Dyspnea associates to a widely impaired quality of life in idiopathic pulmonary fibrosis patients: a longitudinal study using 15D

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Running Title:

QOL in IPF in terms of 15D

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Authors' Disclosure (Conflict of Interest) Statements

Harri Sintonen is the developer of the 15D and obtains royalties from its electronic versions. The other authors have no conflicts of interest to report.

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Key Words: idiopathic pulmonary fibrosis, interstitial lung disease, quality of life, 15D, MMRC, palliative care

Abstract

Background: Research on health-related quality-of-life (HRQoL) is crucial for developing comprehensive palliative care in idiopathic pulmonary fibrosis (IPF).

Objectives: To study IPF patients' HRQoL compared to general population and its association to dyspnea in a longitudinal follow-up.

Design: Assessment of IPF patients' HRQoL by a generic tool. Comparison of baseline data to the general population and a 30-month follow-up with six months intervals.

Setting/Subjects: 246 IPF patients were recruited from the Finnish nationwide real-life study, FinnishIPF.

Measurements: Modified Medical Research Council dyspnea scale (MMRC) for dyspnea and the generic HRQoL tool 15D for the total and dimensional HRQoL.

Results: At baseline, the mean 15D total score was lower (0.786, SD 0.116) in IPF patients compared to the general population (0.871, SD 0.043) ($p<0.001$) and among the IPF patients with MMRC$\geq$2 compared to the ones with MMRC$<$2 ($p<0.001$). In patients with MMRC$\geq$2, significant impairment compared to general population existed in 11 dimensions of HRQoL, such as breathing, usual activities, and sexual activity, while this was true in only four dimensions in MMRC$<$2 category. Mental function was not impaired in either group. During the follow-up, 15D total score decreased in both MMRC categories ($p<0.001$) but stayed constantly worse in the MMRC$\geq$2 group. Seven and two dimensions of HRQoL significantly declined in the categories of MMRC$<$2 and MMRC$\geq$2, respectively.

Conclusions: Patients with IPF, especially if dyspnea limits everyday life, suffer from widely impaired HRQoL, although self-assessed mental capability is preserved. Integrated palliative care is supported to face the multiple needs of IPF patients.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe interstitial lung disease (ILD) affecting mostly the elderly with few surviving beyond a few years from diagnosis. [1 2 3] The etiology of IPF remains unknown, but some risk factors such as smoking, environmental factors, and family history of IPF are acknowledged. [1 4] The disease trajectory is heterogeneous. [1 3] However, IPF leads to decreased lung function and worsened symptoms, especially cough and dyspnea. [1 3 5]

Antifibrotic medication (pirfenidone [6] and nintedanib [7]) slows down the progression of IPF and forced vital capacity (FVC) decline. [6 7] Only a small and select group of patients may benefit from lung transplantation. [8] As there is a lack of disease-modifying and curative therapies, an important goal of treatment is to maintain health-related quality of life (HRQoL) [9] by integrating comprehensive palliative care into the disease trajectories of patients. [10] Additionally, integrating palliative care approach at an early stage of the IPF disease can reduce the burden of the patients' carers. [11] However, despite this knowledge, only a minority of ILD patients are receiving adequate palliative care. [12 13 14] In order to improve the current situation and to find out the actual patient-centered needs for palliative care, knowledge of the HRQoL impairment and the most severely affected dimensions of HRQoL in a follow-up setting is needed. [15] Although previous studies have shown decreased HRQoL in IPF patients [16 17], only a limited number of studies have included a longitudinal follow-up. [18 19 20] Comparing HRQoL of IPF patients to that of the general population is crucial in understanding the impact of IPF on everyday life. Generic health-related questionnaires can provide information on HRQoL.[21 22 23] Previously, 15D has been shown to be a validated, comprehensive, generic, and relatively widely used HRQoL tool in many medical illnesses. [24] To our knowledge, the 15D has not been previously used in monitoring the HRQoL of IPF.

