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Change in gait speed and adverse outcomes in patients with idiopathic pulmonary fibrosis: A prospective cohort study

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Abstract

Background and Objective: Gait speed is associated with survival in individuals with idiopathic pulmonary fibrosis (IPF). The extent to which four-metre gait speed (4MGS) decline predicts adverse outcome in IPF remains unclear. We aimed to examine longitudinal 4MGS change and identify a cut-point associated with adverse outcome.

Methods: In a prospective cohort study, we recruited 132 individuals newly diagnosed with IPF and measured 4MGS change over 6 months. Death/first hospitalization at 6 months were composite outcome events. Complete data (paired 4MGS plus index event) were available in 85 participants; missing 4MGS data were addressed using multiple imputation. Receiver-Operating Curve plots identified a 4MGS change cut-point. Cox proportional-hazard regression assessed the relationship between 4MGS change and time to event.

Results: 4MGS declined over 6 months (mean [95% CI] change: −0.05 [−0.09 to −0.01] m/s; $p = 0.02$). A decline of 0.07 m/s or more in 4MGS over 6 months had better discrimination for the index event than change in 6-minute walk distance, forced vital capacity, Composite Physiologic Index or Gender Age Physiology index. Kaplan–Meier curves demonstrated a significant difference in time to event between 4MGS groups (substantial decline: >−0.07 m/s versus minor decline/improvers: ≤−0.07 m/s; $p = 0.007$). Those with substantial decline had an increased risk of hospitalization/death (adjusted hazard ratio [95% CI] 4.61 [1.23–15.83]). Similar results were observed in multiple imputation analysis.

Conclusion: In newly diagnosed IPF, a substantial 4MGS decline over 6 months is associated with shorter time to hospitalization/death at 6 months. 4MGS change has potential as a surrogate endpoint for interventions aimed at modifying hospitalization/death.

KEYWORDS
gait speed, hospitalization, idiopathic pulmonary fibrosis, IPF, morbidity, mortality

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is characterized by a progressive functional decline and poor prognosis.[1] There is interest in validating surrogate endpoints that are associated with adverse outcomes, such as hospitalization or death, since these could potentially reduce the sample size, duration and costs of clinical trials.[1,2]

The most commonly used surrogate endpoint in IPF is the forced vital capacity (FVC). Change in FVC %predicted

is associated with disease progression and mortality.[3] A >10% absolute decline in FVC %predicted over 6 months indicates significant deterioration in pulmonary function[4] that is associated with increased mortality risk.[5] However FVC may not capture the non-pulmonary manifestations of IPF, and dyspnoea or cough may prevent FVC measurement, leading to missing data.[6] In some individuals, FVC remains stable prior to death.[7] Six-minute walk distance (6MWD), another proposed surrogate endpoint, requires a 30-metre course and a practice test, which may limit its utility in some settings and in individuals with severe disease.[8] Its prognostic validity has not been demonstrated in advanced disease[9,10] and severe dyspnoea may preclude testing leading to missing data.

Four-metre gait speed (4MGS) is a measure of usual walking speed and a surrogate marker of frailty.[11] It is simple and quick to perform, acceptable to patients and requires little space, making it feasible in various settings.[12] In large epidemiological studies of community-dwelling elders, usual gait speed is a consistent predictor of all-cause mortality and hospitalization.[13,14] Moreover, there is increasing data in chronic respiratory disease and acute respiratory distress syndrome (ARDS) survivors that stratification according to 4MGS can identify subgroups at increased risk of adverse prognosis.[15,16]

In IPF, we have previously demonstrated that 4MGS is reliable, valid, responsive to pulmonary rehabilitation.[17] and that 4MGS at the time of diagnosis is independently associated with all-cause mortality and hospitalization.[18] To date, the relationship between 4MGS change and prognosis has not been investigated in IPF. We aimed to examine longitudinal change in 4MGS (over 6 months), and to identify a cut-point of 4MGS change that is associated with adverse outcome, defined as first hospitalization or death, in the subsequent 6 months.

