

Research Article

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Disease-specific Severity Measures and Health-related Quality of Life in Idiopathic Pulmonary Fibrosis

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Abstract

Objective: To elucidate the correlation between two disease-specific severity measures (CPI, composite physiologic index; GAP, gender, age, lung physiology variables) and health-related quality of life in patients with idiopathic pulmonary fibrosis (IPF).

Methods: We used data from a previously reported observational cohort study using the Medical Outcome Study Short Form 36 (SF-36) for measuring health-related quality of life. Of the 44 patients with IPF who participated in the initial cross-sectional study, 32 patients participated in the follow-up study. The CPI and the GAP index were calculated at baseline and follow-up.

Results: In the cross-sectional study, the CPI only correlated with one SF-36 domain and the GAP index did not correlate with any of the SF-36 domains. In the current longitudinal study (the median follow-up; 14 months), there was a significant increase in both indices: Δ CPI = 11.5 (95% confidence interval; 6.8, 16.1) and Δ GAP index = 0.59 (95% confidence interval; 0.25, 0.93). Within-subject changes in the CPI and the GAP index were significantly correlated with those of 5 and 3 subscales of theSF-36, respectively. Declines in 4 subscales of theSF-36 were significantly more severe in subjects whose CPI increased by \geq 5 than in subjects whose CPI did not. Similarly, declines in 3 subscales were significantly more severe in subjects whose GAP stage increased than in subjects whose GAP stage did not.

Conclusion: Serial changes in the CPI and the GAP index may be useful to predict changes in the healthrelated quality of life of IPF patients.

Keywords: Idiopathic pulmonary fibrosis; IPF; Disease severity; Health-related quality of life; SF-36

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, lifethreatening, interstitial lung disease of unknown etiology. Symptoms, including cough and dyspnea, limit physical activity and reduce the patient's quality of life and independence. Currently there is no good evidence to support the routine use of any specific therapy in the management of IPF. While halting disease progression and improving survival have long been the focus of IPF treatment, improving quality of life is extremely important for many patients and is perhaps a more realistic goal at this time [1,2]. Health status and health-related quality of life (HRQL) are common research outcomes in patients with chronic pulmonary diseases. Our previous study [3] examined HRQL in IPF patients and showed that some clinical parameters, including those identified by physiologic evaluations such as vital capacity (as percent of predicted) or 6-min-walk distance, were significantly related to the HRQL scores in the cross-sectional study and changes in scores in the longitudinal study; however, the HRQL and its longitudinal changes were incompletely predicted by these clinical parameters.

There is an unmet need for an accurate noninvasive measure of severity of IPF. Specifically, methods are needed to assess and monitor disease status and to ultimately predict mortality and response to therapy. Although individual variables have been associated with mortality in IPF, none accurately predicts prognosis in isolation [4-6]. Predicting prognosis in patients with IPF is a challenge for clinicians. Wells et al. [7] developed a severity variable, the composite physiologic index (CPI) that reconciles functional severity and the global morphologic extent of IPF. The CPI, which does not require a full exercise test, is a more accurate prognostic determinant in IPF than an individual pulmonary function test. Ley et al. [8] developed the multidimensional GAP (gender, age, lung physiology variables) index and staging system and GAP calculator commonly used to measure clinical and physiologic variables for predicting mortality in IPF. The predictors included in that model are both simple to obtain and are multidimensional, incorporating clinical and physiologic variables.

Such composite or multidimensional indices as a single method of quantifying IPF are attractive from the viewpoint of HRQL. The reason is that HRQL instruments measure dimensions not fully estimated by usual clinical assessments. Whether there is a correlation between IPFspecific severity measures and HRQL has not been investigated. We hypothesized that the CPI or the GAP index would more closely reflect HRQL in patients with IPF than an individual physiologic test. To test this hypothesis, we used data from a previously reported observational cohort study [3] that used the most widely employed generic HRQL instrument, the Medical Outcome Study Short Form 36 (SF-36). The purpose of this study was to elucidate the correlation between these two composite/multidimensional indexes and HRQL in patients with IPF.

