# Gait speed and prognosis in patients with idiopathic pulmonary fibrosis: a prospective cohort study

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**4MGS independently predicts all-cause mortality and nonelective hospitalisation in patients with newly diagnosed IPF** http://ow.ly/cT9H30mCkUr

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ABSTRACT The 4-m gait speed (4MGS), a simple physical performance measure and surrogate marker of frailty, consistently predicts adverse prognosis in older adults. We hypothesised that 4MGS could predict all-cause mortality and nonelective hospitalisation in patients with idiopathic pulmonary fibrosis (IPF).

4MGS and lung function were measured at baseline in 130 outpatients newly diagnosed with IPF. Survival status and nonelective hospital admissions were recorded over 1 year. We assessed the predictive value of 4MGS (as a continuous variable and as a binary variable: slow *versus* preserved 4MGS) by calculating hazard ratios using Cox proportional regression, adjusting for potential confounding variables. Receiver operating characteristic curves assessed discrimination between the multivariable regression models and established prognostic indices.

Continuous 4MGS and slow 4MGS were independent predictors of all-cause mortality (4MGS: HR 0.03, 95% CI 0.01–0.31; p=0.004; slow 4MGS: 2.63, 95% CI 1.01–6.87; p=0.049) and hospitalisation (4MGS: HR 0.02, 95% CI 0.01–0.14; p<0.001; slow 4MGS: 2.76, 95% CI 1.16–6.58; p=0.02). Multivariable models incorporating 4MGS or slow 4MGS had better discrimination for predicting mortality than either the gender, age and lung physiology index or Composite Physiologic Index.

In patients with IPF, 4MGS is an independent predictor of all-cause mortality and nonelective hospitalisation.

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## Introduction

Idiopathic pulmonary fibrosis (IPF) is characterised by a progressive loss of pulmonary function, functional decline, dyspnoea and poor prognosis with a median untreated survival of 3 years from diagnosis [1, 2]. The development of new therapies requires a standardised approach to end-points in clinical trials [3]. However, there is a lack of consensus as to whether all-cause mortality and nonelective hospitalisations should be considered the only primary end-points of choice [3, 4]. Detractors have argued that using such end-points may be impractical in terms of size and cost of trials, and also requires participants to commit to long-term treatment, despite obvious progression of disease such as worsening symptoms or functional decline (whether due to nonefficacy or enrolment to placebo) [4]. Consequently, there is interest in stratification tools to identify those at higher risk of adverse outcomes such as mortality or nonelective hospitalisation. Depending on purpose, this could be used to enrich or deplete a clinical trial cohort with those at high risk of adverse outcome, or to balance treatment arms at baseline. This may potentially reduce the sample size requirements, duration and costs of IPF clinical trials [5, 6].

The 4-m gait speed (4MGS) test, a measure of usual walking speed, is a surrogate marker of physical frailty [7]. It is quick to perform, acceptable to patients and was designed as a rapid tool to evaluate physical performance in large epidemiological studies of community-dwelling older adults. Gait speed has been shown to be a consistent predictor of adverse prognosis, including all-cause mortality, hospitalisation and disability [8, 9]. It has been identified as the best validated functional performance test for pharmacological trials in sarcopenia and frailty [10], and has been used as a stratification tool and clinical end-point in pharmacological trials in other diseases [11]. Consequently, 4MGS may have potential as a stratification tool of adverse outcomes in IPF.

Previous work has demonstrated that 4MGS is reliable, valid and responsive to change in patients with IPF [12]. Furthermore, stratification according to 4MGS was able to identify patients with significantly worse exercise performance, dyspnoea, health status and prognosis score despite similar lung function and high-resolution computed tomography parameters [12]. However, the longitudinal prognostic ability of 4MGS has not been explored in patients with IPF. We hypothesised that 4MGS could predict: 1) all-cause mortality and 2) all-cause, nonelective hospitalisation, independent of age and lung function, in patients with newly diagnosed IPF.

## Materials and methods

### *Study design and subjects*

Participants were consecutively and prospectively recruited to this longitudinal cohort study from outpatient respiratory clinics at the Royal Brompton and Harefield Hospital NHS Foundation Trust (London, UK) between March 2015 and October 2016. The inclusion and exclusion criteria are described in the supplementary material. All participants provided written informed consent; the study was approved by the London-Riverside Research Ethics Committee (15/LO/0015) and registered at ClinicalTrials.gov (identifier NCT02436278).

