SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2012; 29; 113-118

Health-related quality of life does not predict mortality in idiopathic pulmonary fibrosis

O. Nishiyama[1,3], H. Taniguchi[1], Y. Kondoh[1], T. Kimura[1], K. Kataoka[1], K. Nishimura[4], T. Ogawa[2], F. Watanabe[2], S. Arizono[2], Y. Tohda[3]

[1] Department of Respiratory Medicine and Allergy and [2] Department of Rehabilitation, Tosei General Hospital, Seto, Aichi, Japan; [3] Department of Respiratory Medicine and Allergology, Kinki University School of Medicine, Osaka-sayama, Osaka, Japan; [4] Department of Respiratory Medicine, Rakuwakai Otowa Hospital, Kyoto, Japan

Abstract. *Background:* Although health-related quality of life (HRQL) has recently been considered to be an important outcome in clinical trials of idiopathic pulmonary fibrosis (IPF), its relationship with survival is unknown. *Objective:* To determine the prognostic significance of HRQL scores in IPF assessed with the SGRQ. *Design:* Eighty-seven consecutive patients with IPF, who had undergone evaluations and completed the St. George's Respiratory Questionnaire (SGRQ) at diagnosis were included in this study, as is the general practice. Cox proportional hazards analyses were performed to examine the relationship between HRQL scores and survival. *Results:* The mean observation period was 44.2±29.6 mo, in the course of which 54 patients (62.0%) died. Univariate analysis revealed that the activity scores in the SGRQ (HR: 1.016, 95% CI: 1.004-1.029, P=0.01) were significantly predictive of survival, although the symptoms, impacts, and total scores were not significantly related to mortality from all causes. However, multivariate analysis revealed that only the forced vital capacity percent predicted was a significant predictor of survival, and that the activity score in the SGRQ was not significantly related to mortality. *Conclusions:* There was no significant relationship between HRQL evaluated with the SGRQ and the subsequent mortality in IPF. The present negative result might suggest that HRQL is measuring an aspect other than one from physiological and functional impairment or disability. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 113-118)*

Key words: health-related quality of life; idiopathic pulmonary fibrosis; mortality

Introduction

Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease and the most common entity of idiopathic interstitial pneumonia (1). Prevalence seems to be increasing since a recent report revealed a prevalence range from 17 to 28 cases per 100,000 people (2). The prognosis is poor, being roughly 3 to 4 years (3). However, no effective therapy has been developed. As the disease progresses, breathlessness becomes severe and the patient's activities of daily living often seriously deteriorate.

Quality of life or health-related quality of life (HRQL) in IPF patients is reported to be significantly associated with the degree of breathlessness in daily life (4). Therefore, HRQL gradually worsens as the disease progresses, since dyspnea is also progressive in IPF. Given that there is no effective therapy

Received: 7 February 2011
Accepted after Revision: 16 November 2011
Correspondence: Hiroyuki Taniguchi, MD
Department of Respiratory Medicine and Allergy,
Tosei General Hospital,
160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan.
Tel. +81-561-82-5101
Fax +81-561-82-9139.
E-mail address: taniguchi@tosei.or.jp

This work was supported by a grant-in-aid for interstitial lung diseases from the Japanese Ministry of Health and Welfare

which prolongs their length of survival, IPF patients greatly value their quality of life. Against such a background, IPF researchers are recently focusing on HRQL in IPF patients. However, therapies to improve HRQL in IPF patients have been very limited. No pharmacotherapy was reported to be effective in improving HRQL, with only pulmonary rehabilitation offering some hope (5, 6). However, given this growing emphasis and the great value that patients place on HRQL, it is imperative to understand and evaluate this outcome measure in IPF patients.

Evaluating HRQL is already recognized as one of pivotal outcomes in studies on chronic obstructive pulmonary disease (COPD). An HRQL score assessed using the St. George's Respiratory Questionnaire (SGRQ) (an instrument developed specifically for patients with chronic airflow obstruction including mainly COPD) is reportedly an independent variable predictive of survival in COPD (7, 8).