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Materials and Methods

Study subjects

We used data from a previously reported observational cohort study [3] in 44 patients who met the diagnostic criteria for IPF according to the international consensus statement published in 2000 [1]. Study subjects with IPF who were referred to, or followed at the outpatient pulmonary clinic of the Nishi-Kobe Medical Center, a 500bed teaching hospital, were recruited for the previous study. Subjects were excluded if they were 80 years of age or older or if they had an illness other than IPF that might have an impact on HRQL. In addition, since the CPI needed data on the diffusing capacity of the lung for carbon monoxide (DLco) [4], out of 46 patients in the original study we excluded two patients who could not perform the DLco test because of a severe reduction in lung volume.

Methods

Pulmonary function tests, including forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and DLco, and the 6-min walk test were performed as previously described [3]. The CPI was calculated according to the following formula [7]: 91.0-(0.65 \times percent predicted DLco)-(0.53 \times percent predicted FVC)+ (0.34 \times percent predicted FEV1). The GAP index was also calculated according to the formula previously described [8]; briefly, points were assigned for each variable of the scoring system as follows: gender [G]: Female; 0, Male; 1, age [A: \leq 60; 0, 61-65; 1, >65; 2, and two lung physiology variables [P]: FVC, % predicted: >75; 0, 50-75; 1, <50; 2, and DLco, % predicted: >55; 0, 36-55; 1, \leq 35; 2, cannot perform; 3]. The total point score was used to classify patients as stage I (0-3 points), stage II (4-5 points), or stage III (6-8 points). In both indices higher scores indicate more severe disease.

HRQL was assessed using the SF-36 Japanese test version as previously described [3]. The questionnaire consisted of 36 questions covering 8 health concepts: physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These 8 health components were scored separately and transformed to a 0-100 scale according to the guidelines [9]. An ascending scale was used for scoring, with higher scores indicating a better HRQL and lower scores a worse quality of life.

Those who were available more than one year later again underwent these studies under the same conditions. The same concentration of supplemental oxygen was used for both the baseline and repeated 6-min walk test. Informed consent was obtained from all participants, and the study protocol had the approval of the local ethics committee.

Statistical analysis

In the cross-sectional study, Spearman's rank correlation was used to examine the correlation between the transformed subscales of the SF-36 and the physiologic parameters measured. In the longitudinal study, changes in parameters are expressed as an absolute value from the initial study. Changes in the SF-36 transformed subscales and physiologic parameters were analyzed with a paired *t* test or Wilcoxon signed-rank test. Then Spearman's rank correlation was used to examine the correlation between changes in the transformed subscales and those of the parameters. Furthermore, the authors divided the patients into two groups based on changes in the CPI (i.e., subjects whose CPI increased by \geq 5 and subjects whose CPI did not) and changes in the GAP stage (i.e., subjects whose GAP stage increased and subjects whose GAP stage did not). Comparisons were made between each group and

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within-subject changes in each SF-36 domain using the Student's t-test or Wilcoxon signed-rank test. We adopted a cut-off point of 5 for the magnitude of CPI change because it was reported that an increase in CPI of at least 5 points over 6 or 12 months significantly predicted mortality and is, therefore, clinically relevant [10]. Significance was defined as P<0.05. All analyses were performed using JMP statistical software (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics of the patients (30 males, 14 females; age 55 to 79 y) are shown in Table 1. Of the 44 patients, at the time of the initial study, 7 were dependent on supplemental oxygen and 2 were being treated with prednisolone (25 mg/day and 2.5 mg/day, respectively). The CPI ranged from 16.7 to 70.2 (mean \pm SD, 40.1 \pm 12.9). The GAP total point score ranged from 1 to 7 (mean \pm SD, 3.6 \pm 1.3), and 23, 18, and 3 patients were classified as stage I, stage II, and stage III, respectively. Transformed scales of the 8 health components are presented in Table 2. Spearman correlation coefficients between each SF-36 domain and the CPI and GAP index as well as several physiologic indices at baseline are shown in Table 3. The CPI was only significantly correlated with physical function (ρ =-0.32, p<0.05) while the FVC as a percent of predicted was significantly correlated with 5 items on the SF-36. The GAP index did not correlate with any of the SF-36 domains. There were no significant differences in transformed scales of the 8 health components among GAP stages I, II and III (data not shown).