### *Methods*

4MGS was assessed using the protocol developed by the US National Institute of Ageing on a flat, unobstructed 4-m course by trained staff following a standard operating procedure. Further information on the assessment of 4MGS is described elsewhere [12, 13] and included in the supplementary material.

Other measurements included pulmonary function tests with the following absolute and percentage predicted variables recorded: forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), $FEV_1$/FVC and diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) [14] (Spirostick PC spirometry system; Love Medical, Manchester, UK and Jaeger MasterScreen Pulmonary Function Testing system; Carefusion, Basingstoke, UK), and Medical Research Council (MRC) Dyspnoea score [15] and 6-min walk distance (6MWD) [16] performed at the time of a formal new IPF diagnosis. Established prognostic indices (Composite Physiologic Index (CPI) [17] and gender, age and lung physiology (GAP) index [18]) were calculated. Comorbidities were evaluated using the age-adjusted Charlson Comorbidity Index [19]. Data on all-cause mortality and all-cause, nonelective hospitalisation were collected over the 1-year period following the baseline assessment using primary care records and a national database. Patients who survived or were not hospitalised during the 1-year follow-up were censored at 365 days.

### *Analysis*

The sample size calculation is described in the supplementary material. The baseline characteristics were summarised using descriptive statistics. The differences in baseline characteristics stratified according to survival and hospitalisation status were compared using independent t-tests (Mann–Whitney U-test for nonparametric data) and Chi-squared tests for continuous and categorical data, respectively. 4MGS was

evaluated as a continuous measure, but also a binary variable (slow 4MGS (<0.8 $m \cdot s^{-1}$) *versus* preserved 4MGS (⩾0.8 $m \cdot s^{-1}$)). This threshold was chosen because international consensus statements have shown that it is a consistent predictor of adverse outcomes [8, 20], and we have demonstrated the discriminative validity of this threshold in both IPF [12] and chronic obstructive pulmonary disease (COPD) [21].

Univariable Cox proportional regression was used to assess the association between 4MGS (continuous and binary) and plausible confounding variables with all-cause mortality at 1 year. All of the variables in the univariable analysis were considered in the multivariable Cox proportional regression analysis, with two models considered in the multivariable analysis: continuous and slow 4MGS. Further details of the regression analyses are described in the supplementary material. The same analyses were repeated to evaluate the association with the first all-cause, nonelective hospital admission at 1 year.

Receiver operating characteristic (ROC) plots of the multivariable Cox regression models were constructed for mortality and hospitalisation [22]. The models that were predictive of mortality were compared with established prognostic indices (CPI and GAP index). Kaplan–Meier analyses compared time to all-cause mortality and first hospitalisation between slow and preserved 4MGS groups, with significance assessed using the log-rank test. Analyses were performed using Prism version 7 (GraphPad, La Jolla, CA, USA) and SPSS version 24 (IBM, Armonk, NY, USA). Statistical significance was considered at 5%.

## Results

The study flow diagram and baseline characteristics are shown in figure 1 and table 1, respectively. The majority of patients were male (83%) with mean±SD age 72±7 years, FVC % pred 74.2±18.1, MRC Dyspnoea score 3±1 and 4MGS 0.91±0.23 $m \cdot s^{-1}$ (range 0.29–1.45 $m \cdot s^{-1}$), and median (interquartile range) $D_{LCO}$ % pred 41.0% (33.8–50.4%).

### *Prediction of all-cause mortality*

18% (n=23) of the cohort died during the 1-year follow-up period. The baseline characteristics according to survival status are given in the supplementary material. When patients were stratified according to slow 4MGS (slow: n=46; preserved: n=81), mortality at 1 year was significantly higher in the slow 4MGS group (slow: 32%; preserved: 11%; p<0.01).

