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INTERSTITIAL LUNG DISEASE

8-Foot-Up-and-Go Test is Associated with Hospitalizations and Mortality in Idiopathic Pulmonary Fibrosis: A Prospective Pilot Study

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Abstract

Purpose To assess the prognostic value of the 8-foot-up-and-go test (8-FUGT) in pilot cohort of patients with idiopathic pulmonary fibrosis (IPF).

Methods Thirty-four patients with IPF (68 ± 8 years) underwent 8-FUGT at baseline and were followed for up to 40 months. Receiver operating characteristics and age-adjusted Cox hazard ratios (HR) were analyzed for 8-FUGT, hospitalizations, and mortality. Correlation coefficients were determined between 8-FUGT and other exercise tests.

Results 8-FUGT ≥ 6.9 s was found to be associated with hospitalization (sensitivity = 77%, specificity = 76%, $p = 0.03$) and mortality (sensitivity = 91%, specificity = 70% $p = 0.008$) in patients with IPF. Categorical models demonstrated that 8-FUGT ≥ 6.9 s was associated with 14.1- ($p < 0.001$) and 55.4-fold ($p = 0.001$) increased risks for hospitalization and mortality, respectively. In continuous models, for every 1-s slower performance in the 8-FUGT there were 54% [HR = 1.54, 95% CI (1.11–2.15) $p = 0.01$] increased risk for hospitalization and 94% [HR = 1.94, 95% CI (1.26–2.99) $p = 0.003$] increased risk for mortality. 8-FUGT was inversely related to 6-min walk distance ($r = -0.61$), peak oxygen consumption ($r = -0.58$), and peak work rate ($r = -0.72$), all $p < 0.001$.

Conclusions The 8-FUGT was strongly associated with hospitalizations and mortality in patients with IPF, as well as correlated with established prognostic markers. These novel findings suggest a prognostic value of the 8-FUGT for risk stratification, referral to pulmonary rehabilitation, and considering listing for lung transplantation. 8-FUGT is an inexpensive and practical tool that has prospective for implementation in clinical and research settings in IPF. Future prospective studies should evaluate the effect of changes in 8-FUGT on clinical outcomes.

Trial registration NCT01499745, Clinicaltrials.gov.

Keywords Functional capacity · Survival · Prognostic predictors · Risk stratification · Clinical outcomes

This study was conducted at Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease associated with high morbidity, mortality, and a median survival of 2–5 years from the time of diagnosis [1–3]. IPF is characterized by progressive pulmonary restriction, ventilatory inefficiency, dyspnea, impaired gas exchange, and hypoxemia. These pathophysiological manifestations lead to diminished exercise capacity, reduced quality of life, and poor prognosis [1, 3–6]. Along with an unpredictable and heterogeneous clinical course, mortality rates are the highest among IPF candidates awaiting lung transplantation, warranting a need for better risk stratification for these patients [7]. For an individual patient with IPF, the disease course can range from slow progression to acute decompensation and death, and thus predicting outcomes, disease management, and the optimal timing for lung transplantation is challenging [8, 9].

Although several prognostic variables have been shown to be associated with survival in IPF [1, 10], accurate predictors of clinical outcomes remain elusive, and research in this area has failed to yield reliable models for implementation in clinical practice [11]. The 6-min walk test (6MWT) is an inexpensive and practical test that has been consistently demonstrated to be associated with mortality among patients with IPF [12–17]. However, the test results have many confounders including gender, a given patient's height and stride length, and degree of motivation and encouragement [17, 18]. These confounders have resulted in significant variation and inconsistency with respect to the prognostic utility of the 6MWT in IPF [12–16]. The 8-foot-up-and-go test (8-FUGT) is a well-established test for geriatric population, designed to provide objective assessments of functional mobility, strength, balance, and agility. The test has good sensitivity and specificity to detect elderly individuals at high risk for falls, and has been recommended by the American College of Sports Medicine guidelines as part of functional assessment in elderly individuals and patients with chronic conditions [19–23]. To our knowledge, the prognostic utility of 8-FUGT has not been assessed among patients with IPF, and its utility as a clinical, research, and prognostic tool in IPF is unknown. The aim of the current pilot study was to evaluate the prognostic value of 8-FUGT in patients with IPF. Specifically, we assessed the association between 8-FUGT, hospitalizations, and mortality as well as the optimal prognostic threshold in patients with IPF.