METHODS

The study is reported according to STROBE guidelines.[19] Participants were consecutively and prospectively recruited to this longitudinal cohort study from outpatient respiratory clinics at the Royal Brompton and Harefield Hospitals, United Kingdom. The inclusion criteria were a new IPF diagnosis by a specialist interstitial lung disease multidisciplinary team according to international guidelines,[1] able to walk five metres independently and safely and able to provide informed consent. Exclusion criteria were significant co-morbidities that would limit walking and/or exercise capacity (e.g., severe neurological conditions) or make exercise unsafe (e.g., unstable angina).

Patients were assessed at time of diagnosis (visit 1) and 6 months later (visit 2). 4MGS was measured using the protocol developed by the National Institute of Ageing[20] on a 4 metre course (Appendix S1 in the Supporting Information). Other measurements included anthropometry, pulmonary function testing, Medical Research Council (MRC) Dyspnoea scale, 6MWD[8] and Kings Brief Interstitial Lung Disease (KBILD) questionnaire,[21] Prognostic indices (Composite Physiologic Index [CPI][22] and Gender, Age and Lung Physiology [GAP] Index[23]) were calculated. Co-morbidities were evaluated using the age-adjusted Charlson Co-morbidity Index.[24]

Our primary outcome was a composite of all cause-mortality or first all-cause, non-elective hospitalization in the 6 months after visit 2. We collected hospitalization data from patient self-report, corroborated by primary care records, whilst mortality status was collected from central National Health Service records over the 6-month period from visit 2 (Figure 1). Follow-up for patients who were alive and not hospitalized were censored at 180 days after visit 2.

SUMMARY AT A GLANCE

In people newly diagnosed with IPF, four-metre gait speed (4MGS) declined significantly over 6 months. A decline of more than 0.07 m/s was associated with shorter time to hospitalization/death over the subsequent 6 months. 4MGS change has potential as a surrogate endpoint for interventions aimed at modifying hospitalization/death in IPF.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Differences in measures from visit 1 to 2 were compared using paired sample t-tests (non-parametric: Wilcoxon signed-rank test) and chi-square tests for continuous and categorical data, respectively. Correlations between 4MGS change and change in other measures were assessed using Pearson correlation coefficient.

In order to establish prognostic ability of change in 4MGS, FVC %predicted, 6MWD, CPI and GAP index over 6 months Receiver Operating Characteristic (ROC) curves were constructed for the binary composite outcome (hospitalization or death in the subsequent 6 months after visit 2) and area under the curve (AUC) was reported. The optimal cut-point of change in 4MGS, defined as the point which maximizes both sensitivity and specificity, was established to create a binary variable for use in the analyses; 'substantial decline' defined as less than or equal to −0.07 m/s and 'minor decline/improvers', more than −0.07 m/s.

Kaplan–Meier estimates were used to generate survival curves and the log-rank test was performed to compare time to hospitalization or death between groups (substantial decline vs. minor decline/improvers).

Univariable and multivariable Cox proportional-hazards regression assessed the association between 4MGS change and time to hospitalization or death. 4MGS change was