We hypothesized that IPF widely affects patients' HRQoL and that especially the symptom of dyspnea has a major role in HRQoL deterioration. By using 15D, we aimed to investigate HRQoL in patients with IPF according to the severity of breathlessness and compared these results with the general population. We also evaluated the longitudinal change in HRQoL during a 30-month follow-up period.

Materials and Methods

The patients were recruited from the FinnishIPF study, which is a nationwide, real-life follow-up study of IPF patients in Finland initiated in 2012. [25] The patients met the ATS/ERS 2011/2015/2018 diagnostic criteria [1 26 27] and had given a written informed consent to participate in the FinnishIPF study and an additional consent to participate in the questionnaire subcohort of the study.

The questionnaire subcohort of the FinnishIPF study was initiated in April 2015. An informed consent form and study questionnaires were sent to 300 patients registered in the FinnishIPF study. Of the 300 patients, 42 refused to participate, six did not have IPF, three had died, and two had received lung transplantation. Thus, at baseline, the final study population consisted of 247 patients. [17] After April 2015, follow-up questionnaires have been sent to study attendees every six months for a total duration of two and a half years (30 months). Hence, this study includes the analyses of questionnaires until November 2017.

Data collection

HRQoL was measured using the generic 15D instrument and the level of breathlessness by the modified Medical Research Council dyspnea scale (MMRC). Data on patients' sociodemographic factors, pulmonary function parameters, smoking history, comorbidities, and the diagnosis and death dates from electronic medical records and supplementary questionnaires were collected.

15D questionnaire

The 15D consists of 15 dimensions: breathing, mobility, usual activities, sexual activity, hearing, vision, excretion, sleeping, discomfort and symptoms, vitality, mental function, distress, depression, speech, and eating. [24] All dimensional questions have five choices from best to worst function. [24] The 15D is a comprehensive instrument providing a 15-dimensional profile and a single index score (15D score). [24]

The predefined set of utility or preference weights are used for calculating the total 15D score and the dimensional values from patients' self-rated answers. [24] The scale of total and dimensional scores ranges from 0 to 1. [24] One corresponds to the maximum level and an ideal state of HRQoL and 0 means 'dead'. [24] Up to three missing answers on the dimensions can be replaced reliably with a regression model with age, gender, and the rest of the dimensions as independent variables. [28] The minimal clinically important change or difference in the 15D score has been shown to be ± 0.015. [29]

At baseline, IPF patients' 15D results were compared to that of an age and gender-standardized sample of the general Finnish population (n=3598). These data were obtained from the Health 2011 Health Examination Survey. [30]

MMRC scale

MMRC (modified Medical Research Council) is a commonly used, self-assessed scale for evaluating the level of impairment on physical strain caused by dyspnea. [31] [32] The five levels of the MMRC scale are: 0: having dyspnea only with strenuous exercise; 1: having dyspnea only when hurrying on level ground or walking up a slight incline; 2: needing to walk slower than people of the same age due to dyspnea on level ground or needing to stop to catch their breath when walking on level ground at own pace; 3: needing to stop for breath after walking on level ground approximately 100 yards/meters or after a few minutes; 4: too breathless to leave home, or breathless when dressing/undressing. [31]

Statistical analysis

Descriptive data are presented as frequencies, percentages, means, standard deviations (SD), confidence intervals (CI), medians, and interquartile ranges (IQR). The statistical significance of differences between patient groups in the means of continuous variables was tested with an independent samples T-test. The normality of variables was assessed by Shapiro-Wilks's test and visual estimation. One-way repeated measures ANOVA (normally distributed variables) and Friedmann's test (non-normally distributed variables) were used to examine the longitudinal change in the 15D total and dimensional scores. P-values <0.01 were regarded as statistically significant. All our data analyses were performed with IBM SPSS Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical aspects

Authorization for screening patient records for the identification of patients suitable for the FinnishIPF study was obtained from the National Institute for Health and Welfare, Finland (THL amendment Dnro THL/568/5.05.00/2020 18.3.2020). A statement was received for the present quality-of-life sub-study by the Helsinki University Hospital ethical committee of Medicine (Dnro HUS 381/13/03/01/14 28.1.2015). Written informed consent was obtained from all participants.