Methods

Patients and Setting

This study was a secondary analysis of our exercise rehabilitation study previously described [clinicaltrials.gov (NCT01499745)]. The testing were conducted at baseline, after 12 weeks, and at 11-month follow-up [24, 25]. The study was approved by the institutional review board at the Rabin Medical Center, Israel. In brief, 34 patients with clinical–radiological criteria for IPF according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines were recruited between January and December 2012 [1]. Exclusion criteria were severe co-morbid illnesses, unstable cardiac disease, and any neurological or orthopedic contraindications for exercise testing. We have previously reported that at 30-month and 40-month follow-up, group allocation did not affect survival; however, the sample size was underpowered to detect such changes [24, 26].

8-Foot-Up-and-Go Test (8-FUGT)

The test began with the patient fully seated on a chair (43 cm height) placed against the wall for safety. On the signal "go," the patient got up from the chair, walked around a cone that was placed 8 feet (2.40 m) from the chair, and returned to a seated position on the chair as fast as possible. Performance was quantified in seconds, a time that took the patient to complete the task [20]. The 8-FUGT is a well-established test for geriatric populations developed through a large-scale community-based study of over 7000 men and women between 60 and 94 years [20, 21]. The 8-FUGT objectively evaluates functional mobility, strength, balance, and agility in a single task, thus providing an opportunity for functional evaluation in research and clinical practice. The test is part of a comprehensive evaluation of elderly individuals and patients with chronic conditions recommended by American College of Sports Medicine [19–21]. The test results also play an important role in assessment of balance and fall risk in older adults [19, 22, 23].

Pulmonary Function, Cardiopulmonary Exercise Test, 6-min Walk Test, and 30-s-Chair-Sit-to-Stand Test

Pulmonary function tests were performed according to standard techniques and ATS/ERS guidelines (nSPIRE, ZAN 530 Oberthulba, Germany) [27, 28]. The results are presented as percentage of predicted (% predicted) values using normal standards of the European Community for Coal and Steel [29]. Cardiopulmonary exercise tests were performed according to

established guidelines on an electromagnetically braked cycle ergometer (Ergoline-800S) using breath-by-breath respiratory gas exchange (nSPIRE, ZAN 600, Oberthulba, Germany) [19, 30, 31]. The 6- min walk test (6MWT) was conducted according to ATS guidelines in a 35-m corridor in the pulmonary unit within the hospital [18]. The 30-s-chair-sit-to-stand test was conducted according to "senior fitness tests" guidelines to evaluate strength and endurance of lower extremities [20]. Patients were encouraged to complete as many full stands as possible from a sitting position on a chair (43 cm height) during 30 s [20]. A 30–45-min rest period of recovery was provided between each test. Detailed descriptions of these procedures can be found in our previous reports [24, 25].

Mortality and Hospitalizations Ascertainment

The hospital medical records system was used for capturing cardiorespiratory-related hospitalizations and death as outcomes. The hospital medical records system is linked to national death records and a general health services network allowing the capture of 100% of cases of death and hospitalizations. Records were carefully reviewed by a qualified research coordinator who was otherwise blinded to all test results and other study information. The vital status of each patient was ascertained as of March 2015.

Statistical Analysis

Statistical analyses were conducted using SPSS v.23 software (IBM, Chicago, IL, USA). The significance level was set at $p < 0.05$. Demographics, clinical, and physiological data of the participants are presented as means and standard deviations. Categorical variables are presented in absolute values and percentages. Receiver operating characteristic (ROC) curve analysis was performed for detecting significant cut-off points for hospitalizations and mortality using a threshold of ≥ 70% for sensitivity and specificity [32–35]. Age-adjusted Cox proportional hazard models for the 8-FUGT were used to assess risk for hospitalizations and mortality in continuous and categorical models. The risk categories were determined based on significant cut-off points detected in ROC curve analysis. Kaplan–Meier survival analysis and the log-rank test were utilized for 8-FUGT categories, hospitalization, and mortality. Pearson's correlations were performed between 8-FUGT and other exercise testing variables.

Results

All patients completed the tests without adverse events. Demographics and general characteristics of the patients are presented in Table 1. Nine percent of the sample used Pirfenidone at baseline, while 24% used the drug during the follow-up. There were no other changes in IPF medications during the study period. Eleven patients (32%) died and 17 (50%) were hospitalized at least once during a mean follow-up of 31.6 ± 9.4 months. Mean values from the exercise tests were 8-FUGT; 7.2 ± 1.6 s, peak VO_2; 13.7 ± 3.3 mL/kg/min, peak work rate; 75.9 ± 30.7 watts, 6-min walk distance; 479 ± 124 m and 30-s-chair-sit-to-stand test; 12.5 ± 3.9 repetitions (Table 1).