The univariable analysis for risk of all-cause mortality is shown in table 2. The unadjusted hazard ratio for mortality decreased for each 1.00 $m \cdot s^{-1}$ increase in 4MGS (continuous variable) (HR 0.03, 95% CI 0.01–0.25; p<0.01). Similarly, when analysed as a binary measure, those with slow 4MGS had an increased unadjusted hazard ratio for mortality compared with individuals with preserved 4MGS (HR 3.71, 95% CI 1.56–8.85; p<0.01). The multivariable analysis confirmed that 4MGS (continuous and binary) remained an independent risk factor for all-cause mortality (table 2). The ROC plot demonstrated that both

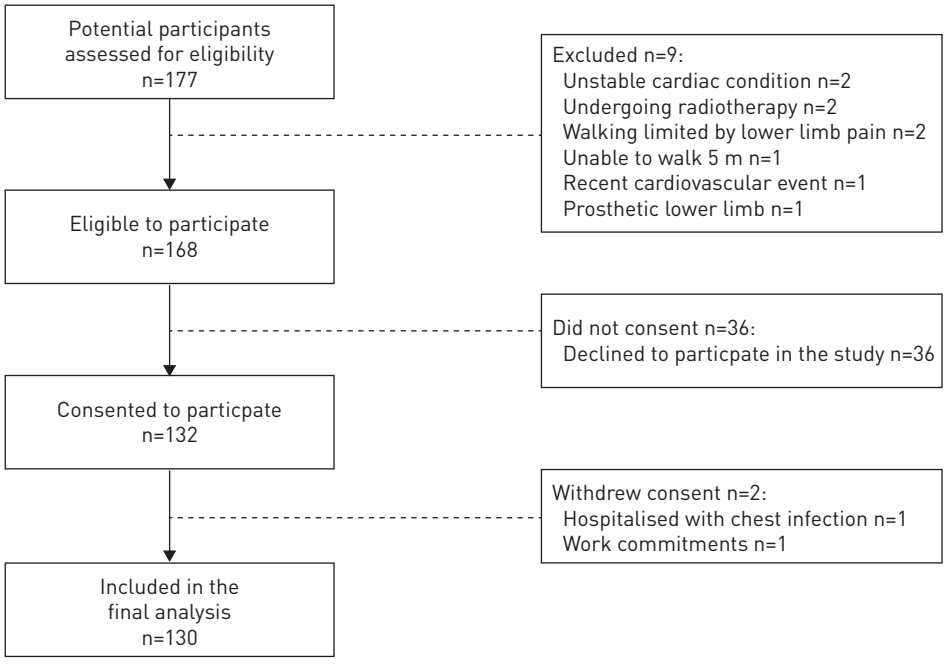


FIGURE 1 Study flow diagram.

TABLE 1 Baseline characteristics

| | |
|---|---|
| **Subjects** | 130 |
| **Male n (%)** | 108 (83) |
| **Age years** | 72±7 |
| **MRC Dyspnoea score** | 3±1 |
| **BMI kg·m$^{-2}$** | 27.8±4.7 |
| **FEV$_1$/FVC** | 0.82±0.07 |
| **FVC L** | 2.5±0.7 |
| **FVC % pred** | 74.2±18.1 |
| ***D*$_{LCO}$ mL·min$^{-1}$·kPa$^{-1}$** | 3.3 (2.6–4.1) |
| ***D*$_{LCO}$ % pred** | 41.0 (33.8–50.4) |
| **CPI** | 49.8±12.6 |
| **GAP index** | 4.4±1.3 |
| **Smoking status n (%)** | |
| Never-smoker | 38 (29) |
| Ex-smoker | 89 (68) |
| Current smoker | 3 (3) |
| **Age-adjusted Charlson Comorbidity Index** | 0 (0–4) |
| **COPD n (%)** | 12 (9) |
| **Pulmonary hypertension n (%)** | 21 (16) |
| **Ischaemic heart disease n (%)** | 33 (25) |
| **Obstructive sleep apnoea n (%)** | 5 (4) |
| **Self-reported hospitalisations in previous year n** | 0 (0–1) |
| **Self-reported chest infections in previous year n** | 0 (0–1) |
| **Oxygen n (%)** | |
| Long-term | 6 (5) |
| Ambulatory | 15 (12) |
| **Walking aid** | 8 |
| **Prescribed antifibrotic medication during the study period n (%)** | 74 (57) |
| **6MWD m** | 365±121 |
| **4MGS m·s$^{-1}$** | 0.91±0.23 |

Data presented as n, mean±SD or median (interquartile range), unless otherwise stated. MRC: Medical Research Council; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; *D*$_{LCO}$: diffusing capacity of the lung for carbon monoxide; CPI: Composite Physiologic Index; GAP: gender, age and lung physiology; COPD: chronic obstructive pulmonary disease; 6MWD: 6-min walk distance; 4MGS: 4-m gait speed.

