Clinical Investigations

Respiration

Respiration 2015;90:460–467
DOI: 10.1159/000441302

Received: June 3, 2015
Accepted after revision: September 24, 2015
Published online: November 27, 2015

Self-Report Daily Life Activity as a Prognostic Marker of Idiopathic Pulmonary Fibrosis

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Key Words
Six-minute walk test · Dyspnea · Health-related quality of life · Idiopathic interstitial pneumonia · Idiopathic pulmonary fibrosis

Abstract
Background: Idiopathic pulmonary fibrosis (IPF) is a progressive disease, leading to substantial physical impairment. The distance walked in 6 min (6MWD) is a measure of exercise tolerance and is of prognostic relevance in IPF. While 6MWD is a punctual measurement which may not be representative, self-reported daily life activity may represent the patients' functional capacity more globally even in less severe affected patients. ***Objectives:*** We evaluated and characterized a simple classification system based on the patients' self-reported daily activity and analyzed if this would add significantly to the prognostic information of the 6MWD alone in IPF patients. ***Methods:*** Daily life activity was assessed in IPF (n = 156) patients with standardized questions and categorized in activity classes (AC I–IV), comprising the less severe impaired in AC I and II. The 6MWD was also assessed. ***Results:*** ACs were related to the lung functional impairment and inversely correlated to the 6MWD. Thirty-two patients were in AC I/II, 98 in AC III and 26 patients in AC IV. Thirty-seven (23.7%) patients died during a median follow-up of 14.9 months, comprising 1 patient in AC I/II. In addition, a 6MWD <470 m predicted mortality. Combining AC I/II and a 6MWD >470 m identified a subgroup of patients with favorable outcome. ***Conclusions:*** AC is a novel scoring system which can easily be obtained and correlates with lung functional and physical impairments as well as mortality. Moreover, AC adds prognostic information to the 6MWD.

Introduction

Idiopathic pulmonary fibrosis (IPF) is an incurable and progressive disease leading to respiratory insufficiency with consecutive functional impairment and death, usually within 3–5 years [1, 2]. Despite new therapeutic options, satisfactory medical therapies are lacking [3, 4], and lung transplantation remains the ultimate therapeutic alternative in selected patients [5, 6]. However, the clinical course and survival is widely variable and donor

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organs are limited [7]. Therefore, individual risk stratification has been attempted. This has mainly been based on scores that use and/or combine clinical and lung functional parameters, radiographic findings as well as exercise parameters [8–12].

Dyspnea and exercise limitation are the main complaints of patients with IPF, leading to reduced physical capacity and social activities. While exercise limitation may be multifactorial in the individual patient, it can be objectified measuring the distance walked during the 6-min walk test (6MWD) [13] which is of prognostic relevance in selected IPF patients evaluated for lung transplantation [14]. It remains unclear whether the 6MWD alleviates prognostication also in a population outside the transplantation window. In addition, the 6MWD is a point-in-time measurement and underlies considerable variability and, therefore, it could be questioned, whether additional prognostic information can be retrieved from a more general assessment of functional capacity.

Disease severity of IPF and comorbidities seem to have an impact on the average physical capacity of IPF patients in daily life. This could be especially true for those patients being less severely affected with regard to lung function or radiographic parameters. However, although it seems reasonable to quantify impairment of average daily life activities, a structured quantification of IPF patients' daily life activities has not been attempted so far.

We sought to characterize two easy-to-obtain parameters that reflect functional impairment in a singular (6MWD) and an average (daily life activity) fashion and relate these parameters to outcome in a nonpreselected cohort of IPF patients.

Therefore, we intended to define a prognostic threshold value of the 6MWD in a less advanced IPF population. Second, we sought to establish a simple classification of self-reported daily life activities and to relate this to mortality of IPF patients with a wide range of disease severity. Finally, we analyzed whether the combination of these two parameters provides additional prognostic information.