ROC curve analysis detected a significant threshold of 6.9 s in the 8-FUGT that was associated with hospitalization and mortality. Seventeen patients (50%) exhibited 8-FUGT ≥ 6.9 s and had 14.1- and 55.4-fold-increased risks for hospitalizations and mortality, respectively. Patients with 8-FUGT < 6.9 s showed significantly fewer adverse events and longer survival time (Table 2; Figs. 1, 2). In continuous models, for every 1-s slower 8-FUGT, there were 54% and 94% increased risks for hospitalizations and mortality, respectively (Table 2). In both continuous and categorical models, age was not associated with hospitalizations and mortality outcomes. The 8-FUGT was significantly correlated with peak VO_2, peak work rate, 6-min walk distance, and 30-s-chair-sit-to-stand test (Table 3).

Discussion

In the current study, we aimed to evaluate the prognostic value of the 8-FUGT among patients with IPF as well as to determine a significant threshold for elevated risk. The main findings indicate that 6.9 s is sensitive prognostic threshold associated with clinical outcomes in patients with IPF. Slower performance in the 8-FUGT in both continuous and categorical models was associated with significantly higher risk for hospitalizations, mortality, and shorter survival time (Table 2; Figs. 1, 2). The 8-FUGT was significantly correlated with well-established physiological and functional prognostic markers, strengthening its validity for functional evaluation and risk stratification (Table 3). While the study involves a small pilot sample of patients with IPF and the results require further confirmation in larger cohorts, the findings support the prognostic value of the 8-FUGT for clinical and research applications.

The current results are consistent with previous reports demonstrating the utility of 8-FUGT for prediction of falls in the geriatric population [20, 22, 23]. These studies generally reported a threshold of 8.5 s that was associated with increased risk of falling [20, 22, 23]. In addition, previous studies reported the prognostic value of functional assessments such the 6MWT in patients with IPF [12–16]. The current study strengthens these previous studies among both the general geriatric population and patients with IPF, and adds novel insights to existing knowledge with respect to

Table 1 Baseline characteristics of the study population ($n=34$)

Variables	Values
Age (years)	68 ± 8
Male/female (n/%)	22/12 (65/35%)
Body mass index (kg/m^2)	29 ± 4
Time from diagnosis (year)	2.4 ± 3.4
Patients with smoking history (*n*/%)	20 (59%)
Pack/year	27 (0–112)
Supplemental oxygen users	
At rest	4(12%)
On exertion	9 (26%)
Co-morbidities	
Pulmonary hypertension according to echocardiography (*n*/%)	13 (38%)
Coronary artery disease (*n*/%)	14 (41%)
Systemic hypertension (*n*/%)	24 (71%)
Chronic obstructive pulmonary disease (Emphysema) (*n*/%)	8 (24%)
Type 2 diabetes (*n*/%)	13 (38%)
Osteoporosis (*n*/%)	5 (15%)
Medications	
Corticosteroids (n/%)	23 (68%)
Pirfenidone (n/%)	3 (9%)
Beta blockers (n/%)	13 (38%)
Resting parameters	
FVC %predicted	68 ± 17
FEV_1 %predicted	70 ± 18
TLC % predicted	64 ± 15
DLCO % predicted	50 ± 15
SpO_2 at rest (%)	96 ± 3
Exercise parameters	
VO_2 peak (mL/kg/min)	13.7 ± 3.3
Peak work rate (watts/min)	75.9 ± 30.7
6-min walk distance (m)	479 ± 124
30-s-chair-sit-to-stand test (number of repetitions)	12.5 ± 3.9
8-Foot-up-and-go test (s)	7.2 ± 1.6

Values are presented as mean and standard deviation

FVC forced vital capacity, *FEV1* forced expiratory volume in 1 s, *DLCO* diffusion capacity for carbon monoxide, *TLC* total lung capacity, *SpO_2* oxygen saturation by pulse oximeter, *VO_2* oxygen uptake

Table 2 Receiver operating characteristic curves, age-adjusted Cox hazard ratios, and survival time of 8-foot-up-and-go test in patients with idiopathic pulmonary fibrosis

	Cut-Off point for 8-FUGT	AUC 95% (CI) *p* value	Sensitivity (%)	Specificity (%)	HR 95% (CI) *p* value Categorical model	Mean survival time(months) in those with 8-FUGT < 6.9 s vs. ≥ 6.9 s		HR 95% (CI) *p* value Continuous Model Per 1-s Increase
Hospitalizations	≥ 6.9 s	0.72 (0.53–0.9) $p=0.03$	77	76	14.1 (3.5–56.8) $p<0.001$	N/A		1.54 (1.11–2.15) $p=0.01$
Mortality	≥ 6.9 s	0.78 (0.62–0.95) $p=0.008$	91	70	55.4 (5.2–592.6) $p=0.001$	39.1 (38–40) $p=0.001$	28.1 (22.3–33.9)	1.94 (1.26–2.99) $p=0.003$

