

DOES 1-MINUTE WALK TEST PREDICT RESULTS OF 6-MINUTE WALK TEST IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS?

Flavia S. Nunes, Jean Pastre, Anne W. Brown, Oksana A. Shlobin, Christopher King, Nargues A. Weir, Steven D. Nathan

Inova Advanced Lung Disease and Transplant Program, Inova Fairfax Hospital, Falls Church, VA, USA

ABSTRACT. Background: The six-minute walk test (6MWT) is a readily available tool used to evaluate functional capacity in patients with idiopathic pulmonary fibrosis (IPF). However, it is often logistically challenging to perform in the context of a busy clinical practice. We sought to investigate if the 1MWT distance (1MWD) predicts the 6MWT distance (6MWD), and if an abbreviated walk could accurately predict outcomes in IPF patients. **Methods:** Baseline demographics and pulmonary function testing of IPF patients evaluated at a tertiary referral center between 2010 and 2017 were collected. 6MWT variables at baseline as well as 1 and 6 minutes were collected. Time to death, lung transplantation, or most recent follow-up was ascertained. **Results:** There were 177 patients, the majority of whom (80%) were male. The mean age was 67 ± 9 years and mean FVC was $64 \pm 18\%$ predicted. Forty eight (27%) patients used oxygen supplementation during the 6MWT. The median 6MWD was 366 meters (IQR: 268–471) while the median 1MWD was 65 meters (IQR: 46–81). Stratified by the median, 89 patients were “High Walkers” based on the $6MWD \geq 366m$ (HW_6) and 88 patients were “Low Walkers” (LW_6). HW_6 had a higher FVC% (70 ± 15 vs 57 ± 18 , $p = 0.001$), higher DLCO% (45 ± 12 vs 34 ± 14 , $p = 0.001$) and higher 1MWD (83 ± 28 vs 47 ± 16 , $p = 0.001$). Median transplant-free survival was better in HW_6 vs LW_6 (27 ± 16 vs 22 ± 18 months, log rank $p = 0.018$). There was a strong correlation between the 1MWD and the 6MWD ($r = 0.91$, Spearman’s correlation, $p < 0.0001$). Also, the transplant-free survival curves stratified by 1MWD were very similar to the curves for 6MWD, showing a lower survival in the LW_1 cohort (log rank $p = 0.009$). **Conclusion:** The 1MWD obtained during the first minute of a 6MWD shows a strong correlation to total 6MWD and retains its ability to predict transplant-free survival. 1MWT may serve as a practical substitute for the more cumbersome 6MWT. Our findings require further validation prospectively in larger cohorts of IPF patients.

KEY WORDS: idiopathic pulmonary fibrosis, 6-minute walk test, 1-minute walk test, prognostic

BACKGROUND

The 6-minute walk test (6MWT) is a simple, objective, and reproducible measurement of functional capacity. It is a submaximal exercise test used

in the clinical evaluation of patients with various forms of cardiovascular and pulmonary diseases, including idiopathic pulmonary fibrosis (IPF). IPF is a chronic, progressive, fibrotic interstitial lung disease of unknown etiology occurring predominantly in patients over sixty and is characterized by reduced lung volumes and impaired gas exchange (1). The natural history of IPF varies, but it is associated with a poor prognosis, with a median survival after diagnosis of 2 to 5 years (2). Among the clinical and physiologic predictors associated with survival in IPF, the 6MWT has been increasingly used over the

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Correspondence: Jean Pastre
Inova Advanced Lung Disease and Transplant Program
Falls Church
VA 22042
E-mail: Jean.Pastre@inova.org

past 5 years as a secondary endpoint in IPF clinical trials (3-5). The primary outcome measurement is the six-minute walk distance (6MWD), but other parameters have been investigated as predictors of outcomes, including the rest and nadir oxygen saturation (SpO_2), Borg Dyspnea Index Scale, and heart rate recovery. Validation of a shorter walk test may result in a logistically easier test, and therefore more universally applicable in routine clinical care.