Methods

Patient Selection

In this prospective study, 156 consecutive IPF patients who were diagnosed in accordance to the ATS criteria [15] were included during their first visit to our tertiary referral center between March 2008 and March 2012. The diagnosis was based on histopathologic and radiographic findings in 90 patients and 66 patients solely had typical radiographic characteristics on high-resolution CT. All patients were evaluated for potential lung transplantation.

Patients with significant comorbidities that would significantly affect survival (such as malignant and/or significant cardiovascular disease) were excluded as were patients not being able to perform the 6-min walk test due to orthopedic reasons. Finally, patients (n = 13) with very advanced disease who were not able to perform basic personal hygiene as a minimum of inquired daily life activity were excluded.

Treatments at the time point of inclusion varied with an overlap between supportive care, no specific therapies, cortisone (usually prednisolone), high-dose acetylcysteine, azathioprine and cyclophosphamide. Since we did not perform a prospective treatment trial with predefined treatment regimen, we were not able to evaluate different therapeutic effects.

The study involved no specific interventions but a standardized protocol that reflected our clinical practice and was in accordance with our local ethic committee requirements.

Assessment of Activity Class

All patients were asked the following simple questions reflecting their functional capacity in daily life, such as: 'Are you able to perform basic personal hygiene?'; 'Are you able to perform light housework?'; 'Are you physically capable to work on a regular basis?', while the capability of performing all housework was scored equal; 'Are you able to participate in sports?', while manual labor that requires physical activity was considered equal.

When all 4 questions were affirmed, a patient was classified as daily activity class (AC) I, answering 3 questions with 'yes' qualified for AC II, 2 positive votes for AC III and the capability of performing personal hygiene was scored as AC IV. As mentioned above, patients who were not able to perform personal basic hygiene were excluded from the study. Assessment was done, before any supervised training or rehabilitation program was started (online suppl. fig. 1; see www.karger.com/doi/10.1159/000441302).

Six-Minute Walk Test

All patients conducted this test according to the ATS and supplemental oxygen was allowed for patients who were on long-term oxygen therapy (n = 99) [13].

Lung Function Test

Standard parameters, such as total lung capacity (TLC) and forced vital capacity (FVC) were measured with spirometry and body plethysmography from all patients. Blood gas analysis (without supplemental oxygen) was performed in arterialized capillary blood from the ear lobe. The diffusing capacity for carbon monoxide (D_{LCO}) was measured employing the single breath method (n = 138). All parameters included were calculated as percent of the individual predicted value [16].

Survival Estimates

The individual observation period began with the first examination/test and ended when the patient either died (n = 37) or received lung transplantation (n = 60). Those who received lung transplantation were included as 'alive' until the day of transplantation and censored thereafter. All nonsurvivors died of cardiorespiratory failure. No patient was lost to follow-up.

Statistical Analysis

Data are shown as mean and standard error of mean and/or median and 95% confidence interval (CI). Correlation analysis was

Table 1. Characteristics of ACs

	Study population (n = 156, 100%)	AC I (n = 2, 1.3%)	AC II (n = 30, 19.2%)	AC III (n = 98, 62.8%)	AC IV (n = 26, 16.7%)
Age, years	55.8±0.8	49.7±13.3	57.9±1.9	55.8±1.0	53.8±1.8
Weight, kg	74.4±1.6	66.0	82.0±4.2	73.1±2.0	77.8±3.3
Gender (m/f)	97/59	1/1	22/8	56/42	18/8
Lung function					
FVC, l	2.04±0.1	3.1±0.4	2.8±0.1***	1.9±0.1	1.5±0.1***
FVC, %	55.6±1.9	74.9±10.1	73.0±3.8***	54.1±2.4	39.3±2.3***
TLC, l	3.4±0.1	4.7±0.2	4.2±0.2***	3.2±0.1*	2.8±0.2**
TLC, %	55.7±1.4	72.0±3.6	67.1±3.2***	54.5±1.6	45.6±2.2***
D_{LCO}	2.9±0.1	6.6±0.7***	4.3±0.3***	2.4±0.1***	1.9±0.1***
D_{LCO}, %	31.8±1.4	67.6±11.3	47.9±3.0***	27.5±1.3***	20.6±1.7***
pO_2, mm Hg	56.0±1.0	75.0±8.0	67.4±3.2***	53.8±1.2*	49.3±2.6*
LTOT, n (%)	99	none	4 (13.3)	69 (70.4)	26 (100)
6MWD, m	331±12.2	545±25.3*	482±16.3***	323±12.1***	166±22.3***