AUC area under the curve, *8-FUGT* 8-foot-up-and-go test, *HR* hazard ratio, *CI* confidence interval, *N/A* not applicable

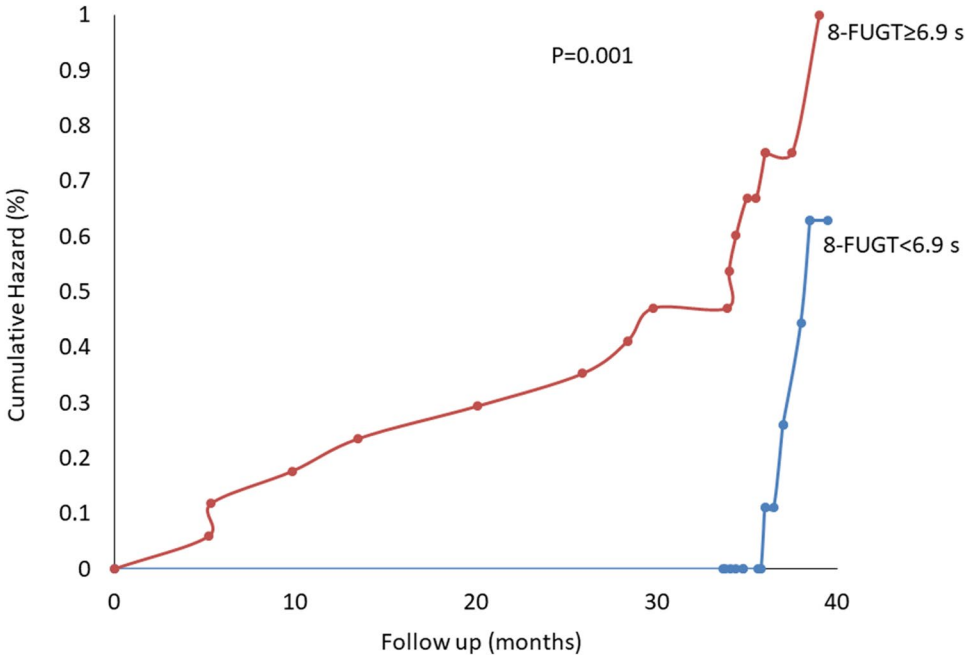

Fig. 1 Cumulative hazard of 8-foot-up-and-go test categories and hospitalizations in patients with idiopathic pulmonary fibrosis

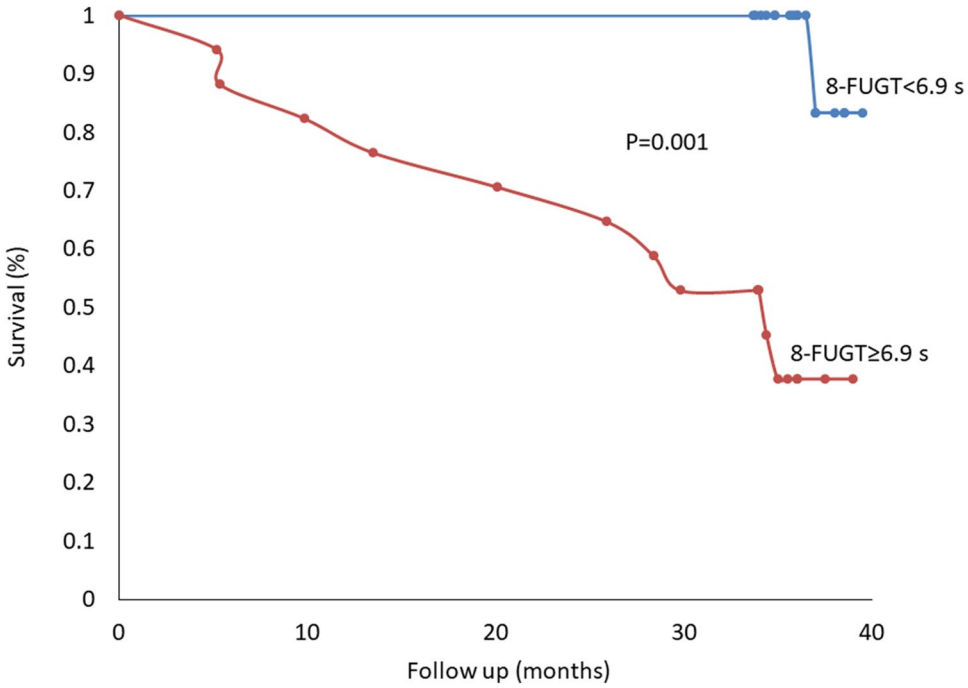

Fig. 2 Survival probability of 8-foot-up-and-go test categories in patients with idiopathic pulmonary fibrosis