The 6MWT initially evolved from a 12-minute walk and indeed high correlation coefficients between the two-minute, six-minute, and 12-minute tests have previously been demonstrated (6,7). This data suggests that the time chosen to assess exercise tolerance by walking tests may not be critical. Therefore, since the 6MWT is a reliable, valid, and responsive measure of disease status in IPF, we sought to investigate if the distance during first minute of a 6MWT (1MWD) predicts the 6MWD, and if an abbreviated walk is also predictive of outcomes in IPF patients.

Methods

We conducted a retrospective study of IPF patients presenting to the Inova Advanced Lung Disease Clinic from May 2010 to February 2017. Eligible patients had a confident IPF diagnosis according to the criteria of the *American Thoracic Society/European Respiratory Society* (8,9). Patients were excluded if they were deemed to be clinically unstable or acutely ill, requiring more than 6 Liters/min O_2 via nasal cannula, or had a major comorbidity (e.g., ischemic heart disease, malignancy) that could impact their performance on the walk. Local IRB committee approval was obtained (# 17-2673), the need for informed consent was waived.

Baseline demographics were collected including: age, gender, height, weight, body mass index (BMI), and date of initial consultation. Pulmonary function tests (PFT) including the forced vital capacity (FVC %), forced expiratory volume in first second (FEV_1 %), FEV_1/FVC ratio, single breath diffusing capacity for carbon monoxide (DLCO %), total lung capacity (TLC %) were recorded. PFTs were performed according to American Thoracic Society (ATS) standards (10,11) (*V6200 Autobox DL*; *SensorMedics, Yorba Linda, CA*) and expressed as percent predicted (12-14).

6MWT

Each patient performed the 6MWT according to the ATS guidelines with the instruction to walk as far they could in 6 minutes by an experienced operator using standard verbal prompts (15). Patients were instructed to walk without jogging or running. They were permitted to slow down or stop to rest, if needed, and were encouraged to resume walking as soon as they were able. Patients walked on room air or using their usual oxygen flow rate, which was established during a prior oxygen titration study to maintain SpO_2 at least 88%. Oxygen saturation, heart rate and Borg score were measured and recorded at the start of the 6MWT, at 1 minute intervals during the test, at the end of the study, and at one minute of recovery after conclusion of the walk test. Cutaneous pulse oximetry and heart rate (*Nellcor N-20PA*; *Puritan Bennett, Inc., Pleasanton, CA*) were obtained using a forehead probe. The 6MWT was stopped if the patient experienced chest pain, intolerable dyspnea, leg cramps, diaphoresis, or SpO_2 dropped below 80%. All analyses were performed from measurements taken at 1 and 6 minutes of the same test.

The primary outcome was transplant-free survival. Data was obtained from the Social Security death index and the electronic medical record. Date of last follow-up, death, or lung transplantation was recorded.

Statistical considerations and data analysis

All demographic and pulmonary function data are presented as the mean \pm standard deviation (SD) or the median, depending on the distribution, and according with interquartile ranges if continuous, or as frequencies, if categorical. Group comparisons were performed using *Student's* t-test or *Wilcoxon's* rank sum test for continuous variables; or Pearson's chi-square test or *Fisher's* exact test, for categorical variables, where appropriate.

The Spearman correlation between the 1MWD and 6MWD was analyzed. Patients were divided into groups based on their 1MWD and 6MWD: high walker (\geq median distance); and low walker ($<$ median distance). *Kaplan-Meier* survival analysis and the log-rank test were used to compare the one minute and six minute high vs low walker groups in terms of transplant-free survival times. All the

statistical analyses were performed using GraphPad (*GraphPad; ver. 7, La Jolla, CA*) or SAS (*ver. 9.4, Cary NC*). p-values ≤ 0.05 were considered as statistically significant.

RESULTS

There were 177 patients identified with data available for analysis. The majority (80%) was male (Table 1). The baseline characteristics included age: 67 ± 9 years, BMI: 28 ± 5 kg/m², FVC% predicted: 64 ± 17 (n= 153), FEV₁% predicted: 69 ± 16 , (n= 153), DLCO% predicted: 40 ± 14 (n= 115). The median survival of the group from the time of the 6MWT was 24 (10 - 35, 95% IQR) months.

In terms of the 6MWT, 27% of the patients required supplemental O₂ during the walk (Table 1).