LTOT = Long-term oxygen therapy. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Comparisons are performed between the study population and the respective AC.

performed using the Pearson or the Spearman rho procedure, according to the distribution of parameters. Depending on the normal distribution, a comparison between two groups was performed using Student's t test for unpaired samples or the Mann-Whitney U test, respectively. For a comparison of more than two groups, a one-way ANOVA test with Bonferroni correction for multiple testing was conducted.

The prognostic value of each variable was tested by univariate COX proportional hazards regression analysis followed by a stepwise multivariate analysis. Survival was derived from Kaplan-Meier curves. In general, a p value <0.05 was considered statistically significant. The software used for statistical calculation was SPSS 15.0 for Windows®.

Results

Characterization of Daily AC (Table 1)

Demographic data were equally distributed between the different ACs. Patients in ACs I and II had a limited disease with slight-to-moderate lung functional impairment and blood gases. The majority of patients were classified as AC III (63%). In this group, patients already had a severe restrictive impairment (FVC 54.1%pred) with a significant diffusion deficit (DLCO 27.5%) and hypoxemia at rest.

Overall, ACs were correlated with the lung functional impairment (AC vs. FVC %pred: r = –0.43, AC vs. TLC %pred: r = –0.4), diffusion capacity for carbon monoxide (AC vs. DLCO %pred: r = –0.6), hypoxemia (AC vs. pO_2: r = –0.59) and the 6MWD (AC vs. 6MWD: r = –0.67) (all $p < 0.001$). AC and age were not correlated.

Characteristics of Survivors versus Nonsurvivors and Lung Transplant Recipients (Tables 2, 3)

The overall mean observation time was 21.6 months (median 14.9; minimum 0.2, maximum 79.9).

Demographic data, lung function parameters and the 6MWD of the whole study population are included in table 2. Overall, patients had significant restrictive functional impairment, reduced DLCO and hypoxemia. Lung function was slightly less affected in the surviving patients. However, this did not reach statistical significance. Patients who died during the observational period received long-term oxygen therapy more often and the 6MWD was significantly lower. The distribution of AC between survivors and patients who died was not significantly different.

A comparison between patients who received lung transplantation during follow-up and those who did not revealed a significantly more severe lung function impairment and lower 6MWD.

AC and 6MWD as Predictors of Mortality

In the univariate analysis, a 6MWD <470 m and an AC >II were associated with a 2.9-fold (1.2–7.1) and 16.9-fold (2.3–123.6) mortality risk, during a median follow-up of 14.9 months. Independent of the AC, a 6MWD <470 m was still a predictor of mortality during multivariate analysis [hazard ratio 1.8 (1.1–4), $p < 0.05$].

In terms of a potential survival benefit, we calculated the hazard ratio for a 6MWD ≥470 m and an AC <III.

Table 2. Patient characteristics (including survivors vs. nonsurvivors)