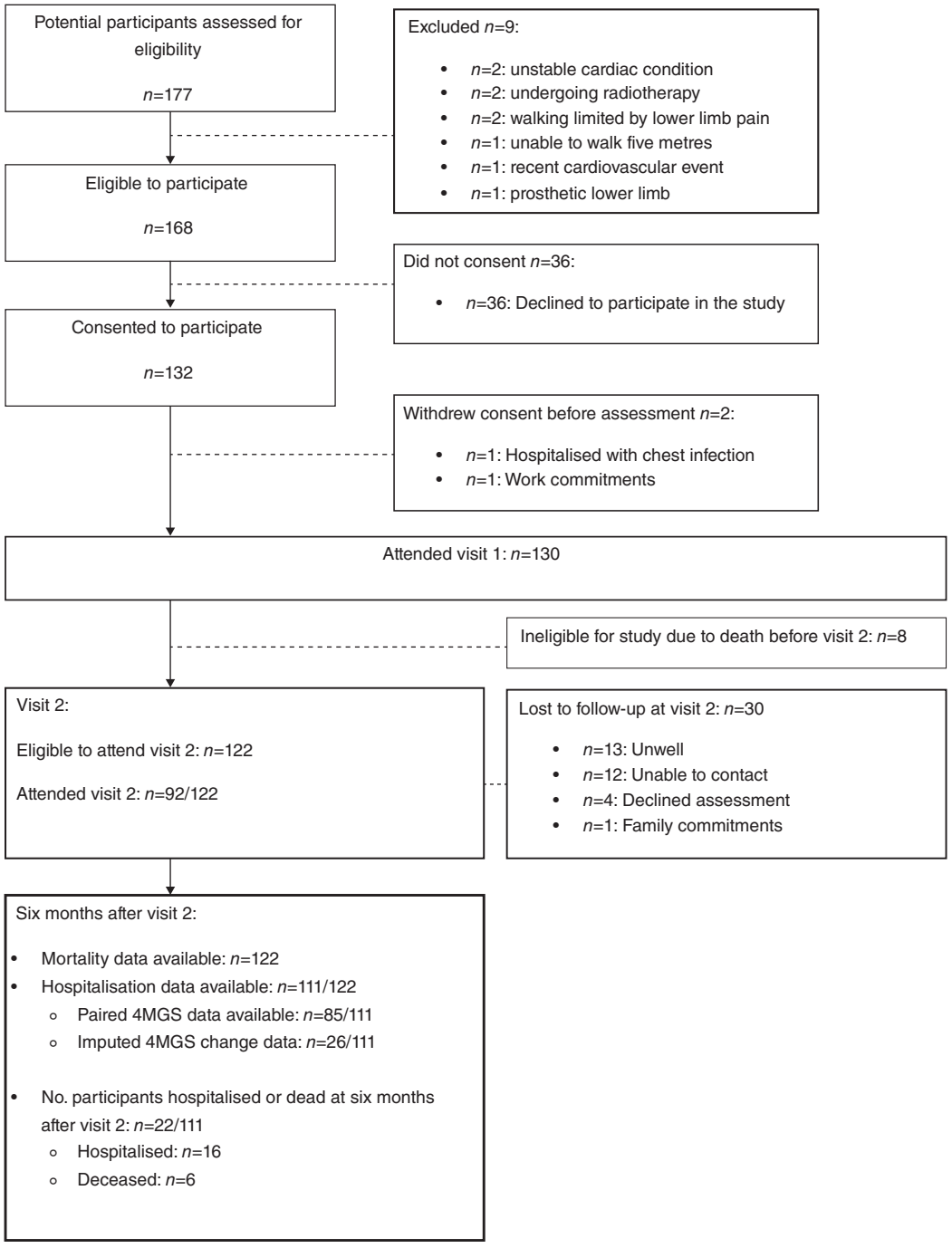

FIGURE 1 Study flow diagram. 4MGS, four-metre gait speed.

expressed as both categorical (substantial decline vs. minor decline/improvers) and continuous (0.1 m/s). A priori confounders identified in the literature were age, sex, body mass index (BMI: <25, 25–30, >30 kg/m^2: categorized to satisfy the proportional hazards assumption), FVC %predicted, baseline 4MGS, diffusing capacity of the lung for carbon monoxide (DL_{CO}) %predicted, prescribed anti-fibrotic therapy before visit 2 (yes/no). Schoenfeld residuals assessed the proportional hazard assumption on the complete data set ($n = 85$).

Missing data on change in 4MGS ($n = 26$) were addressed in a sensitivity analysis using multiple imputation ('mi impute chained' command in Stata 16; see Appendix S1 in the Supporting Information for further details on the methods) under the assumption of missing at random, in that the missing 4MGS change data may be dependent on other covariates but not on the value of the missing data. Only missing data on 4MGS were imputed.