The mean 6MWT distance was 363 (268 - 471, 95% IQR) meters, with a corresponding 1MWD of 65 (46 - 81, 95% IQR) meters. Patients were stratified according to the 6MWD median (366 meters) into high (HW₆) and low walkers (LW₆) (89 and 88 patients respectively).

Comparison between HW₆ and LW₆ revealed that HW₆ had a younger age (64 ± 9 vs 67 ± 8 years, p= 0.001), higher FVC% predicted (70 ± 15 vs 57 ± 18 , p= 0.001), higher DLCO% predicted (45 ± 12 vs 34 ± 14 , p= 0.001), and a higher 1MWD (83 ± 28 vs 47 ± 16 , m p= 0.001). The 1-year mortality after the initial 6MWT was significantly lower in the HW₆ group compared to the LW₆ group (31 vs 16%, p= 0.019).

Patients were also stratified according 1MWD median into high walkers (HW₁) (≥ 65 m) and low

Table 1. Demographics and functional characteristics of patients, stratified by median 6MWD (≥ 366 meters (n= 89) versus < 366 meters (n= 88))

Variables	All patients n = 177	HW ₆ (6MWD ≥ 366 meters) n = 89	LW ₆ (6MWD < 366 meters) n = 88	p value
Age	67 ± 9	64 ± 9	67 ± 8	0.001*
Gender, male (%)	142 (80)	81 (91)	61 (69)	0.001*
BMI	28 ± 5	28 ± 5	29 ± 5	0.51
FVC %	64 ± 18	70 ± 15	57 ± 18	0.001*
FEV ₁ %	69 ± 16	76 ± 15	62 ± 18	0.001*
DL _{CO} %	40 ± 14	45 ± 12	34 ± 14	0.001*
FEV ₁ /FVC %	81 ± 12	79 ± 15	84 ± 9	0.02*
1 MWT, meters	65 ± 29	83 ± 28	47 ± 16	0.001*
6 MWT, meters	363 ± 141	478 ± 68	246 ± 90	0.001*
Supplemental O ₂ (%)	48 (27)	8 (9)	40 (45)	0.001*
GAP Index				
1 (%)	37 (21)	30 (34)	7 (8)	
2 (%)	60 (34)	33 (37)	27 (31)	
3 (%)	30 (17)	10 (11)	20 (23)	0.004*
Mortality, 1 year (%)	42 (24)	14 (16)	28 (32)	0.02*
Mortality, overall (%)	62 (35)	25 (28)	37 (42)	0.03*
Median Survival, months	24 ± 17	27 ± 16	22 ± 18	0.02*

Data reported as mean \pm SD, or frequency with percent (%)

*Significance tests for comparisons between high and low walker patients (HW₆ and LW₆) based on paired t-test for continuous patient characteristics and Fisher's exact test for categorical patient characteristics

Abbreviations: 6MWT: 6-minute walk test; 6MWD: 6-minute walked distance; HW₆: High Walkers patients stratified according to the 6MWD median (≥ 366 m); LW₆: Low Walkers patients stratified according to the 6MWD median (< 366 m); BMI: body mass index; FVC %: forced vital capacity, % predicted; FEV₁ %: forced expiratory volume in 1 second, % predicted; DL_{CO} %: monoxide carbon diffusion capacity, % predicted; 1MWD: walked distance during first minute of 6MWT; GAP index: Gender Age and Pulmonary function test index

walkers (LW_1) (< 65 m). For the most part, patients who were High Walkers during the 6MWT were also High Walkers in the 1 minute time interval, and vice versa, with the exception of about less than 10% of patients who had inconsistent results between time intervals, reflective of pacing variability or perhaps fatigue (8 HW_1 (9%) became LW_6 , while 81 HW_1 (91%) stayed HW at 6 minutes).

There was a strong correlation between 1MWD and 6MWD ($r= 0.91$, Spearman's correlation, $p < 0.0001$) (Figure 1a). However we did observe a less favorable, but still statistically significant correlation between SpO_2 at 1 and 6 minutes (Figure 1b, $r=0.69$, $p < 0.0001$). With regards to qualifying for supplemental oxygen, 38 patients desaturated below 88% based on the 6MWT, while only 7 did so on the 1MWT (Figure 1b).