	Study population (n = 156)	Survivors (n = 119, 76.3%)	Nonsurvivors (n = 37, 23.7%)	p value
Age, years	55.8±0.8	55.2±1.0	57.6±1.5	n.s.
Weight, kg	74.4±1.6	75.5±2.0	72.6±2.5	n.s.
Gender (m/f)	97/59	73/47	24/14	n.s.
Lung function				
FVC, l	2.0±0.1	2.1±0.1	1.8±0.1	n.s.
FVC, %	55.6±1.9	56.4±2.1	52.6±4.5	n.s.
TLC, l	3.4±0.1	3.5±0.1	3.2±0.2	n.s.
TLC, %	55.7±1.4	56.5±1.7	53.0 ±2.2	n.s.
TLCO	2.9±0.1	2.9±0.1	2.5±0.3	n.s.
TLCO, %	31.8±1.4	32.8±1.6	28.1±2.5	n.s.
pO_2, mm Hg	56.0±1.0	56.7±1.2	53.6±2.3	n.s.
LTOT, n (%)	99 (63.5)	68 (57.1)	31 (81.7)	
AC assessment				
AC I, n	2	2	0	
Mean observation time, months	39.2 [6.6–71.9]	39.2 [6.6–71.9]	n.a. [n.a.]	n.a.
AC II, n	30	29	1	
Mean observation time, months	34.2 [5.9–79.9]	35.2 [13.8–79.9]	5.9 [n.a.]	n.s.
AC III, n	98	73	25	
Mean observation time, months	19.9 [0.2–77.5]	21.3 [0.2–77.5]	15.8 [3–62]	n.s.
AC IV, n	26	15	11	
Mean observation time, months	11.8 [0.8–46.7]	13.4 [0.8–46.7]	9.2 [1.9–28.2]	n.s.
6MWD, m	331±11.7	350±12.8	271±25.2	<0.01

LTOT = Long-term oxygen therapy; n.a. = not available. Figures in square brackets indicate ranges.

While an AC <III alone was associated with a survival benefit [hazard ratio 0.06 (0.01–0.4), p < 0.01], a 6MWD ≥470 m was not associated with a statistically significant survival benefit. However, combining these two parameters revealed a significant survival benefit for those patients in AC <III who were able to walk ≥470 m during the walk test [n = 19, hazard ratio 0.1 (0.02–0.9); p < 0.05].

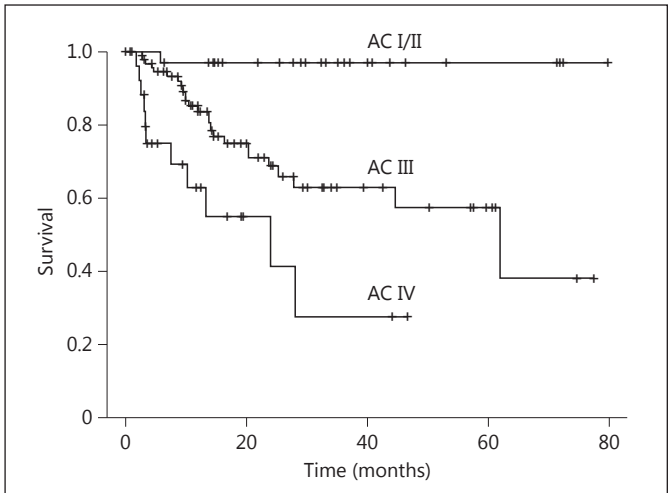
Survival Estimates

Survival Estimates Based on AC (Fig. 1). Thirty out of 156 patients (~19%) were classified as AC II. One patient died, resulting in an estimated mean survival time of 77.6 ± 2.3 months in this group. Ninety-eight patients (~63%) were in AC III with a mean survival time of 49.4 ± 4.6 months (median 62; 95% CI 32.6–91.4). Twenty-five (~25%) patients in this class died during the follow-up. Finally, AC IV comprised 26 patients (~17%) and 11 pa-

Table 3. Patient characteristics (including LTx vs. non-LTx)