TABLE 2 Univariable and multivariable Cox proportional regression analysis for time to all-cause mortality at 1 year

| | Univariable analysis | | Multivariable analysis: Model 1[#] | | Multivariable analysis: Model 2[#] | |
|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **4MGS m·s$^{-1}$** | 0.03 (0.01–0.25) | 0.001 | 0.03 (0.01–0.31) | 0.004 | | |
| **Slow 4MGS (reference: preserved 4MGS)** | 3.71 (1.56–8.85) | 0.003 | | | 2.63 (1.01–6.87) | 0.049 |
| **Age years** | 0.98 (0.92–1.04) | 0.45 | 0.95 (0.88–1.02) | 0.15 | | |
| **Sex (reference: female)** | 2.15 (0.50–9.21) | 0.30 | | | | |
| **Smoking status (reference: never-smoker)** | 2.87 (0.85–9.69) | 0.09 | | | 2.24 (0.65–7.75) | 0.20 |
| **FVC % pred** | 0.96 (0.94–0.98) | <0.001 | 0.95 (0.92–0.99) | 0.005 | 0.94 (0.91–0.97) | 0.001 |
| ***D*$_{LCO}$ % pred** | 0.99 (0.95–1.02) | 0.36 | | | | |
| **6MWD m** | 0.99 (0.99–0.99) | 0.001 | | | | |
| **Prescribed antifibrotic medication during the study period (reference: no)** | 0.88 (0.38–2.04) | 0.77 | | | | |
| **Respiratory hospitalisations in previous year n** | 1.25 (1.02–1.52) | 0.03 | | | | |

4MGS: 4-m gait speed; FVC: forced vital capacity; *D*$_{LCO}$: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance. Multivariable model 1: 4MGS (continuous format), age, sex, smoking status, FVC % pred, *D*$_{LCO}$ % pred, 6MWD, prescribed antifibrotic medication during the study period, number of respiratory hospital admissions in the previous year. Multivariable model 2: slow 4MGS (binary format), age, sex, smoking status, FVC % pred, *D*$_{LCO}$ % pred, 6MWD, prescribed antifibrotic medication during the study period, number of respiratory hospital admissions in the previous year. [#]: final model presented.

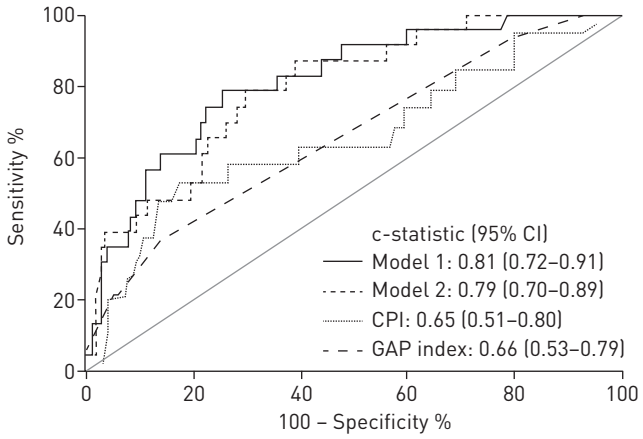


FIGURE 2 Receiver operating characteristic plots demonstrating the ability of multivariable model 1 (4-m gait speed (4MGS), age, forced vital capacity (FVC) % pred), multivariable model 2 (slow 4MGS, age, FVC % pred), Composite Physiologic Index (CPI), and gender, age and lung physiology (GAP) index to predict all-cause mortality at 1 year.

multivariable models demonstrated good discrimination for mortality with c-statistics of 0.81 and 0.79 for models 1 and 2, respectively, which were better than currently established prognostic indices (CPI: 0.65; GAP index: 0.66) (figure 2). The Kaplan–Meier curve demonstrated a shorter time to death in those with slow compared with preserved 4MGS (log-rank test: p=0.004) (figure 3a).