The transplant-free survival of LW_6 was significantly lower than the HW_6 group (Figure 2). Interestingly, when we stratified the patients based on HW_1 versus LW_1 , the transplant-free survival curve was very similar, showing a lower survival in the LW_1 cohort (Figure 3).

DISCUSSION

In this paper, we demonstrate that the 1MWD obtained from the 6MWT has a strong correlation with the 6MWD in IPF patients. In addition, the information gleaned at one minute during the course

of a 6MWT imparts similar prognostic information. We postulate that this modification could render a walk test more feasible to obtain on a more frequent basis in patients with IPF during the course of their routine clinical follow-up.

The 6MWT has evolved over time. As a simple measure of physical fitness, Balke *et al.* developed the specific time of 12 minutes and was responsible for the introduction of the 12-minute walk test (6). In 1982, Butland and colleagues evaluated the possibility of reducing the time patients would be required to walk (7). The health status of patients under study was often so poor that patients would frequently lack the motivation for even 12 minutes of physical activity. Their validation study demonstrated that after a slight initial burst of speed, patients walked at a constant speed, suggesting that shorter tests may be as informative. Subjects showed a remarkable ability to pace themselves during this test. The high correlation coefficients between the 2-minute, 6-minute, and 12-minute tests indicated that they were all similar measures of exercise tolerance. This data suggests that the time chosen to assess exercise tolerance by walking tests may not be critical.

The association between 6MWD and survival in IPF patients has been well demonstrated by several authors. In 2006, Lederer *et al.* analyzed survival of 454 patients with IPF listed for lung transplant. The area under the receiver operator curve (ROC) showed that the 6MWD was better than the FVC

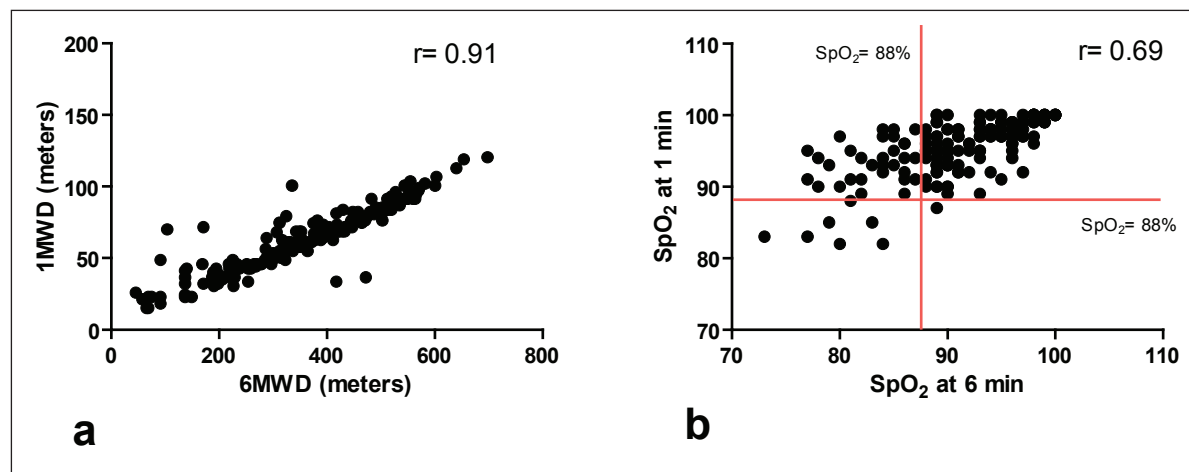


Figure 1. Correlation between a) 1-minute walked distance and 6-minute walked distance (1MWD and 6MWD) and b) 1-minute SpO_2 and 6-minute SpO_2

Abbreviations: r: Pearson's correlation coefficient; 6MWD: 6-minute walked distance; 1MWD: walked distance during first minute of 6MWT; 6MWT: 6-minute walk test; SpO_2 : arterial oxygen saturation

