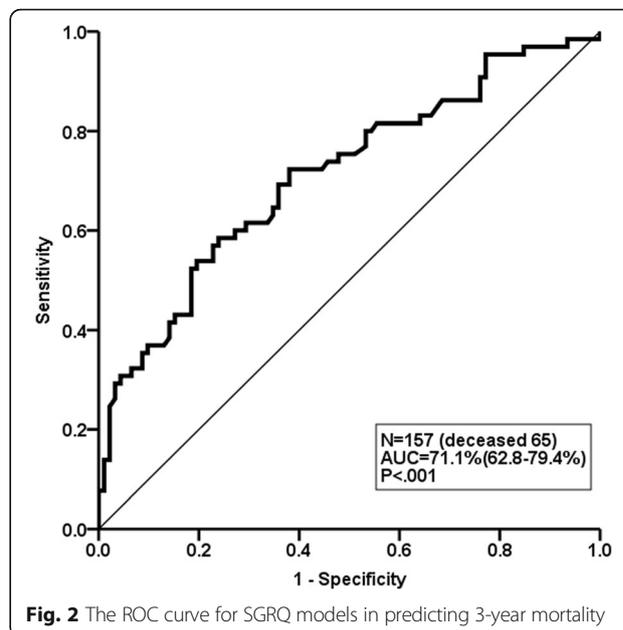


Fig. 2 The ROC curve for SGRQ models in predicting 3-year mortality

However, there has been no study on an appropriate cut off value for the SGRQ total score in predicting mortality in patients with IPF. We showed that patients with SGRQ total scores higher than 30 points had a remarkably higher mortality, with a hazard ratio of 2.047. In contrast to the present results, SGRQ was not a significant predictive value for mortality in a previously reported multivariate analysis [33]. The authors of that study examined a smaller sample size and made diagnoses from 2000 to 2005 based on 2000 guidelines that were different from the 2011 ones with a formal multidisciplinary discussion (MDD) used in the present study.

The mean value of the SGRQ total score was reported by Swigris and colleagues to be around 45 points with

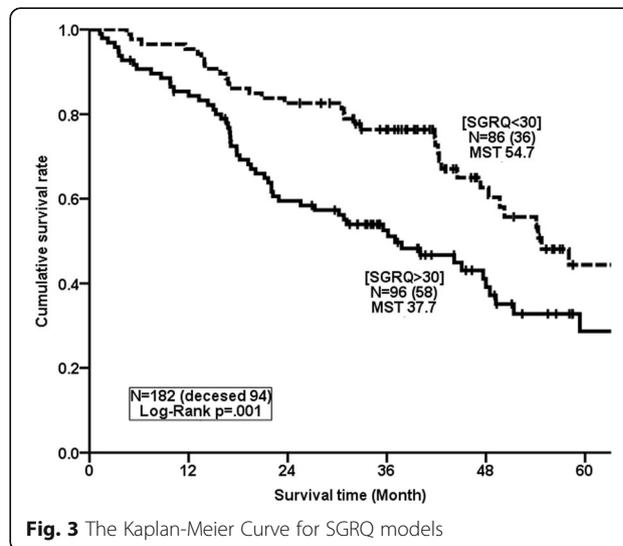


Fig. 3 The Kaplan-Meier Curve for SGRQ models

56.9–73.1% in FVC from a literature review [5], versus 34.5 points with 79.7% in FVC in the present study. Interestingly, the latest rigorous clinical trial of INPULSIS showed a SGRQ total score (39.6 points) and FVC (79.6%) closer to our findings. Considering the grave prognosis with a score higher than 30 points, these scores should be explicitly considered in the administration of anti-fibrotic drugs, even though FVC may be preserved.

Recently the importance of comorbidities in IPF was reported, however, the relationship between HRQL and comorbidity in IPF has not been fully examined. The present study showed that comorbidities, especially diabetes and orthopedic disease, were related to total score, however, they didn't have predictive value in age and gender adjusted models.

The present study had some limitations. First, this is a retrospective, single-centered study, and so there may be selection bias. Further large prospective studies will be needed to assess the relationship between the SGRQ and mortality rate. Next, because we examined mild to moderate cases, results may differ in a different cohort. Lastly, all the patients in the present study were Japanese, and it is unclear whether the findings will apply to people of different ethnicities.

Conclusion

The SGRQ total score was found to be an independent prognostic factor in patients with IPF, along with percent predicted FVC. Total scores higher than 30 points were associated with a higher mortality rate.

Additional file

Additional file 1: Table S1. Spearman's correlation coefficients between SGRQ and baseline physiological measures. **Table S2.** The relationship between SGRQ and comorbidities. **Table S3.** SGRQ domain as predictors for mortality. (DOCX 29 kb)

Abbreviations

6MWD: 6-min walk distance; 6MWT: 6-minute-walk test; BDI: Baseline Dyspnoea Index; CI: Confidence interval; DLco: Diffusion capacity for carbon monoxide; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; HR: Hazard ratio; HRQL: Health-related quality of life; IPF: Idiopathic pulmonary fibrosis; MMRC: Modified Medical Research Council; MST: Median survival time; ROC: Receiver operating characteristic; SGRQ: St. George's Respiratory Questionnaire

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Authors' contributions

HT is the guarantor of the paper and takes responsibility for the integrity of the work as a whole. YK, KK, ON, KS, and YH contributed to the study design, the analysis and interpretation of the data, and the writing of the paper. MA contributed to the analysis of the data and the writing of the paper. TJ and

JF contributed to the diagnosis of IPF as a radiologist and a pathologist respectively, the analysis and interpretation of the data, and the writing of the paper. All authors gave final approval for publication.