The SGRQ has also been validated in IPF (4) and is often used in many IPF clinical trials (9-14). An HRQL score assessed with the SGRQ is frequently used as a secondary outcome, although apparent positive results have yet to be obtained in pharmacologic studies. While HRQL is an important outcome in itself, it can be even more significant if HRQL scores predict survival in IPF. The present authors have hypothesized that HRQL score would predict mortality in patients with IPF, given that no reports have demonstrated the relationship between HRQL and survival. The purpose of this study was to determine the prognostic significance of HRQL scores in IPF assessed with the SGRQ.

Methods

Subjects

Eighty-seven consecutive IPF patients, who had undergone evaluations and completed the SGRQ at diagnosis (as is standard practice in Tosei General Hospital), were included in this study, covering the period from April 2000 to July 2005. A diagnosis of IPF was made in accordance with the ATS/ERS statement (1) using the following major criteria: a) exclusion of other known causes of interstitial lung disease; b) abnormal pulmonary function with restriction and impaired gas exchange; c) bibasilar reticular abnormalities on high-resolution computed tomography (HRCT); and d) transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis. Minor criteria included: a) age > 50 yr; b) insidious onset of otherwise unexplained dyspnea; c) duration of illness > 3 mo; and d) bibasilar inspiratory crackles. All the major and at least three of the four minor criteria had to be satisfied. For those with a surgical lung biospy specimen showing usual interstitial pneumonia (UIP), only the major criteria were considered relevant. Surgical lung biopsies were performed in 18 (19.4%) patients, and each pathological diagnosis of UIP was also based on the consensus statement (1). Patients were excluded if they exhibited any of the following: obvious COPD, collagen vascular disease, active coronary artery disease, or any other severe comorbid illness. All patients enrolled in the study were newly diagnosed with IPF and had not yet received any other treatment, such as corticosteroids or cytotoxic agents at the enrollment. Patients who were receiving long-term oxygen therapy at the time of enrollment were also excluded. Because this study is based on a retrospective analysis of clinically indicated studies of patients with IPF performed in our hospital, the informed consent requirement was waived. These patients comprised almost the same group as those previously reported (15). Approval for the use of these data was provided by our Institutional Review Board (approval number 232).

Pulmonary function tests

All patients underwent spirometry (CHESTAC-55V; Chest, Tokyo, Japan), according to the method described in the 1994 American Thoracic Society update (16). Single-breath diffusing capacity (DLco) was also measured (CHESTAC-55V; Chest, Tokyo, Japan). The values for forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and DLco were related to predicted values calculated using equations of the Japanese Society of Chest Disease (17).

Assessment of health-related quality of life

The SGRQ was used to assess health-related quality of life. The SGRQ score comprises three

component scores (symptoms, activity, and impacts) and a total score (18). Although the SGRQ was developed to assess health-related quality of life in COPD patients, it has also been used for assessments in IPF and has been considered validated (4, 19).

Statistical analysis

Continuous variables were summarized by the mean (±SD), while categorical variables were summarized by the actual number. As to the reasons for death, respiratory failure due to end-stage IPF and acute exacerbation of IPF were categorized as IPF deaths. Univariate Cox's proportional hazard models were used to examine the association of selected variables with survival. The multivariate Cox's proportional hazards model was then used among variables related to survival in the univariate model ($P<0.1$) so as to select more significant variables. The analyses were also performed on a subset of patients excluding those who expired for reasons other than IPF death. All tests were performed at a significance level of 0.05. Analyses were performed with the PASW statistical package ver.18 (SPSS Japan Inc., Tokyo, Japan).