### *Prediction of all-cause, nonelective hospitalisation*

31% (n=40) of patients had at least one all-cause, nonelective hospital admissions within the 1-year follow-up period. The baseline characteristics of those hospitalised and not hospitalised are reported in the supplementary material. More patients with slow 4MGS had at least one nonelective hospitalisation compared with those with preserved 4MGS (57% *versus* 19%; p<0.001).

The univariable analysis for risk of all-cause, nonelective hospitalisation is shown in table 3. There was a decreasing unadjusted hazard ratio for hospitalisation for each 1.00 $m \cdot s^{-1}$ increase in 4MGS (continuous variable) (HR 0.03, 95% CI 0.01–0.18; p<0.001). Similarly, when analysed as a binary variable, patients with slow 4MGS had an increased, unadjusted hazard ratio for hospitalisation compared with the preserved 4MGS group (HR 3.97, 95% CI 1.94–8.11; p<0.001). The multivariable analysis confirmed that continuous and slow 4MGS were independently associated with hospitalisation (table 3). Both multivariable models had good discrimination for hospitalisation with c-statistics of 0.78 and 0.79 for models 1 and 2, respectively (figure 4). Furthermore, the Kaplan–Meier analysis demonstrated a shorter time to first hospital admission in individuals with slow 4MGS (log-rank test: p<0.0001) (figure 3b).

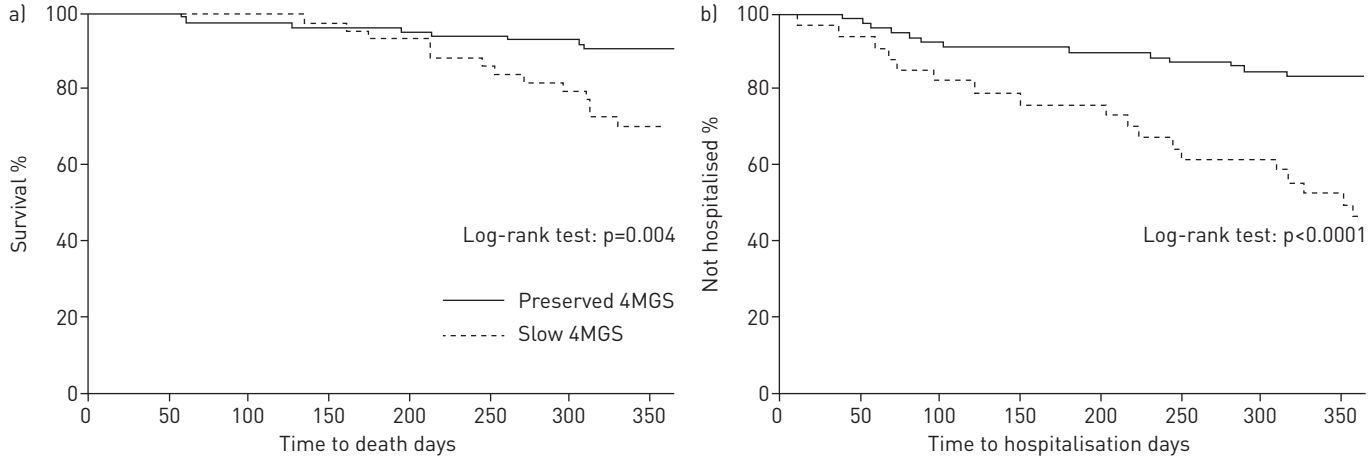


FIGURE 3 Kaplan–Meier curves demonstrating time to a) all-cause death and b) all-cause, nonelective hospitalisation within 1 year according to slow (<0.08 $m \cdot s^{-1}$) and preserved (⩾0.08 $m \cdot s^{-1}$) 4-m gait speed (4MGS).