	Study population (n = 156)	LTx (n = 60, 38.5%)	Non-LTx (n = 96, 61.5%)	p value
Age, years	55.8±0.8	51.2±1.0	58.6±1.0	n.s.
Weight, kg	74.4±1.6	77±2.4	72±2.1	n.s.
Gender (m/f)	97/59	37/22	60/37	n.s.
Lung function				
FVC, l	2.0±0.1	1.7±0.1	2.2±0.1	<0.001
FVC, %	55.6±1.9	43.9±2.0	62.9±2.6	<0.001
TLC, l	3.4±0.1	2.9±0.1	3.7±0.1	<0.001
TLC, %	55.7±1.4	47.5±1.9	60.9±1.7	<0.001
TLCO	2.9±0.1	2.4±0.2	3.1±0.2	<0.005
TLCO, %	31.8±1,4	25.8±1.8	35.6±1.8	<0.001
pO_2, mm Hg	56.0±1.0	51.7±1.6	58.6±1.3	<0.005
LTOT, n (%)	99 (63.5)	50 (84.7)	49 (50.5)	n.s.
6MWD, m	331±11.7	301±17.1	349±15.5	<0.05

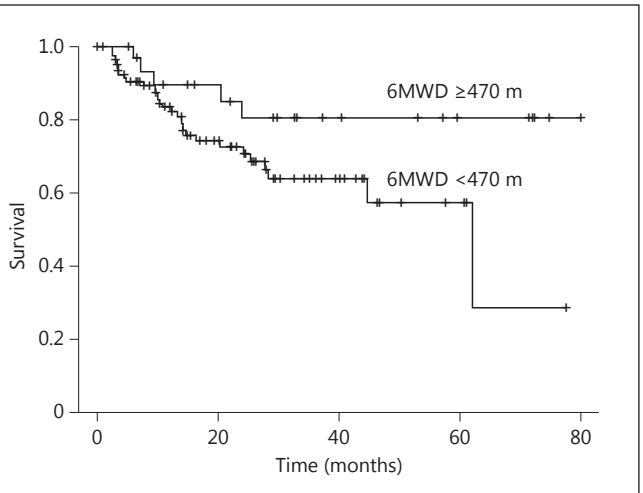
LTx = Lung transplantation; LTOT = long-term oxygen therapy.



Numbers at risk

	baseline	12 months	24 months	36 months	48 months	60 months	72 months
AC II	30	29	23	13	5	4	2
AC III	98	57	30	13	10	6	2
AC IV	26	9	4	2	0	0	0
Sum	154	95	57	28	15	10	4

Fig. 1. AC and overall survival in IPF. Impact of the functional classes on overall survival in IPF.



Numbers at risk

	baseline	12 months	24 months	36 months	48 months	60 months	72 months
6MWD ≥470 m	30	24	17	10	8	5	3
6MWD <470 m	126	73	40	18	7	5	1
Sum	156	97	57	28	15	10	4

Fig. 2. Six-min walk test and survival in IPF. Impact of a 6MWD cutoff value of 470 m on survival in IPF.

tients out of this group (~46%) died with a mean survival time of 22.9 ± 4.5 months (median 11.6; 95% CI 1.2–46.9). Comparison between groups revealed statistical significance ($p < 0.001$).

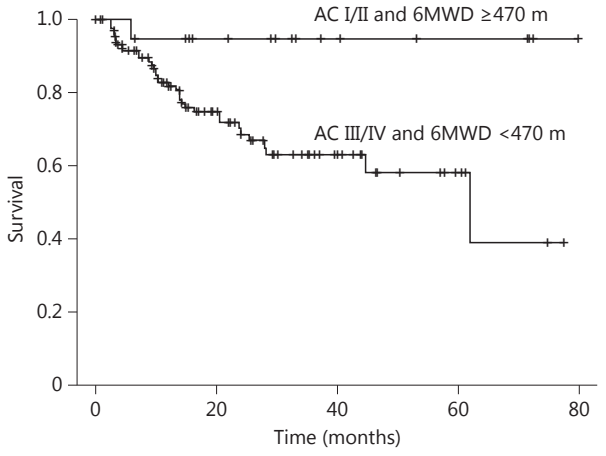
Survival Estimates Based on the 6MWD (Fig. 2). One hundred and twenty-six patients (~81%) had a 6MWD <470 m, while 30 patients performed better. Thirty-two patients (~25%) in the 6MWD <470 m group died during an estimated mean survival of 47.9 ± 4.6 (median 62; 95% CI 37.5–86.5) months, whereas only 5 patients (17%) of those who walked ≥470 m died with an estimated mean survival time of 67 ± 5.2 months ($p < 0.05$).