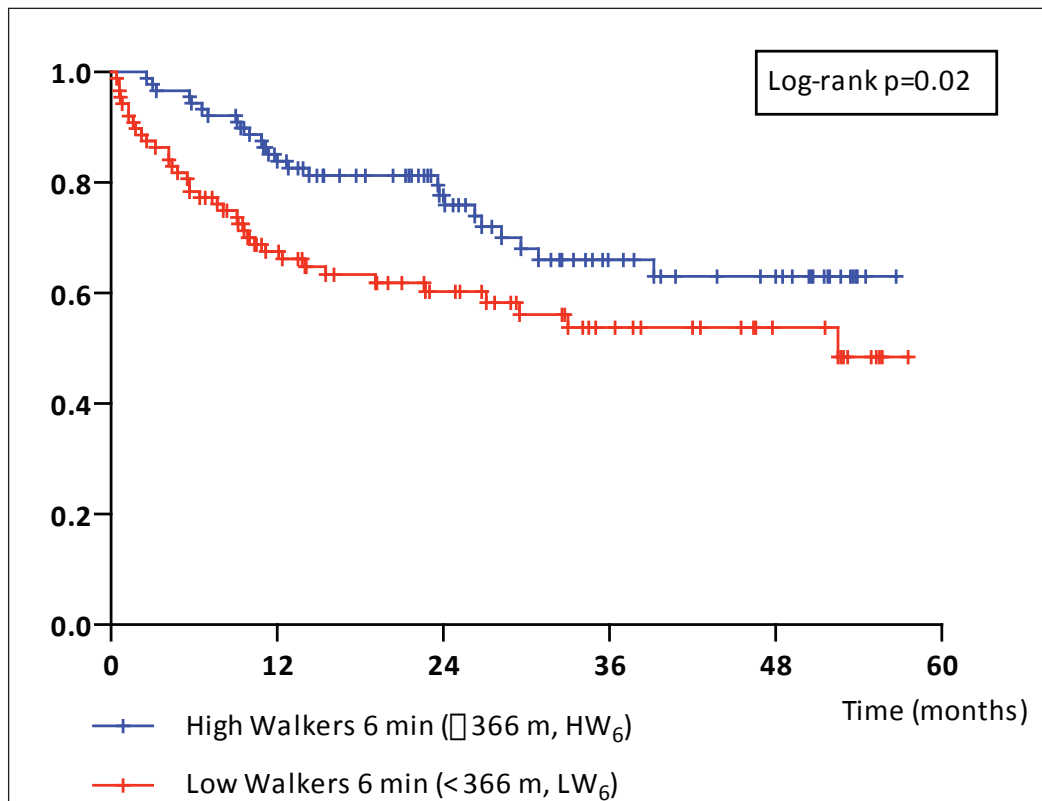


Figure 2. Transplant-Free Survival of IPF Patients, stratified by 6-minute walked distance (6MWD)
Abbreviation: 6MWD: six-minute walked distance

% predicted in discriminating survival at 6 months with a distance lower than 207m strongly and independently associated with an increased mortality rate for wait-listed IPF patients (16). In 2014, du Bois *et al.* provided additional evidence of the independent contribution of 6MWD to prediction of mortality in IPF. They found that a baseline 6MWD lower than 250 m was associated with increase in mortality risk (hazard ratio, 2.12; 95% CI, 1.15-3.92) and also a decline of 50 m or more at 24 weeks was associated with nearly 3-fold increase in mortality risk (hazard ratio, 2.73; 95% CI, 1.60-4.66) (17). In another study, change in 6MWD was also highly predictive of mortality; a 24-week decline of greater than 50 m was associated with a fourfold increase in risk of death at 1 year (hazard ratio, 4.27; 95% CI, 2.57-7.10; $p < 0.001$) (18). Although we did not evaluate serial change in the 1MWT, we hypothesize that this will impart similar prognostic information. This hypothesis should ideally be validated in a future prospective study.

The reliability, validity, and responsiveness of the 6MWT has been demonstrated in reports from large cohorts of prospectively collected data in the context of independent clinical trials (18-20). From these studies, the 6MWD was weakly correlated with other physiologic measures, which attests to its providing complimentary physiologic information not reflected in standard physiologic pulmonary function testing. The estimated minimal clinically important difference (MCID) for the 6MWT in IPF has been estimated between 24-45 m (18). We speculate that the MCID for a 1MWT would be relatively less given that there is less time for other factors to confound distance to manifest during the course of the study performance. This could prove to be an additional advantage of a shorter test.