TABLE 3 Univariable and multivariable Cox proportional regression analysis for time to all-cause, nonelective hospitalisation at 1 year

| | Univariable analysis | | Multivariable analysis: Model 1# | | Multivariable analysis: Model 2# | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| **4MGS m·s$^{-1}$** | 0.03 (0.01–0.18) | <0.001 | 0.02 (0.01–0.14) | <0.001 | | |
| **Slow 4MGS (reference: preserved 4MGS)** | 3.97 (1.94–8.11) | <0.001 | | | 2.76 (1.16–6.58) | 0.02 |
| **Age years** | 1.03 (0.97–1.09) | 0.34 | | | | |
| **Sex (reference: female)** | 2.19 (0.67–7.22) | 0.20 | 4.33 (1.10–17.09) | 0.04 | 3.76 (1.03–13.70) | 0.045 |
| **Smoking status (reference: never-smoker)** | 2.34 (0.96–5.69) | 0.06 | | | | |
| **FVC % pred** | 0.98 (0.96–1.00) | 0.02 | | | | |
| ***D*LCO % pred** | 0.96 (0.94–0.99) | 0.003 | 0.96 (0.93–0.99) | 0.005 | 0.96 (0.94–0.99) | 0.01 |
| **6MWD m** | 0.99 (0.99–0.99) | <0.001 | | | 0.99 (0.99–1.00) | 0.09 |
| **Prescribed antifibrotic medication during the study period (reference: no)** | 0.82 (0.40–1.65) | 0.57 | | | | |
| **Respiratory hospital admissions in previous year n** | 1.19 (1.01–1.41) | 0.04 | | | | |
| **Chest infections in previous year n** | 1.10 (0.93–1.31) | 0.26 | 0.02 (0.01–0.14) | 0.15 | | |

4MGS: 4-m gait speed; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance. Model 1: 4MGS (continuous format), age, sex, smoking status, FVC % pred, *D*LCO % pred, 6MWD, prescribed antifibrotic medication during the study period, number of hospital admissions in the previous year, number of chest infections in the previous year. Model 2: slow 4MGS (binary format), age, sex, smoking status, FVC % pred, *D*LCO % pred, 6MWD, prescribed antifibrotic medication during the study period, number of hospital admissions in the previous year, number of chest infections in the previous year. #: final model presented.

## Discussion

This is the first study to determine the prognostic ability of 4MGS to predict all-cause mortality and all-cause, nonelective hospitalisation in patients with IPF. Both continuous and slow 4MGS (<0.80 m·s$^{-1}$) were independently associated with all-cause mortality and all-cause, nonelective hospitalisation after adjusting for potential confounding variables. Multivariable models incorporating continuous or slow 4MGS demonstrated better discrimination for predicting all-cause mortality than established composite prognostic indices. Individuals with slow 4MGS had a shorter time to all-cause mortality and first hospital admission than those with preserved 4MGS. We propose that 4MGS may have value as a stratification tool of adverse outcomes in clinical trials. It may also aid clinicians to monitor functional performance, identify patients at increased risk of poor prognosis and guide management strategies (*e.g.* frequency of clinical review and referral to other services).

### *Previous prognostic studies of gait speed*

In a meta-analysis of nine cohort studies of 34 485 community-dwelling older adults followed for up to 21 years, STUDENSKI *et al.* [8] demonstrated that gait speed was consistently associated with mortality (HR

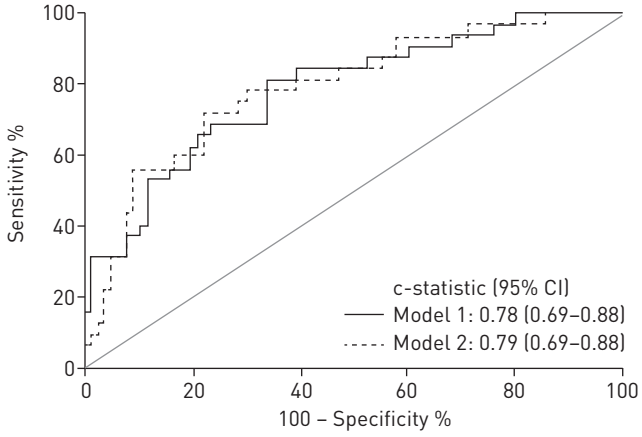


FIGURE 4 Receiver operating characteristic plots demonstrating the ability of multivariable model 1 (4-m gait speed (4MGS), sex, diffusing capacity of the lung for carbon monoxide (*D*LCO) % pred, number of chest infections in the previous year) and multivariable model 2 (slow 4MGS, sex, *D*LCO % pred, number of chest infections in the previous year) to predict all-cause, nonelective hospitalisation at 1 year.