Survival Estimates Based on a Combination of AC and 6MWD (Fig. 3). A subgroup of 19 patients (~12%) in AC <III was able to perform a 6MWD ≥470 m. One patient out of this group died and the estimated mean survival was 76 ± 3.8 months. Thirty-six of the remaining 137 patients died with a mean survival time of 49.4 ± 4.1 months (median 62; 95% CI 33.1–90.9; $p < 0.05$).

Discussion

In this study, we propose AC as a novel classification of global functional impairment with prognostic relevance in IPF patients. AC comprises 4 classes (I–IV) based on the patients' self-reported daily life activity, including the less severe in AC I and the most severe in AC IV. AC is understood as a measure of the average physical performance status of patients with IPF, balancing daily fluctuations. Therefore, we characterize AC as a marker of disease severity and prognosis in a reasonable cohort of IPF patients. In addition, we observed that in a nonpreselected cohort a 6MWD below 470 m already identifies a subgroup of IPF patients with worse prognosis. The combination of both an AC <III and a 6MWD ≥470 m identified a subgroup of IPF patients with a favorable outcome.

Different tools for the risk stratification of IPF patients have been suggested including clinical, lung functional and radiographic data [1, 2, 10, 14]. However, variability of symptoms may have a negative impact on a single measurement of the 6MWD and may also influence physio-



	Numbers at risk						
	baseline	12 months	24 months	36 months	48 months	60 months	72 months
AC I/II and 6MWD >470 m	19	17	12	7	5	4	2
AC III/IV and 6MWD <470 m	137	80	45	21	10	6	2
Sum	156	97	57	28	15	10	4

Fig. 3. Combination of the AC and the 6MWD and its impact on survival in IPF. Impact of the AC and the 6MWD cutoff value of 470 m on survival in IPF.

logical measurements. Therefore, a marker that reflects average physical performance status could add significantly to a singular physiologic measure. Accordingly, AC was established to facilitate the assessment of the physical capabilities and disabilities and hence the functional status of these patients, averaging fluctuations. Thereby, AC includes not only dyspnea as a major complaint of IPF patients, but also integrates an additional aspect of the disease and, therefore, provides more information as compared to a dyspnea questionnaire or classification alone (e.g. NYHA class or MRC score). However, AC is not a replacement of valuable questionnaires for respiratory diseases, e.g. the St. George's Respiratory Questionnaire (SGRQ) [17, 18], which calculates 3 component scores out of 76 items, concerning symptoms, activity, and impacts (on daily life). This and other questionnaires have been used in clinical IPF trials [4, 19, 20]. However, implementation of such questionnaires into daily routine is often not feasible.

In contrast, AC is based on 4 standardized questions and the number of positive answers can simply be converted into 4 classes of daily life impairment (AC I–IV). In this current study, AC served as a marker of disease severity of IPF and had a good (inverse) correlation with lung functional parameters and the 6MWD. Moreover, patients in AC III or IV had a worse observed outcome as compared to those in AC I or II. Finally, when AC I or II patients were able to walk ≥470 m, this indicated an additional survival benefit. Although intuitively we cannot demonstrate that keeping or reestablishing functional capacity (i.e. AC I or II) would affect outcome in IPF, this seems to be a reasonable treatment goal for future studies. However, although we cannot conclude how transition of a worse to a better AC would impact individual prognosis, we think that staying in an AC III or IV should be considered as a parameter of worse clinical outcome and, therefore, should include lung transplantation as a therapeutic option for eligible patients.

Another aspect of this study was to characterize the prognostic value of the 6MWD in a nonpreselected cohort, comprising less affected IPF patients as well as patients who are already candidates for lung transplantation.