Although widely studied, there are ongoing issues which require further investigation to improve the performance characteristics of the 6-minute walk test. Weir *et al.* analyzed if changing the wording from “far” to “fast” might facilitate a better effort and

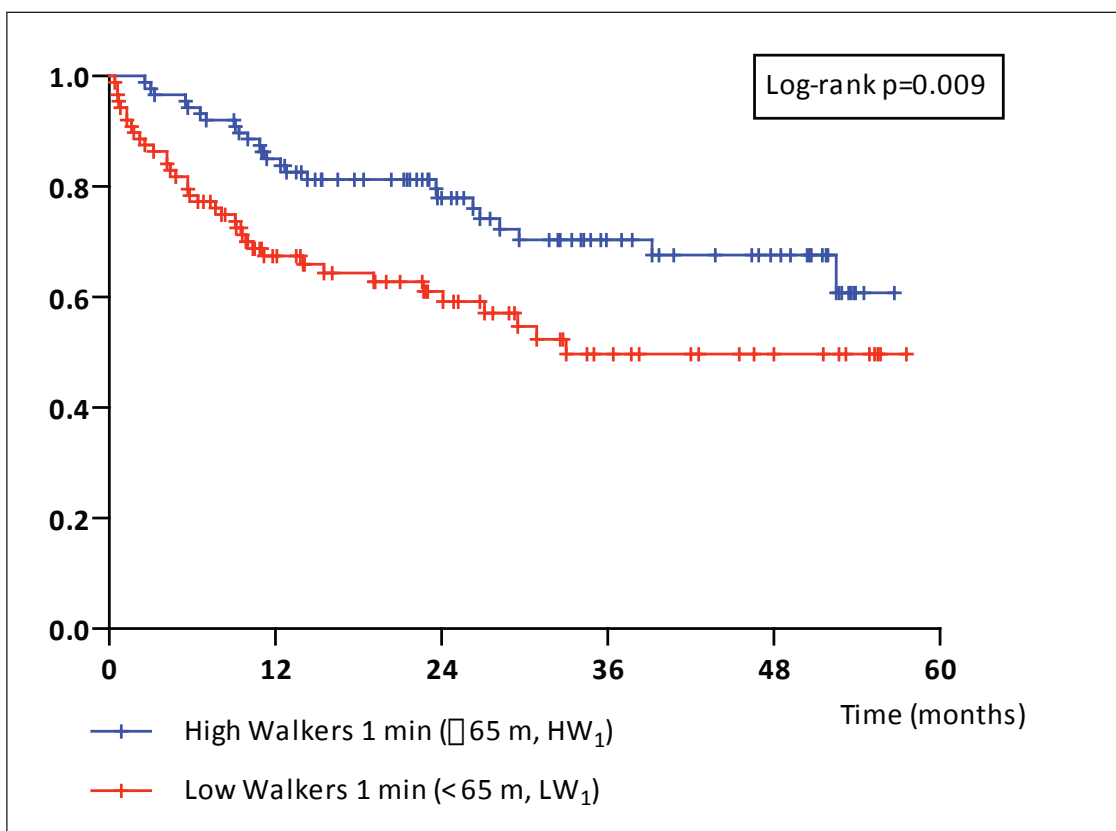


Figure 3. Transplant-Free Survival of IPF patients, stratified by 1-minute walked distance (1MWD)
Abbreviation: 1MWD: 1-minute walked distance

greater distance during the 6MWT (21). Twenty-four patients (ten with pulmonary hypertension, eight with IPF, six with non IPF-ILD) were enrolled and completed 6MWTs in random order with differing instructions. Interestingly, the greatest distance was obtained with the fast instruction, exceeding the standard (“far”) instruction distance by a mean of 52.7 meters. This highlights that patients may not walk as far as they are able with the standard ATS instruction for 6MWT. This is likely due to feedforward subconscious pacing (or tele-anticipation) of having to walk 6 minutes. It is likely that patients, including those in our current cohort, would walk further if they know that they only have to complete one minute of walking. This would likely lead to less variability and greater reproducibility of the test. This is supported by prior data demonstrating that the variance of the 12-minute test was slightly greater than that of the six-minute test, which was slightly

greater than that of the two-minute test; that is, the longer the patients walked, the greater the spread of results.