As a sensitivity analysis we assessed the association between 4MGS change and time to hospitalization and

death as separate endpoints. The methods and results are described in Appendix S1 and S2 in the Supporting Information.

Sample size calculation

We hypothesized that change in 4MGS would predict hospitalization or death in IPF. From previous data in IPF, we estimated adverse outcomes to occur in 20% of patients over the follow-up period.[18] A sample size of 105 patients (21 cases and 84 controls) would be needed to obtain an AUC above 0.5 where the true value is 0.7 with 80% power at the 5% significance level. To account for an estimated 20% drop-out,[25] a total of 132 patients were recruited. Statistical significance was considered at 5%. Analyses were performed using the GraphPad Prism 7 (GraphPad Software, USA), SPSS version 26 (IBM, USA) and Stata version 16 (StataCorp LP, USA).

RESULTS

The study flow diagram is shown in Figure 1. Of the 132 consenting participants, two withdrew consent and eight died between the assessment visits. Of the remaining 122, hospitalization data could not be corroborated in 11 participants due to lack of access to primary care or hospital records and were excluded from the analysis. Of the remaining 111, complete data, including paired 4MGS measurements were available in 85 participants, with data imputed for 26 failing to attend repeat 4MGS assessment. Baseline characteristics of the whole cohort and participants with paired and missing 4MGS change data are outlined in Table 1. Differences in participants with paired and missing 4MGS change data are outlined in Table S1 in the Supporting Information.

Over 6 months, there was a statistically significant deterioration in 4MGS and lung function parameters (FVC %predicted, DL_{CO}, but not in MRC, CPI, GAP index, 6MWD or KBILD; Table 2). 4MGS change was

TABLE 1 Baseline characteristics of the whole cohort, participants with paired 4MGS change data and participants with missing paired 4MGS change data.

Variable	Whole cohort $n = 111$	Observed 4MGS paired data $n = 85$	Missing 4MGS paired data $n = 26$
Gender: male %	82	82	81
Age: years	72 (6)	72 (6)	72 (7)
MRC score	3 (1)	3 (1)	3 (1)
BMI: kg/m^2	27.9 (4.5)	28.3 (4.4)	26.7 (4.9)
FVC: L	2.57 (0.68)	2.65 (0.66)	2.29 (0.70)
FVC % predicted	75.8 (18.2)	77.6 (17.7)	69.9 (18.8)
DL_{CO}: mL/min/kPa	3.44 (1.21)	3.31 (2.78, 4.11)	3.34 (1.31)
DL_{CO} % predicted	43.2 (15.1)	41.1 (34.7, 50.3)	40.1 (32.2, 53.5)
CPI	49.3 (13.1)	49.2 (12.8)	51.8 (43.0, 59.1)
GAP index	4.3 (1.3)	4.3 (1.2)	4.4 (1.5)
Age-adjusted Charlson Co-morbidity Index	0 (0, 4)	0 (0, 4)	1 (0, 4)
Ischaemic heart disease %	23%	22%	25%
Pulmonary hypertension %	16%	16%	17%
Self-reported hospitalisations in previous year	0 (0, 0)	0 (0, 0)	0 (0, 1)
Self-reported chest infections in previous year	0 (0, 1)	0 (0, 1)	0 (0, 1)
Oxygen therapy: %			
Continuous	5	6	4
Ambulatory	11	11	12
Walking aid: %	5	7	0
Prescribed anti-fibrotic medication at visit 1: %	7	8	4
Prescribed anti-fibrotic medication during study: %	55	55	55
4MGS: m/s	0.93 (0.22)	0.94 (0.22)	0.88 (0.23)
6MWD: m	378 (115)	378 (121)	376 (99)
KBILD-Total score	57.5 (13.4)	57.4 (11.6)	57.5 (18.6)

Note: Baseline data reported as mean (standard deviation) or median (25th, 75th centile) unless stated otherwise.
Abbreviations: 4MGS, four-metre gait speed; 6MWD, Six-Minute Walk Test; CPI, Composite Physiologic Index; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GAP, gender age and lung physiology; KBILD, King's Brief Interstitial Lung Disease questionnaire; MRC, Medical Research Council Dyspnoea score.

significantly associated with the change in MRC, 6MWD and KBILD (Figure 2) but not with change in FVC % predicted ($r = 0.14$; $p = 0.23$), DL_{CO} %predicted ($r = 0.09$; $p = 0.56$), CPI ($r = -0.07$, $p = 0.70$) or GAP index ($r = 0.08$, $p = 0.64$).