Competing interests

The authors have reported to the following conflicts of interest: *Furukawa T, Ando M, Kataoka K, Johkoh T, Fukuoka J, and Sakamoto K* have nothing to disclose; *Taniguchi H* reports personal fees from Shionogi & Co., Ltd., Nippon Boehringer Ingelheim, Asahi Kasei Pharma Corp., Bayer in Japan, Chugai Pharmaceutical Co., Ltd., GlaxoSmithKline plc., Ono Pharmaceutical Co., Ltd., TEIJIN PHARMA LIMITED, AstraZeneca K.K, DAIICHI SANKYO COMPANY, LIMITED, Eli Lilly Japan K.K, Novartis Pharma K.K, Fukuda Denshi Co., Ltd., TERUMO CORPORATION, TAIHO Pharmaceutical Co., Ltd., KYORIN Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Philips Respironics GK, Pfizer Japan Inc., ABBOTT JAPAN CO., LTD, NIPPON SHINYAKU CO.,LTD, Eisai Co., Ltd., MSD K.K., outside the submitted work; *Kondoh Y* reports personal fees from Shionogi & Co., Ltd., KYORIN Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim, TEIJIN PHARMA LIMITED, Novartis Pharma K.K, Eisai Co., Ltd., outside the submitted work; *Nishiyama O* reports personal fees from Boehringer Ingelheim, Shionogi & Co., LTD., outside the submitted work; *Hasegawa Y* reports grants and personal fees from Shionogi & Co., Ltd., Boehringer Ingelheim Japan, and Astellas Pharma Inc, outside the submitted work. These sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The present study was approved by a local institutional review board of Tosei General Hospital without the consent because of retrospective study (IRB No. 509).

Author details

¹Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan. ²Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8650, Japan. ³Department of Respiratory Medicine and Allergology, Kindai University, Faculty of Medicine, 377-2 Onohigashi, Osaka-sayama, Osaka 589-8511, Japan. ⁴Department of Radiology, Kinki Central Hospital of Mutual Aid Association of Public Health Teachers, 3-1 Kurumazuka, Itami, Hyougo 664-8533, Japan. ⁵Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Nagasaki 852-8501, Japan. ⁶Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.

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References

- Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King Jr TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schönemann HJ, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011; 183(6):788–824.
- Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, Wamboldt FS. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med.* 2010;104(2):296–304.
- Cella DF. Measuring quality of life in palliative care. *Semin Oncol.* 1995;22:73–81.
- Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology.* 2008;13(3):394–9.
- Swigris JJ, Esser D, Conoscenti CS, Brown KK. The psychometric properties of the St George's Respiratory Questionnaire (SGRQ) in patients with

- idiopathic pulmonary fibrosis: a literature review. *Health Qual Life Outcomes*. 2014;12:124.
6. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321–7.
 7. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, Khalaf A, Marrades RM, Monsó E, Serra-Batles J, Antó JM. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166(5):680–5.
 8. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med*. 2003;167(4):544–9.
 9. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Respir J*. 2010;36(5):1067–72.
 10. King Jr TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med*. 2001;164(7):1171–81.
 11. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Swartzberg J, Thomeer M, Valeyre D, King Jr TE. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;184(4):459–66.
 12. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King Jr TE, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med*. 2012;156(10):684–91.
 13. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174(6):659–64.
 14. Collard HR, King Jr TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003;168(5):538–42.
 15. Best AC, Meng J, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Idiopathic pulmonary fibrosis: physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. *Radiology*. 2008;246(3):935–40.
 16. du Bois RM, Albera C, Bradford WZ, Costabel U, Leff JA, Noble PW, Sahn SA, Valeyre D, Weycker D, King Jr TE. 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J*. 2014;43(5):1421–9.
 17. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. *Respir Med*. 2009;103(1):117–23.
 18. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch 3rd JP, Martinez FJ. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*. 2003;168(9):1084–90.
 19. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. *Chest*. 2007;131(5):1448–53.
 20. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157:785–90.
 21. Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. *Thorax*. 2006;61(9):744–6.
 22. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720–35.
 23. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–7.
 24. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klüglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*. 2011;365(12):1079–87.
 25. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071–82.
 26. Raghu G, King Jr TE, Behr J, Brown KK, du Bois RM, Leconte I, Roux S, Swigris J. Quality of life and dyspnoea in patients treated with bosentan for idiopathic pulmonary fibrosis (BILD-1). *Eur Respir J*. 2010;35(1):118–23.
 27. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, King Jr TE. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. Idiopathic Pulmonary Fibrosis Study Group. *N Engl J Med*. 2004;350(2):125–33.
 28. Han MK, Bach DS, Hagan PG, Yow E, Flaherty KR, Toews GB, Anstrom KJ, Martinez FJ, IPFnet Investigators. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. *Chest*. 2013;143(6):1699–708.
 29. Horton MR, Santopietro V, Mathew L, Horton KM, Polito AJ, Liu MC, Danoff SK, Lechtzin N. Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. *Ann Intern Med*. 2012;157(6):398–406.
 30. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, INDORSE Study Investigators. Long-term safety and efficacy of indacaterol, a long-acting β_2 -agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest*. 2011;140(1):68–75.
 31. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M, UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–54.
 32. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med*. 2008;177(1):19–26.
 33. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishimura K, Ogawa T, Watanabe F, Arizono S, Tohda Y. Health-related quality of life does not predict mortality in idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29(2):113–8.

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