Results

The patient characteristics are shown in Table 1. The median time from IPF diagnosis to the first study questionnaire was 3.4 years (IQR 2.2-5.2). Of the study participants, 24.7% (n=61) had no comorbidities, 29.6% (n=73) had one comorbidity, 21.5% (n=53) had two comorbidities, and 24.3% (n=60) had three or more comorbidities. By the end of the 2.5-year follow-up period, 42.9% (n=106) of patients had died or had received lung transplantation.

HRQoL at baseline

All but one patient (246/247) gave valid responses to the 15D questionnaire at baseline. For IPF patients, the mean total 15D score at baseline (0.786, SD 0.116) was lower than in the age and gender-standardized general population (0.871, SD 0.043, p<0.001). The difference also exceeded the minimal clinically important difference. [29]

At baseline, 232 patients answered the MMRC question and were divided into two categories: MMRC 0-1 and MMRC 2-4. The mean 15D profiles of all patients, MMRC 0-1 and MMRC 2-4 groups compared to those of the age and gender-standardized general population are shown in Figure 1. In MMRC 2-4 group the HRQoL was significantly worse compared to the general population on several dimensions (p<0.001 for breathing, depression, distress, sexual activity, vitality, mobility, discomfort and symptoms, and usual activities; p<0.01 for speech, eating, and vision). In MMRC 0-1 the mean 15D dimension scores were worse in breathing, vitality, distress, and depression (p<0.001 for breathing and vitality; p<0.01 for distress and depression) compared to the general population.

The mean 15D total scores were higher for IPF patients with MMRC 0-1 (mean of 0.858, SD 0.084, n=111) than in those with MMRC ≥2 (mean of 0.721, SD 0.104, n=121, p<0.001). Most of the 15D dimensions were impaired for IPF patients with MMRC 2-4 compared to those with MMRC 0-1 (p<0.001 for breathing, mobility, sexual activity, depression, vitality, mental function, usual activities, eating, and vision; p<0.01 for distress, discomfort and symptoms, and speech). The dimensions of sleeping, excretion, and hearing did not show a statistically significant difference.

Changes in the HRQoL during follow-up

A valid 15D total score at every time point was obtained from 97/126 patients who answered the MMRC question at baseline and participated in the study until the end of the follow-up. At baseline, 64 (66.0%) patients had MMRC level 0-1 and 33 (34.0%) MMRC level 2-4. The changes in the

mean 15D total scores during the follow-up in the two MMRC categories are presented in Figure 2. The mean 15D total scores decreased over the 2.5-year follow-up in both groups ($p<0.001$), and the difference between the two MMRC categories remained constant over the course of time.

The changes in mean dimensional 15D scores in patients with MMRC 0-1 and 2-4 during the 2.5-year follow-up are shown in Figure 3. In both MMRC categories, sexual activity and vitality showed a marked decrease longitudinally. In addition, dimensions of mobility, usual activities, breathing, depression, and distress declined in the MMRC 0-1 category.

Discussion

In this study we showed that IPF patients have a significant deterioration in most dimensions of HRQoL compared to the age and gender-standardized general population. A widespread impairment in HRQoL was pronounced in IPF patients with severe breathlessness (MMRC 2-4). During the follow-up, a deterioration of HRQoL was observed irrespectively of the baseline severity of the breathlessness. Our results underline the importance of comprehensive and early integrated palliative care for patients suffering from this progressive disease.