Our study cohort incorporated patients with a wide range of functional impairment and in this heterogeneous group of IPF patients, a 6MWD ≥470 m was a positive predictor of survival during a median follow-up period of 14.9 months. We think that this emphasizes the value of this functional test in severely but also in mild-to-moderately affected IPF patients.

The 6-min walk test is an easy, inexpensive, safe, and reproducible submaximal exercise test in chronic lung disease, including IPF [13]. The distance walked during this test is of prognostic significance in severely affected IPF patients waiting for lung transplantation [14]. Variations (e.g. the timed walk test [21]) and special aspects of this test, such as the desaturation that occurs during the walk test or the longitudinal development, add significantly in terms of estimation of prognosis in mixed collectives of idiopathic interstitial pneumonias [22] and IPF populations [11, 23]. However, with regard to desaturation, there is still some uncertainty, since the applied test protocols vary, especially with respect to the use of supplemental oxygen during the test. In addition, to stop the test whenever oxygen saturation falls below 87% (or any other cutoff value) could interfere with the distance walked, while the safety aspect is unproven. In addition, from our experience, measuring transcutaneous saturation during the test may be hampered by technical difficulties and the reproducibility is low. Since this is a submaximal exercise test, and the test person is urged to per-

Respiration 2015;90:460–467
DOI: 10.1159/000441302

form at her or his own speed, it seems to be plausible that patients require more physical exercise during not supervised daily activities as compared to this walk test. Whatsoever, without controlling transcutaneous saturation, the walk test was a safe test in our study population comprising mild but also severely affected patients. Nevertheless, due to the fact that we did not measure saturation in our patients during the test, we cannot conclude on distance-desaturation products or similar parameters.

Our results are in line with the findings of Lederer et al. [14] who reported the impact of the 6MWD on prognosis of IPF patients who were already listed for lung transplantation during a median follow-up of 4 months. Study objects in our trial were very differently affected from IPF and not uniformly listed for lung transplantation at study entry. This gave us the opportunity to report already a distance of 470 m to be of prognostic relevance during a median follow-up of 14.9 months. The difference between the two study populations is even more obvious, since patients with a 6MWD >396 m were included in the best quartile of the earlier study, but even patients with a 6MWD of up to 470 m had an increased mortality in our study.

Our study has clear limitations. First, this is an observational study which does not allow concluding on any therapeutic effects. Second, although we included a mixed population with regard to functional impairment, patients were initially evaluated and were definitive candidates for lung transplantation at some time point, taking into account the severely impaired prognosis. This might blur our observation, since we might not appropriately cover the whole spectrum of IPF severities. However, a significant portion of 20% of the patients was only mild-to-moderately affected. In addition, our observations are not driven by the most conceivable severe IPF patients who were excluded from the study. This is also underlined by the fact that we report a rather high cutoff of the 6MWD of 470 m to be of prognostic value in this population. Also, the rather young age of our population could have biased our observation, and it may not be self-evident that the data of the 6MWD may be transferred to the 'typical age' IPF cohort. Also, the high number of combined histological and radiological assessment in our study has to be interpreted in the context of the rather 'atypical age' IPF cohort. We are also aware of the fact that the AC is influenced by the individual perception and cofactors such as depression, especially as we demonstrate a large variability of (lung) functional data within the AC. In addition, comorbidities (e.g. pulmonary hypertension) may have influenced AC and the 6MWD besides lung functional impairment. However, we think that it is advantageous to integrate different disease aspect in the AC, although we are not able to differentiate the driving factors leading to a reduction of daily life activity. Finally, we did not compare AC with other disease activity scores.

Despite these limitations, we suggest the AC score as an inexpensive and independent test that can easily be integrated in daily practice, providing prognostic information alone and in combination with the 6MWD.

Acknowledgements

We thank Elisabeth Becker and her team for excellent technical support. This work contains a significant portion of the doctoral thesis of Mr. Philipp Mernitz at the LudwigMaximilian University of Munich, Germany.

Financial Disclosure and Conflicts of Interest

The authors declare that there are no financial disclosures or conflicts of interest.

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