Of the 44 subjects who participated in the initial cross-sectional study, 32 patients (21 males) completed the follow-up study. Followup data were not available for the remaining 12 patients because of deathdue to respiratory failure (n=5) or gastrointestinal bleeding

Gender, Female / Male	14 / 30			
Age (years)	69.9 ± 5.9			
Duration of symptoms (months)	28.4 ± 26.7			
Pulmonary function tests				
FEV1 (% of predicted)	75.3 ± 15.1			
FVC (% of predicted)	72.8 ± 16.4			
DLco (% of predicted)	58.3 ± 18.2			
Six-min walk test				
Distance (m)	400 ± 105			
Lowest SaO2 (%)	91.0 ± 5.3			
Composite physiologic index	40.1 ± 12.9			
GAP index total point score	3.6 ± 1.3			

Plus-minus values are means ± SD.

DLco = carbon monoxide diffusing capacity GAP = gender, age, 2 lung physiology variables

Table 1: Baseline Characteristics of Patients (n= 44).

	Median	Interquartile Range	Minimum	Maximum
PF	77.5	55.0-85.0	25.0	95.0
RP	25.0	0-100	0	100
BP	63.0	41.3-96.0	11.0	100
GH	45.0	35.0-52.0	10.0	82.0
VT	47.5	35.0-65.0	10.0	95.0
SF	75.0	62.5-96.9	12.5	100
RE	16.7	0-100	0	100
MH	58.0	45.0-76.0	12.0	100

PF - physical function; RP - role-physical; BP - bodily pain; GH - general health; VT - vitality; SF - social functioning; RE - role-emotional; MH - mental health.

Table 2: Transformed Scales of the SF-36 Domains at Baseline (n=44).

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	PF	RP	BP	GH	VT	SF	RE	MH
FVC (% predicted)	0.37*	0.23	0.22	0.46†	0.20	0.33*	0.31*	0.37*
DLco (% predicted)	0.23	0.10	0.03	0.09	0.12	0.02	0.18	0.14
Six-min-walk distance (m)	0.65†	0.28	0.06	0.16	0.36*	0.11	0.12	0.17
Lowest SaO2 (%)	0.11	0.02	-0.01	0.27	-0.01	0.23	0.19	0.31*
Composite physiologic index	-0.32*	-0.18	-0.13	-0.23	-0.23	-0.14	-0.25	-0.25
GAP index total point score	-0.12	0.03	0.001	-0.07	0.01	0.003	-0.04	-0.15

See Table 1 and 2 for abbreviations

*P< 0.05. †P <0.01.





Figures show the number of patients that are represented in each line that overlie one another.

There was a significant increase in the composite physiologic index and the GAP index: Δ composite physiologic index = 11.5 (95 % CI; 6.8, 16.1, p<0.0001) and ΔGAP index = 0.59 (95 % CI; 0.25, 0.93, p = 0.0017).

Figure 1: Within-subject changes in the composite physiologic index and the GAP index at baseline and at follow up (N=32).

(n=1), being lost to follow-up (n=3) or the occurrence of other disorders (lung cancer, gastric cancer, and thrombocytopenic purpura, n=1, respectively). Periods from the initial study to the follow-up study were 12 to 31 months (median 14 months). Treatment newly begun during the follow-up period was as follows: corticosteroid (n=4) and aerosolized N-acetylcysteine (n=11). Although 4 patients developed the need for supplemental oxygen during the follow-up, all 4 underwent the 6-min-walk test without supplemental oxygen in the follow-up study. With regard to 5 patients in whom follow-up data were not available because of respiratory failure death, the CPI at baseline ranged from 43.9 to 70.0 and the GAP total point score at baseline ranged from 3 to 7.

There were significant increases from baseline data in both the CPI $(\Delta CPI = 11.5, 95\%$ confidence interval (CI), 6.8 to 16.1, P<0.0001) and GAP index (ΔGAP index = 0.59, 95% CI, 0.25, 0.93, p=0.002) (Figure 1). Classification of the GAP stage had worsened in 8 patients: stage I to II in 4 patients and stage II to III in 4 patients. The GAP stage was unchanged in the remaining 24 patients, indicating stability. Table 4 shows the correlations between changes in physiologic variables, the CPI, and the GAP index and changes in SF-36 domains. Withinsubject changes in the CPI were significantly correlated with changes in 5 items, i.e. physical function (P<0.001), bodily pain (P<0.005), general health (P<0.001), role-emotional (P<0.05) and mental health (P<0.05). Within-subject changes in the GAP index were significantly correlated with those in 3 subscales, i.e. physical function (P<0.05), bodily pain (P<0.01) and general health (P<0.01). With respect to physiological

Intern Med ISSN: 2165-8048 IME, an open access journal parameters, changes in FVC as a percent of predicted, in DLco as a percent of predicted, in the 6-min-walk distance and in the lowest SaO2 during the 6-min-walk were significantly correlated with changes in 4, 3, 4, and 2 items, respectively.