Our study has several limitations that are worth noting. First, it was a retrospective study and the 1MWT distance came from the 6MWT against which it was compared. Ideally, these should have been two separate tests. Since patients may be able to walk further if instructed to walk for only one minute, the correlation between two independent tests may not be as good as we have demonstrated. However, we speculate that since a 1MWT might be more conducive to a maximal effort with less time for variability, the reproducibility and precision of serial 1MWT may be better than 6MWT. These are issues that can only be verified in the context of a prospective study. In addition, the oxygen saturation observed at 1 minute often underestimated the degree of desaturation at 6 minutes and “missed”

17.5% (31/177) of patients who qualified for supplemental oxygen (based on desaturation < 88% at 6 minutes). However, the need for implementing supplemental oxygen in IPF patients whose SpO₂'s breach the 88% threshold has never been validated.

We also didn't account for the influence of any comorbid conditions or antifibrotic therapy in our analysis, however, we feel that any such confounders would have affected both the 6MWT and 1MWT equivalently. It is noteworthy that our cohort had a relatively high mortality rate, possibly because the 6MWTs were not necessarily obtained from the time of the initial presentation, but during the course of follow-up with survival analyzed from the time of the walk.

Although there was a high correlation between the 1MWD and 6MWD, further studies are needed to validate the test performance characteristics and prognostic value of distance walked in a 1MWT compared to the standard 6MWT in an independent cohort of patients with IPF. Shortening the time is just one modification that could improve the walk test for future use. Additionally, the evaluation of alternate instruction, such as changing the wording from "far" to "fast" and the integration of other parameters (such as the oxygen saturation and Borg dyspnea score) may further improve the clinical value of the walk test.

CONCLUSIONS

The 6MWD is a valid and practical method for evaluating disease status in patients with IPF and provides objective information regarding the functional status and near-term prognosis of patients with IPF. One-minute distances ≥ 65 m and < 65 m were defined as high walkers and low walkers, respectively, and a strong correlation appeared between the 6-minute distance and 1-minute distance in terms of predicting survival. Shorter walk times could be easier for both patients and clinicians, but further studies are necessary to identify appropriate thresholds as well as the role of serial changes in the prediction of outcomes among IPF patients.

Although more research is needed to validate the findings, the results suggest that the 1-minute test may be a practical substitute for the 6-minute test by providing similar prognostic information more quickly and easily than the 6-minute test.

List of Abbreviations

1MWT: 1-minute walk test
 1MWD: 1-minute walked distance
 6MWT: 6-minute walk test
 6MWD: 6-minute walked distance
 IPF: idiopathic pulmonary fibrosis
 SpO₂: arterial oxygen saturation
 Borg: Borg Dyspnea Index Scale
 BMI: body mass index
 PFT: pulmonary function tests
 FEV1: forced expiratory volume in first second
 FVC: forced vital capacity
 DL_{CO}: diffusion lung capacity of carbon monoxide
 TLC: total lung capacity
 ATS: American Thoracic Society

DECLARATIONS

Ethics approval and consent to participate

Local IRB committee (Inova Fairfax Hospital) approval was obtained (# 17-2673). The need for informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request

Competing interest

SDN is a consultant for Actelion, Bellerophon, Roche-Genentech, Boehringer-Ingelheim, Pliant, Merck, United Therapeutics and Bayer Pharmaceuticals. He is also on the Speakers' Bureau for Roche-Genentech, Boehringer-Ingelheim, and Bayer Pharmaceuticals.

AWB has served on an advisory board for Pro-medior, Theravance, and Genentech, and serves on the Speakers' Bureau for Genentech.

NAW has served on advisory board for Gilead Sciences.

OAS has served as a consultant and serves on the Speakers' Bureau for Lung Rx/United Therapeutics, Actelion and Bayer.

JP has served as a consultant for Boehringer-Ingelheim

Other authors have no competing interest

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Authors' contributions: FSN, JP, SDN analyzed and interpreted the patient data. FSN, JP, NAW, AWB, OAS, CK, SDN were major contributor in writing the manuscript. All authors read and approved the final manuscript

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