the prognostic value of 8-FUGT among patients IPF. To our knowledge, this is the first study to demonstrate the association between the 8-FUGT and risk of hospitalization and mortality in patients with IPF. The analysis revealed a significant threshold with good sensitivity and specificity to detect high-risk patients for adverse events and shorter survival time (Table 2). Given that, IPF is associated with high mortality rates and poor prognosis in addition to the fact that the disease tends to worsen in an unpredictable manner; our observations have potential clinical importance [1, 3]. In particular, incorporating the 8-FUGT in clinical and research applications of IPF could add an important information for risk stratification, timely referral to pulmonary rehabilitation, and considering candidacy for lung transplantation. The prognostic value of 8-FUGT was supported by the lack of association between age and adverse outcomes, although additional research is needed to further explore the role of 8-FUGT as a predictor in IPF.

Table 3 Pearson's correlations between 8-foot-up-and-go test and other exercise tests variables in patients with idiopathic pulmonary fibrosis

	VO_2 peak (mL/kg/min)	Peak work rate (watts)	6MWD (m)	30-s-chair-stand test (number of stands)
8-foot-up-and-go test (s)	$r=-0.58$ $p<0.001$	$r=-0.72$ $p<0.001$	$r=-0.61$ $p<0.001$	$r=-0.65$ $p<0.001$

VO_2 oxygen consumption, *6MWD* 6-min walking distance

There are several potential mechanisms that may explain these findings. 8-FUGT is a geriatric assessment that encompasses elements of functional strength, mobility, balance, and agility performance in one task [19–23]. Previous observations have demonstrated the prognostic utility of functional evaluations such as 6MWT in patients with IPF [12–16]. These studies indicate that disease severity and progression and overall prognosis are closely related to the functional capabilities of patients with IPF. Poor physical function reflects more advanced pathophysiological impairments that are associated with adverse events and mortality [1, 3, 12–14, 17]. This mechanism is supported by several authors who demonstrated an inverse association between IPF severity and functional performance in the 6MWT [36, 37]. In addition, our group and others, using the cardiopulmonary exercise testing (the gold standard physiological assessment for physical function) have demonstrated that pathophysiological responses to exercise are associated with mortality in IPF, providing further support for the prognostic value of physical function assessment in IPF [25, 32, 33, 38].

The current study has several strengths and limitations. The study utilized a robust methodology from an established test and prospective evaluation of adverse events. The events were captured using the hospital's medical records system, which is highly accurate and complete. The study demonstrates novel prognostic findings in IPF by using a simple and inexpensive test, which has practical applications in clinical and research settings [19, 20]. The study also has several limitations. First, we had a relatively small sample size and low number of events, which limit adjusting the risk model for additional potential confounders. However, previous reports of functional tests and prognosis in IPF utilized similar number of participants [13, 34]. Second, most our patients had moderate severity of IPF (FVC % predicted 68 ± 17), thus future studies may be needed across a broader spectrum of disease. However, the results are consistent with previous large prospective studies in IPF and provide reasonable confidence for generalization of the findings [12, 14, 15]. Finally, as is the case for all epidemiological studies, the results demonstrate an association between exposure and outcomes but do not show a cause and effect relationship [12, 32].

In summary, 8-FUGT ≥ 6.9 s was strongly associated with hospitalization, mortality , and shorter survival time in patients with IPF. These results support the prognostic value of implementing 8-FUGT in clinical and research settings in patients with IPF. Additional research is needed to further explore the clinical applications of the 8-FUGT in IPF.

Author Contributions BV was responsible for study design and conception, data collection, results interpretation, statistical analysis, drafting, writing, and submitting the manuscript. MRK supervising physician of the study was responsible for study design and conception, results interpretation, drafting the article, and revising it critically for important intellectual content. JM was involved in results interpretation, statistical analysis, drafting the article, and revising it critically for important intellectual content. AU and SI participated in results interpretation, statistical analysis, drafting the article, and revising it critically for important intellectual content. JO was involved in study design and conception, results interpretation, statistical analysis, drafting the article, and revising it critically for important intellectual content. All authors have read and approved the manuscript.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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