When within-subject changes in each SF-36 domain were compared between two subgroups divided according to the changes in the CPI, declines in physical function, bodily pain, general health and role-emotional were significantly more severe in subjects whose CPI increased by \geq 5 (worsening of the CPI) than in subjects whose CPI did not (stable CPI) (p<0.01, p<0.001, p<0.005, p<0.05, respectively) (Table 5). Similarly, declines in physical function, bodily pain, and vitality were significantly more severe in subjects with worsening of the GAP stage than in subjects with stable GAP stages (p<0.05, respectively) (Table 6).

Discussion

The main finding of this study is that although there were few correlations between the CPI and the GAP indexand HRQL in the cross-sectional study at baseline, serial changes in these two composite/ multidimensional indices significantly correlated with changes in some domains in the HRQL in the IPF patients. In addition, changes in these indices could discriminate between patients whose HRQL did or did not decline over time. To our knowledge, no study has elucidated the correlation between IPF-specific severity measures and HRQL. Our results suggest that serial changes in the CPI and the GAP index might predict changes in the HRQL of IPF patients.

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	ΔPF	ΔRP	ΔΒΡ	ΔGH	ΔVΤ	ΔSF	ΔRE	ΔΜΗ
ΔFVC (% predicted)	0.35*	0.08	0.41*	0.42*	0.45†	0.25	0.17	0.11
ΔDLco (% predicted)	0.59†	0.26	0.56†	0.48†	0.16	0.23	0.31	0.22
ΔSix-min-walk Distance (m)	0.35	0.14	0.49†	0.61†	0.42*	0.28	0.30	0.52†
ΔLowest SaO2 (%)	0.45*	-0.19	0.16	0.47†	0.14	0.32	-0.01	0.25
∆Composite physiologic index	-0.58†	-0.04	-0.52†	-0.56†	-0.18	-0.16	-0.41*	-0.36*
ΔGAP index total point score	-0.45*	0.03	-0.54†	-0.48†	-0.33	-0.33	-0.26	-0.30

See Table 1 and 2 for abbreviations

*P <0.05. †P <0.01.

Table 4: Spearman Correlation Coefficients (p) between Within-subject Changes in SF-36 Domains and Changes in Physiologic Indices (n=32).

	Worsening of the CPI (n=24)	Stable CPI (n=8)	P value
ΔPF	-20.1 ± 19.0	2.2 ± 16.4	0.006
ΔRP	-8.3 ± 40.8	3.1 ± 54.2	0.53
ΔΒΡ	-22.8 ± 27.9	17.0 ± 19.0	0.001
ΔGH	-7.5 ± 14.1	10.4 ± 13.0	0.004
Δντ	-7.2 ± 19.4	-0.8 ± 28.2	0.48
ΔSF	-10.4 ± 22.0	-1.6 ± 27.9	0.36
ΔRE	-12.5 ± 44.8	41.7 ± 72.9	0.02
ΔΜΗ	-7.5 ± 17.9	-1.0 ± 15.7	0.37

See Table 1 and 2 for abbreviations.

Table 5: Comparison of within-subject Changes (mean \pm SD) in SF-36 Domains between Subjects Whose Composite Physiologic Index (CPI) Increased by \geq 5 (Worsening of the CPI) and Subjects Whose CPI Did Not (Stable CPI).

	Worsening of the GAP stage (n=8)	Stable GAP stage (n=24)	P value
ΔPF	-28.6 ± 22.7	-9.9 ± 18.0	0.04
ΔRP	-9.4 ± 44.2	-4.2 ± 44.6	0.87
ΔΒΡ	-33.5 ± 26.5	-6.0 ± 29.8	0.04
ΔGH	-12.4 ± 17.1	0.1 ± 14.3	0.06
ΔVT	-22.3 ± 19.4	-2.5 ± 19.6	0.02
ΔSF	-20.3 ± 26.7	-4.2 ± 21.4	0.10
ΔRE	-12.5 ± 46.9	5.6 ± 60.3	0.41
ΔΜΗ	-15.3 ± 24.7	-2.8 ± 13.3	0.15

See Table 1 and 2 for abbreviations.