Table 1. Baseline characteristics of 87 patients

Variable	Value
Age, y	66.3 (8.2)
Sex	
Male	77
Female	10
Height, cm	161.2 (7.3)
Body weight, kg	60.7 (11.6)
BMI	22.3 (3.6)
Smoking status	
Current	14
Former	56
Never	17
Baseline pulmonary function testing	
FVC, L	2.37 (0.67)
FVC, % predicted	75.0 (19.2)
FEV_1, L	1.94 (0.52)
FEV_1, % predicted	85.2 (21.7)
DLco, mL/min/mmHg	9.15 (3.96)
DLco, % predicted	56.2 (20.9)
Baseline arterial blood gas values	
PaO_2, mmHg	81.0 (12.0)
$PaCO_2$, mmHg	39.7 (5.4)
pH	7.42 (0.03)
Baseline SGRQ score	
Symptoms	45.0 (23.3)
Activity	48.0 (24.7)
Impacts	31.6 (20.7)
Total	39.0 (20.2)

Continuous variables are expressed as mean values with standard deviations in parentheses.
Definition of abbreviations: BMI: body mass index. FVC: forced vital capacity. FEV_1: forced expiratory volume in 1 second. DLco: diffusion capacity of carbon monoxide. PaO_2: partial pressure of oxygen. $PaCO_2$: partial pressure of carbon dioxide. SGRQ: St. George's Respiratory Questionnaire.

Results

The baseline characteristics of the 87 IPF patients are summarized in Table 1. The mean observation period was 44.2 mo (SD 29.6). During this observation period, a total of 54 patients (62.0%) died, 20 (23.0%) due to respiratory failure, 12 (13.8%) of acute exacerbation of IPF, 6 (6.9%) of cancer, 4 (4.6%) of pneumonia, 5 (5.7%) of other causes, and 7 (8.0%) of unknown causes.

Table 2 shows the results of a univariate Cox proportional hazards model performed to reveal the factors related to mortality. In this model, the FVC percent predicted (HR: 0.970, 95% CI: 0.954-0.987, P=0.0004), DLco percent predicted (HR: 0.982, 95% CI: 0.968-0.996, P=0.01), baseline PaO_2 (HR: 0.970, 95% CI: 0.946-0.996, P=0.02), and the activity score in the SGRQ (HR: 1.016, 95% CI: 1.004-1.029, P=0.01) were all revealed to be significantly predictive of survival. The symptoms, impacts, and total score among the SGRQ were not significantly related to mortality. When patients who had died of other than respiratory failure due to IPF were excluded from the analysis, the FVC percent predicted (HR: 0.962, 95% CI: 0.941-0.984, P=0.0006), DLco percent predicted (HR: 0.978, 95% CI: 0.961-0.995, P=0.01), and the activity score among the SGRQ (HR: 1.026, 95% CI: 1.009-1.043, P=0.003) were found to be significant predictors.

Table 3 shows the results of a multivariate Cox proportional hazards model performed to select more significant variables. In this model, only the FVC percent predicted was revealed to be a significant predictor of survival (HR: 0.975, 95% CI: 0.955-0.996, P=0.017). The activity score in the SGRQ was not significantly related to mortality. When patients who had died of other than IPF were excluded from the analysis, no significant variables were found.

Table 2. Results of univariate Cox proportional-hazard model.

Variable	Hazard Ratio	95% CI	*P* Value
For all deaths (n=87)			
Age	1.018	0.979 – 1.058	0.37
Smoking status			
Current	1.271	0.548 – 2.949	0.58
Former	1.048	0.511 – 2.148	0.90
BMI	0.959	0.878 – 1.046	0.34
FVC, % predicted	0.970	0.954 – 0.987	0.0004
DLco, % predicted	0.982	0.968 – 0.996	0.01
PaO_2, mmHg	0.970	0.946 – 0.996	0.02
SGRQ			
Total	1.008	0.994 – 1.023	0.25
Symptoms	1.006	0.994 – 1.018	0.36
Activity	1.016	1.004 – 1.029	0.01
Impacts	0.999	0.984 – 1.013	0.84
For IPF death (n=65)			
Age	1.000	0.956 – 1.046	0.99
Smoking status			
Current	1.530	0.485 – 4.829	0.47
Former	1.165	0.488 – 2.781	0.73
BMI	0.986	0.892 – 1.091	0.79
FVC, % predicted	0.962	0.941 – 0.984	0.0006
DLco, % predicted	0.978	0.961 – 0.995	0.01
PaO2, mmHg	0.969	0.938 – 1.001	0.06
SGRQ			
Total	1.017	0.999 – 1.036	0.06
Symptoms	1.009	0.994 – 1.024	0.24
Activity	1.026	1.009 – 1.043	0.003
Impacts	1.006	0.989 – 1.024	0.49