0.88, 95% CI 0.87–0.90, per 0.10 $m \cdot s^{-1}$ increase in gait speed). Gait speed has also been shown to be a predictor of hospitalisation in community-dwelling older adults. In the Health Aging and Body Composition study of 3000 older adults, slow gait speed (<1.0 $m \cdot s^{-1}$ over 6 m) was associated with increased risk of hospitalisation (rate ratio 1.48, 95% CI 1.02–2.13) [23]. Similarly, in a cohort of 487 older adults recruited from the primary care, slow gait speed (<0.6 $m \cdot s^{-1}$) independently predicted hospitalisation at 1 year [24]. The relationship between slow gait speed and adverse outcomes has also been demonstrated in chronic conditions such as heart [25] and renal failure [26].

Studies evaluating the prognostic ability of gait speed in patients with chronic respiratory disease are limited. Kon *et al.* [27] measured 4MGS at discharge in 213 patients hospitalised with an acute exacerbation of COPD and identified increasing risk of hospital readmission at 90 days with slower 4MGS. Those in the slowest 4MGS quartile had an increased unadjusted odds ratio for 90-day hospital readmission compared with the fastest quartile (OR 7.12, 95% CI 2.61–19.44) [27]. In a study of acute respiratory distress syndrome survivors Chan *et al.* [28] evaluated two cohorts. In the first cohort, with every 0.11 $m \cdot s^{-1}$ increase in gait speed, decreased unadjusted odds ratios were observed for future hospitalisations (OR 0.78, 95% CI 0.65–0.92) and mortality (OR 0.44, 95% CI 0.26–0.75) [28]. In the second cohort (which included a longer follow-up period), increased gait speed was associated with reduced hospitalisation (OR 0.77, 95% CI 0.65–0.90) but not mortality (OR 0.93, 95% CI 0.70–1.24, per 0.11 $m \cdot s^{-1}$ increase in gait speed) [28].

### *Significance of findings*

Previous studies of gait speed in IPF have been limited to cross-sectional psychometric studies [12, 29–31] or assessing response to exercise-based rehabilitation [12, 31]. We have previously demonstrated that 4MGS is reliable and valid in IPF [12]. Additionally, stratification according to slow 4MGS identified significant impairments in exercise capacity, health status, dyspnoea and composite prognostic index scores despite similar pulmonary function and radiological parameters [12]. Our study is the first to assess the prognostic validity of 4MGS, and the first to demonstrate that 4MGS is an independent predictor of all-cause mortality and all-cause, nonelective hospitalisation in IPF.

Currently there are conflicting opinions about the use of end-points for clinical trials in IPF. Some have argued that "hard" end-points such as death or nonelective hospitalisation are meaningful to patients and that existing surrogate markers of adverse outcomes have limitations or lack validity [3]. Others advocate the use of surrogate end-points in order to make clinical trials more pragmatic and affordable [4], particularly as IPF is a rare condition.

Existing surrogate end-points in IPF include pulmonary function measures. As the most commonly recorded pulmonary function measure in IPF, FVC has many advantages. It is valid, responsive and the physiological measure that best correlates with worsening fibrosis. Change in FVC has been associated with mortality [32, 33] and the regulatory approvals of antifibrotic medication were based on demonstration of their effects on FVC change. However, there are potential limitations associated with using FVC as a surrogate end-point. Missing values occur because a proportion of patients are unable to perform serial measurements due to cough, dyspnoea or infection [6]. A proportion of patients dying in trials appear to have stable FVC prior to death [6]. There is also a degree of measurement variation such that FVC can vary by 5–9% between readings [34]. Furthermore, IPF is a disease of older adults where nonpulmonary manifestations may influence mortality or hospitalisation; these manifestations are not captured by FVC. Of note, although FVC was shown to be an independent predictor of mortality in this study, the inclusion of 4MGS in the multivariable model improved predictive ability. Moreover, in contrast to 4MGS, FVC was not an independent predictor of hospitalisation.

Established composite prognostic indices, derived from pulmonary function, such as the CPI and GAP index, predict mortality in IPF [17, 18]. However, although the GAP index accounts for missing *D*LCO values if an individual is unable to perform the manoeuvre, both the CPI and GAP index may become limited as surrogate markers of mortality due to missing pulmonary function data. These prognostic indices were also originally derived from analyses of retrospective datasets [17, 18], in contrast to our prospective study where multivariable models incorporating 4MGS demonstrated greater predictive capacity for all-cause mortality than either CPI or GAP index.