 Table 6: Comparison of within-subject Changes (mean ± SD) in SF-36 Domains between Subjects Whose GAP stage Increased (Worsening of the GAP stage) and Subjects Whose GAP stage Did Not (Stable GAP stage).

The HRQL and its longitudinal changes are incompletely predicted by clinical parameters in isolation. In general, the results of pulmonary function testing (e.g., FVC, total lung capacity, and DLco) or other physiologic tests correlate with HRQL scores, but many of the correlations are not statistically significant and are not strong [3,11-16]. Therefore, our hypothesis was that a composite or multidimensional index would be a closer reflection of the HRQL in patients with IPF than an individual physiologic test. The present results of the crosssectional study suggested that, contrary to our hypothesis, these two indices were not useful in predicting impairment in HRQL of IPF patients because the CPI only correlated with one domain of the SF-36 and the GAP index correlated with no domain. Also, the SF-36 scores did not differ among patients according to GAP index stages. Classification of severity is essentially made based on the prognosis of the disease and the treatment response; however, it should reflect the HRQL of patients if possible. For example, it was demonstrated that the Global Initiative for Chronic Obstructive Pulmonary Disease (COPD) staging of severity corresponded to significant differences in the generic HRQL as assessed by EuroQoL five-dimension questionnaire (EQ-5D) scores [17].

On the other hand, serial changes in the CPI or the GAP index might be useful to predict changes in HRQL of IPF patients. In fact, serial changes in these two indices correlated significantly with changes in some domains of the HRQL of IPF patients. Especially, withinsubject changes in the CPI were significantly correlated with changes in 5 domains. Not only were there a greater number of items with a significant correlation, but also higher correlation coefficients were observed compared with individual physiologic tests. These findings indicate that this composite index is a more accurate determination of HRQL changes in IPF than individual pulmonary function testing. Serial changes in the GAP index only correlated significantly with three SF-36 domains, and the magnitude of those correlations was weak in comparison with those of the CPI. However, in the GAP index and staging system an indicator was created, not only for those who could do the DLco test, but also for those who could not [8]. The use of the GAP index would be more practical when the DLco test becomes impossible as the disease progresses.

Furthermore, serial changes in these indices could discriminate between patients whose HRQL over time did or did not decline. The minimal important differences in SF-36 scores have not been established for IPF, although ranges from 2-4 points were reported [18]. In the present study the magnitude of decreases in SF-36 scores in subjects whose CPI increased by \geq 5 and those in subjects with worsening of the GAP stage exceeded the threshold value of these points, suggesting that deterioration in both indices represents not only progressive disease severity but also specific deterioration in HRQL. The present study highlights that longitudinal changes in these two composite/multidimensional indices are important but imperfect predictors of HRQL changes. Although the longitudinal changes in these two indices covered almost all the physical function domains, changes in psychosocial domains were difficult to be predicted. Especially, within-subject changes in the GAP index were not significantly correlated with those of any psychosocial domain. From results of a longitudinal study to examine HRQL in IPF, it was reported that reductions in the emotional and psychosocial aspects of HRQL are not as apparent as those in physical health domains [3,15]. That indicates that an individual's adjustments to IPF would result in changes in the HRQL over time, which may address the question of whether changes in psychosocial domains were difficult to be predicted.

This study has some limitations. First, it was limited to one medical center, so the small sample size weakened the power of the study and limited the analysis and interpretation. Second, although a revised international statement has been published [19], in our study IPF was diagnosed on the basis of the previous international consensus statement [1]. The use of the new statement might have yielded different results. Third, although there are HRQL instruments that are either generic or disease-specific, we used only a generic questionnaire, the SF-36. In IPF, however, the SF-36 possesses reasonable validity for differentiating subjects whose disease severity changes over time equal that of the St. George Respiratory Questionnaire, a disease-specific although non-IPF respiratory disease-specific questionnaire [18]. Since the initial phase of our study some IPF-specific instruments have been developed [20,21], and such instruments, which include items most relevant to IPF patients, would have been ideal for evaluating the correlation between IPF severity and HRQL.

In conclusion, serial changes in the CPI and the GAP index may be useful to predict changes in HRQL of IPF patients. Although these IPFspecific severity measures are not satisfactory with respect to HRQL at one specific point, deteriorations in both indices may represent exacerbation of HRQL. Future research should study correlations between the CPI or the GAP index and IPF-specific HRQL instruments.

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