Impairment in breathing can be regarded as obvious since dyspnea is a common symptom in IPF. [1 27] However, our results showed how IPF could also be associated with vitality, depressive symptoms, anxiety, physical function, and ability to perform usual activities, especially when the disease progresses and exertional breathlessness increases. Our finding of low vitality is coherent with an earlier study by Bloem et al. [33] demonstrating the high level of fatigue in patients with IPF and another ILD (sarcoidosis). In that study, fatigue was associated with dyspnea, depression, and patients' functional ability. [33] Our group has previously shown that IPF symptom clusters correlate with vitality and respiratory and emotional factors, while physical functioning correlates more with respiratory factors. [34] Our results, as well as previous studies, [33 34] clearly indicate that the IPF disease seems to have a significant impact on day-to-day living and activities and psychosocial well-being. Hence, all patients with IPF, and especially those with more advanced disease and severe dyspnea (MMRC 2-4), need early integrated palliative care. Furthermore, palliative care should include psychosocial support and rehabilitative efforts to maintain the functionality of the patients. As the patients' access to palliative care services and the quality of dying and death

(QODD) are still worse in ILDs compared for instance to lung cancer, development of palliative care for IPF patients is of an urgent need. [35]

Interestingly, in this study the mental function of IPF patients exceeded the level of the general population. This finding indicates that IPF does not seem to harm subjectively assessed cognition (clear and logical thinking) and memory function. Thus, the capacity of IPF patients to participate in shared decision-making and discussions of advanced care planning (ACP) is probably maintained even in an advanced state of a disease. This is valuable knowledge to physicians as advanced care planning and shared decisions on goals of care are of utmost importance and highly recommended in recent guidelines. [10] In addition, this comforting message of sustained mental function should also be transferred to patients and their families. It has been recognized that IPF patients' caregivers are benefiting from discussions about advance care planning. [11] For instance, it facilitates them to target support to the patients' wishes and reduce their own psychological burden. [11] Therefore, our finding of patients' well-preserved mental capability should encourage palliative care specialists to arrange family meetings to facilitate beneficial communication on advance care planning and about the goals of therapy.

Furthermore, a notable and novel finding was the impairment of sexual capability among IPF patients with severe dyspnea compared to the general population. The reason for this is probably multifactorial, and to our knowledge, research on this topic is scarce. Sexuality is not commonly brought up in the palliative care guidelines of respiratory diseases. [10] However, our finding calls for further research to find out, for instance, whether offering sexual therapies during early palliative care interventions in IPF would be valuable.

Our findings with a generic HRQoL tool support the previous understanding that the level of breathlessness has a major impact on the HRQoL of IPF patients. [34] [36] In IPF patients who barely suffer from dyspnea according to the MMRC scale (level from 0 to 1), poorer results can be seen on only four (breathing, vitality, depression, and distress) out of 15 dimensions compared to the general population. In contrast, in the MMRC 2-4 group at baseline, impairment existed on as many as 11 out of 15 dimensions when compared to the general population. Our research group has previously shown that MMRC stage 2-4 is related to decreased HRQoL and an increased severity of symptoms, by using the instruments of RAND-36 and modified Edmonton symptom Assessment Scale (ESAS). [36] In line with our findings, in a multivariate analysis of the Australian IPF study, breathlessness had a strong association with impaired HRQoL status. [20] These results indicate that a patient's subjective estimate on the deteriorating status of one's own breathing triggers the

worsening of the HRQoL status on a broader scale. Therefore, the MMRC could be utilized as an easy-to-use tool for more comprehensive symptom and HRQoL assessment for IPF patients, which could, in turn, trigger a referral to a specialized palliative care consultation. [36]

In addition, the significance of impaired pulmonary function as a trigger for palliative care need is highlighted by a longitudinal German INSIGHTS-IPF registry study, which observed an association between poorer pulmonary function status at baseline and declined HRQoL at follow-up. [18] Furthermore, the markedly longitudinally worsening pulmonary function tests affected detrimentally to the HRQoL assessed with St. George's Respiratory Questionnaire (SGRQ). [18] In summary, recognizing the need for palliative care is crucial not only for patients with high MMRC score but also those with reduced pulmonary function levels.