Our data suggest that 4MGS may have potential as a stratification tool of adverse outcomes in IPF. Depending on purpose, 4MGS could be used to enrich or deplete a clinical trial cohort with those at high risk of adverse outcome, or to balance treatment arms at baseline. This could potentially reduce sample size requirements, follow-up, duration and cost of clinical trials.

We propose that 4MGS may also have a role as a trial end-point. Although our study population comprised patients with newly diagnosed IPF, and consequently 4MGS may have reflected frailty status or

the extrapulmonary manifestations more than lung function impairment, the relative contribution of extrapulmonary manifestations becomes less prominent as IPF disease and symptoms progress. In these patients, 4MGS may be more reflective of lung function impairment. In these circumstances, a "successful" trial end-point might be slowing of deterioration of 4MGS. Accordingly, change in, rather than baseline, gait speed may be more indicative of IPF burden (the pulmonary and nonpulmonary manifestations) and should be explored in future research. Furthermore, 4MGS could also be used in trials where the intervention might have a positive effect on nonpulmonary outcomes, such as physical functioning. We have previously shown that 4MGS is responsive to pulmonary rehabilitation [12]. Indeed, it should be noted that gait speed has been used as a trial end-point in other chronic diseases and led to the regulatory approval of drugs for multiple sclerosis [11].

### *Limitations*

There were some limitations to this study. First, the participants in this study had a new IPF diagnosis and were recruited from a specialist centre. Therefore, the findings need to be corroborated in other settings and centres, and in other IPF populations, particularly in those with more established disease. Second, patients unable to walk 5 m were excluded from the study, which may have influenced results. However, only one person was excluded for this reason and it is likely that inclusion would have improved the predictive capacity of 4MGS [35]. Third, only all-cause mortality and all-cause, nonelective hospitalisation were reported. Neither the national database nor primary care records allowed the cause of death nor reason for hospitalisation to be ascertained accurately, corroborating previous data suggesting it is difficult to reliably discern if a death or hospital admission is IPF- or non-IPF-related [36, 37]. Nonetheless, identifying the cause of death or reason for hospitalisation may have established whether 4MGS was a clinical indicator of multisystem wellbeing [7] or provided some measure of IPF severity. Fourth, we did not validate our results in an external cohort. However, as we specified an *a priori* hypothesis, this partially mitigates against concerns about external validation. Given the consistent demonstration of the predictive ability of gait speed in other populations [8, 20], the need for a validation cohort in this study is less pronounced. This is in contrast to the validation of biomarkers as surrogate end-points, where typically multiple measures are being compared in a hypothesis-generating way.

### *Future research*

Future work should include the corroboration and external validation of our findings in alternative settings and populations, *e.g.* primary care, acute and home settings, as well as the evaluation of the role of 4MGS as a surrogate end-point of adverse outcomes.

Further work on exploring the responsiveness of 4MGS over time and in response to an intervention is required to fully understand the potential utility of this tool. For example, evidence to support the prognostic utility of 4MGS and its role as a surrogate end-point of adverse outcomes would include demonstrating that a change in 4MGS (either with an intervention or as part of disease progression) can predict survival and hospital admission. Additionally, comparing the predictive ability of baseline and change in 4MGS to change in FVC % pred may identify whether 4MGS is superior or adds further information to change in FVC % pred, the surrogate end-point of survival accepted by regulatory bodies. The evaluation of the predictive ability of 4MGS over a longer duration of follow-up may enhance estimates of prognostic risk and be of value in planning end-of-life care for patients with IPF. As yet, it is not known whether 4MGS can predict acute exacerbation, future disability or long-term outcomes in IPF and further studies are needed to evaluate a stratified management approach to help individualise treatment strategies for patients at increased risk of adverse prognosis.

In summary, in patients with a new IPF diagnosis, 4MGS can independently predict all-cause mortality and nonelective hospitalisation at 1 year. We propose that 4MGS has potential as a stratification tool of adverse outcomes for use in research and clinical settings.

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