In the lower model, an analysis was performed excluding 22 patients who died of other than IPF death.
Hazard ratios in smoking status are in relation to never smokers.
Definition of abbreviations: BMI: body mass index. FVC: forced vital capacity. DLco: diffusion capacity of carbon monoxide. PaO_2: partial pressure of oxygen. SGRQ: St. George's Respiratory Questionnaire. CI: confidence interval.

Table 3. Results of multivariate Cox proportional-hazard model

Variable	Hazard Ratio	95% CI	*P* Value
For all deaths (n=87)			
FVC, % predicted	0.975	0.955 – 0.996	0.017
DLco, % predicted	1.000	0.983 – 1.017	0.96
PaO_2, mmHg	0.982	0.953 – 1.011	0.22
SGRQ			
Activity	1.008	0.995 – 1.021	0.24
For IPF death (n=65)			
FVC, % predicted	0.970	0.940– 1.001	0.06
DLco, % predicted	1.001	0.977 – 1.026	0.91
PaO_2, mmHg	0.990	0.950 – 1.032	0.63
SGRQ			
Activity	1.017	0.999 – 1.035	0.07

In the lower model, an analysis was performed excluding 22 patients who died of other than IPF death.
Definition of abbreviations: FVC: forced vital capacity. DLco: diffusion capacity of carbon monoxide. PaO_2: partial pressure of oxygen. SGRQ: St. George's Respiratory Questionnaire. CI: confidence interval.

Discussion

The purpose of the present study was to investigate the relationship between HRQL assessed with the SGRQ and the subsequent mortality in patients with IPF. It was demonstrated that the total score of the SGRQ was not a predictor of survival in the analysis of either all-cause or IPF mortality. In subdomains of the SGRQ, only the activity score was significantly related to survival in the univariate analysis of either all-cause or IPF mortality. However, this relationship was demonstrated to be weak, since the significance disappeared after adjusting with FVC, DLco, and PaO_2 in the multivariate analysis. Although baseline pulmonary function, diffusing capacity, and oxygenation had already been reported to predict survival in IPF (20), HRQL assessed with the SGRQ was unable to supersede them in the present study. The results were almost the same when the analysis was performed excluding patients who had died due to reasons other than IPF-related death. Although the results of the present study were negative, the information obtained is important, because, to our knowledge, this is the first study that revealed the relationship between the HRQL and survival in IPF.

HRQL has recently become an important outcome in clinical trials of IPF (9-14). Since there is still no therapy that has been confirmed to prolong survival, assessing and improving HRQL constitutes an important target in IPF treatment. HRQL is apparently a unique outcome apart from other physiologic parameters. Although daily dyspnea is a major contributing factor to HRQL in IPF (4, 21), various other aspects also play a role. For this reason, it is difficult to estimate HRQL in IPF from other physiological parameters such as FVC and DLco, and so HRQL should be evaluated individually. Because HRQL is a comprehensive aspect of IPF patients including functional impairments, disability, etc, the authors have hypothesized that HRQL might predict mortality. However, it was not proven to be predictive of survival in the present analysis. It is interesting to note that HRQL was not predictive of survival, although daily dyspnea reportedly predicts mortality (15). HRQL in IPF is mainly determined by daily dyspnea (4, 21). Thus, it can be easily supposed that HRQL can also predict mortality. Though the reason for this negative result is unknown, one possibility is that the SGRQ was originally developed for patients with obstructive lung disease. Although both IPF and COPD are chronic respiratory disorders, differences can exist because one is a restrictive while the other is an obstructive lung disease. If we develop a validated and useful IPF-specific questionnaire, the HRQL score could be made more sensitive and discriminative, and may also predict survival. The other possible reason is that HRQL represents a more comprehensive aspect of patients, since it apparently consists of various aspects other than physiological impairment such as pulmonary function, oxygenation, and exercise capacity. It is possible that HRQL has failed to be predictive of survival because of its characteristic mixture of several factors. In this context, it must also be said that HRQL should be measured independently in clinical studies and daily practice for patients with IPF.