Despite the level of breathlessness at baseline, HRQoL decreased among all IPF patients during the 2.5-year follow-up, especially in the areas of vitality and sexual activity. Additionally, we found that during the follow-up in the MMRC 0-1 group, the HRQoL worsened in mobility, breathing, usual activities, depression, and distress. In other words, a broad multidimensional failure of HRQoL in a 2.5-year follow-up also evolved for the patients who did not have a significant dyspnea impairment in the beginning. This calls for symptom and HRQoL follow-up in all IPF patients concomitantly with pulmonary function tests to face the palliative care needs beyond breathlessness. The previous longitudinal research on HRQoL have given us valuable knowledge, for instance, on IPF patients' survival. [18 20] We provide novel and detailed HRQoL data on the welfare of IPF patients using 15D adding to previous findings. To our knowledge, the available data on the comparison of both generic and disease-specific questionnaires are limited and, therefore, should constitute a part of future IPF-HRQoL research.

Our study has several strengths. This study has a long follow-up period and a consistently good response rate to our HRQoL survey. Furthermore, we assessed the HRQoL in IPF with a generic HRQoL assessment tool with real-life data. We gained novel information on the psychosocial and cognitive aspects of IPF, which are crucial for HRQoL. We had a holistic approach to HRQoL and were not concentrating on somatic (or respiratory) insights alone. This allowed us to show more widespread palliative care needs in patients with IPF.

Our study also had some limitations. We lacked data on pulmonary function in follow-ups. Thus, we could not investigate pulmonary function progression in relation to the HRQoL scores.

Additionally, some patients dropped out, even though the majority adhered to the study remarkably well.

Conclusions

IPF impairs HRQoL comprehensively. While dyspnea is a dominant and detrimental symptom in IPF, our results emphasize that IPF patients experience a more widespread impairment in HRQoL than previously thought but not in all areas of life. For instance, the patients' sexual well-being worsens significantly but IPF patients maintain their cognitive functions. Our results encourage advanced care planning (ACP) discussions and support early integrated palliative care for IPF patients to face their multiple needs falling beyond breathlessness.

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Figure Legends

Figure 1. The mean 15D profiles of idiopathic pulmonary fibrosis (IPF) patients compared to age and gender-standardized Finnish population; A: All IPF patients (n=246). B: IPF patients with modified Medical Research Council (MMRC) level of from 0 to 1 (n=111). C: IPF patients with MMRC level of from 2 to 4 (n=121).

Figure 2. Changes in 15D total scores (mean, confidence interval (CI)) in idiopathic pulmonary fibrosis patients divided at baseline into modified Medical Research Council (MMRC) categories 0-1 and 2-4. P-value < 0.001 for the change over time in both groups.

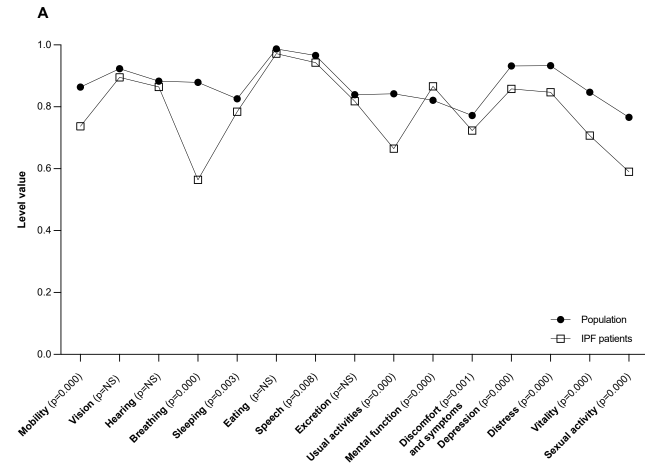
Figure 3. Idiopathic pulmonary fibrosis patients' 15D dimensional scores longitudinally; mean, confidence interval (CI).