Among the results of the present study, it was interesting to discover that only the activity score of the SGRQ predicted survival, though it was observed only in the univariate analysis of both all deaths and IPF deaths. The activity score is considered to be directly associated with the daily activity and performance of patients. Considering those results, it may be necessary in daily practice to put more emphasis on everyday activity of patients with IPF. However, this relationship between activity scores and survival was weak, since its significance disappeared in the multivariate analysis. Further studies are needed to clarify the importance of daily activity on mortality in IPF.

Some limitations should be mentioned. First, the majority of patients showed mild to moderate severity, in which mean FVC percent predicted was 75%. Patients who were receiving long-term oxygen therapy were excluded. Had more severe cases been included, the results might have been different. Second, HRQL was not measured using a disease-specific questionnaire for IPF as mentioned above. However, there is currently no disease-specific instrument developed exclusively for IPF. The SGRQ has been widely used in clinical trials for IPF and is recognized as validated for substitution (4, 19). More research is, however, needed to identify or design appropriate measurement instruments for patients with IPF. If a disease-specific questionnaire for IPF is eventually developed, the property of predicting

mortality using HRQL score should be re-evaluated. Finally, it may be that the present sample size was not large enough to reach statistical significance. A cohort with a larger sample is warranted to confirm the results.

Although the HRQL score did not predict survival in IPF patients in the present study, evaluating HRQL remains important. HRQL comprises several aspects of not only physiology but also emotions, functions, and activity in daily living. Therefore, even though its correlation with mortality is not significant, HRQL represents a more comprehensive aspect of patients with IPF. It can be said that, other than longevity, HRQL should be one of main outcomes in clinical trials and daily practice.

In conclusion, the present study demonstrated no significant relationship between HRQL evaluated with the SGRQ and subsequent mortality in IPF. The present negative results have shown that evaluation of HRQL means measuring more comprehensive and various aspects than physical and functional impairment or disability in IPF.

References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. Am J Respir Crit Care Med 2000; 161: 646-64.
2. Fernández Pérez ER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest 2010; 137: 129-37.
3. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 157: 199-203.
4. Nishiyama O, Taniguchi H, Kondoh Y, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? Respir Med 2005; 99: 408-14.
5. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax 2008; 63: 549-54.
6. Nishiyama O, Kondoh Y, Kimura T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology 2008; 13: 394-9.
7. Domingo-Salvany A, Lamarca R, Ferrer M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 166: 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: 544-9.
9. Raghu G, Brown KK, Bradford WZ, et al. Idiopathic Pulmonary Fibrosis Study Group. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004; 350: 125-33.
10. Demedts M, Behr J, Buhl R, et al. IFIGENIA Study Group. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005; 353: 2229-42.
11. King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008; 177: 75-81.
12. Raghu G, Brown KK, Costabel U, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med 2008; 178: 948-55.
13. King TE Jr, Albera C, Bradford WZ, et al. INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomized, placebo-controlled trial. Lancet 2009; 374: 222-8.
14. The Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010; 363: 620-8.
15. Nishiyama O, Taniguchi H, Kondoh Y, et al. A simple assessment of dyspnea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur Respir J 2010; 36: 1067-72.
16. Medical Section of the American Lung Association. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995; 152: 1107-36.
17. Guideline of respiratory function tests: spirometry, flow volume curve, diffusion capacity of the lung. Nihon Kokyuki Gakkai Zasshi 2004; Suppl: 1-56.
18. 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: 1321-7.
19. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. Chest 1999; 116: 1175-82.
20. King TE Jr, 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: 1171-81.
21. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax 2005; 60: 588-94.