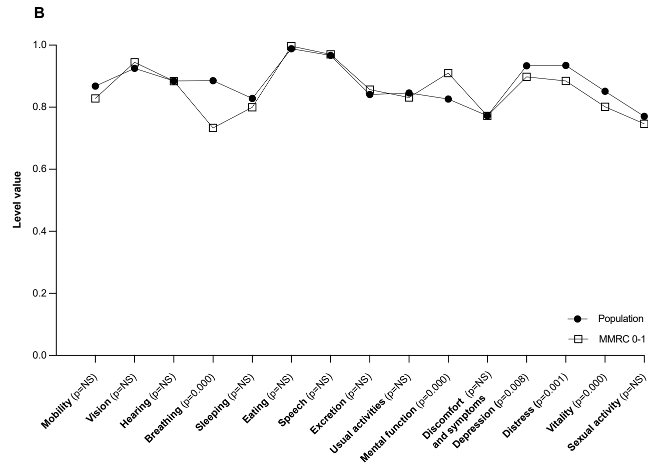
Table 1. Patient characteristics

	n (%) or mean (SD)
Number	247
Gender, females	84 (34.0%)
Age at baseline, years	74.3 (8.7)
Smoking [a]	
Never	117 (47.4%)
Before	106 (42.9%)
Current smoker	24 (9.7%)
Living, alone	69 (27.9%)
Comorbidities, number	1.57 (1.34)
MMRC [b]	
0	28 (12.0%)
1	83 (35.6%)
2	71 (30.5%)
3	34 (14.6%)
4	17 (7.3%)
15D total score [c]	0.786 (0.116)
FVC% [a d]	82.9 (17.0)
DLco% [a e]	60.0 (14.8)
Died or received lung transplantation before end of November 2017	106 (42.9%)

[a] values at the time of diagnosis
[b] answered, n=233 (94.3%)
[c] received answer, n=246 (99.6%)
[d] FVC% (forced vital capacity, % predicted), value not found, n=16 (6.5%)
[e] DLco% (diffusing capacity, % predicted), value not found, n=35 (14.2%)

Figure 1.





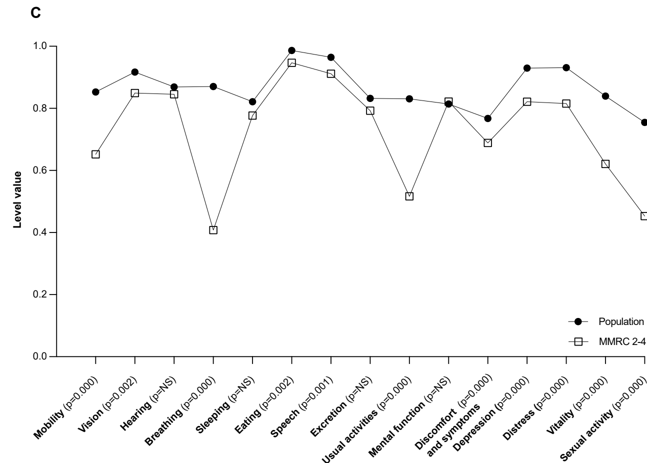


Figure 2.

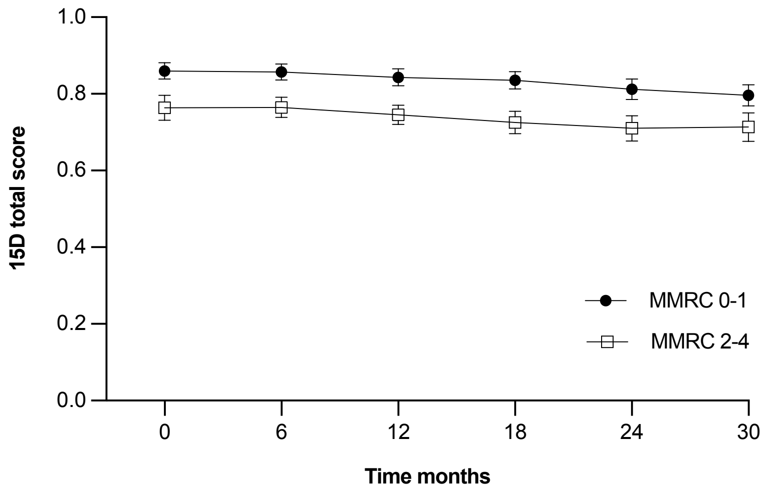


Figure 3.