In total, 16 (19%) experienced an adverse event (hospitalized $n = 6$, died $n = 10$, of which seven were hospitalized before they died) during the follow-up period for the complete case analysis. Similar proportions were observed in the multiple imputed set (20%: 22/111). The ROC plot for hospitalization/death demonstrated an AUC of 0.74 (4MGS change threshold >−0.07 m/s; sensitivity: 69%; specificity: 70%; $p = 0.003$; positive predictive value 33%, negative predictive value 91%) (Figure 3). This compared favourably to change in 6MWD, FVC %predicted, CPI and GAP index (AUC: 0.69, 0.62, 0.67, 0.57, respectively; Figure 3).

The Kaplan–Meier curve demonstrated a significant difference in time to hospitalization/death between 4MGS groups (substantial decline vs. minor decline/improvers) log-rank: $p = 0.007$; (Figure 4). Cox regression models demonstrated a greater risk of hospitalization/death at 6 months in those with substantial decline compared to minor decline or improvers (Table 3). After adjustment, the risk remained similar (HR [95% CI]: 4.61 [1.23–15.83]). Results for the multiple imputed sensitivity analyses were similar (Table 3).

DISCUSSION

In this prospective study, we demonstrate that 4MGS declines significantly over 6 months in patients with IPF. This change in 4MGS is significantly associated with the change in respiratory disability, exercise capacity and health-related quality of life, but not with change in lung function or composite predictors of mortality. We identified a decline in 4MGS of more than 0.07 m/s over 6 months as being clinically significant and associated with a shorter time to hospitalization or death. This is the first study to explore the prognostic potential of 4MGS change in IPF. Given that it is a simple, inexpensive test, we propose that change in 4MGS may have value as a surrogate endpoint of adverse outcome in IPF.

Most literature on the longitudinal change in gait speed have focused on community-dwelling older adults, and demonstrated that gait speed slows significantly over time.[25–27] Limited longitudinal data exist in other groups. Lai and colleagues reported a significant reduction in fast gait speed in 309 people listed for a liver transplant with a mean (standard error) reduction of 0.05 (0.05) m/s every 3 months.[28] In survivors recovering from Acute Respiratory Distress Syndrome, there was a 0.10 m/s improvement in 4MGS from six to 12 months,[16] whilst Kon et al. reported a mean (standard deviation) reduction in 4MGS of 0.04 (0.16) m/s over 1 year in 162 outpatients with COPD.[29]

Our study is the first to report decline in gait speed over time in people with IPF. We observed a decline in 4MGS over 6 months in IPF that was comparable to the decline observed in patients with COPD over 12 months,[29] consistent with different disease trajectories and more rapid functional decline in IPF compared to COPD. This decline correlated with decline in established exercise capacity (6MWD), increased respiratory disability (MRC) and deterioration in health-related quality of life measures (KBILD). However, there was no significant correlation with lung function parameters, which would suggest that change in 4MGS provides additional information to traditional lung function measurements, for example as a surrogate marker of frailty,[11] or reflecting the effects of extrapulmonary manifestations (such as heart disease). This supports previous data demonstrating that 4MGS measured at time of diagnosis provides additional prognostic information to FVC and established prognostic indices.[18]

TABLE 2 Baseline characteristics and change over 6 months (complete case analysis $n = 85$).

Variable	Baseline	Change	*p*-value
4MGS: m/s	0.94 (0.22)	−0.05 (−0.09 to −0.01)	0.02
MRC score	3 (1)	0.2 (−0.1 to 0.4)	0.06
BMI: kg/m^2	28.3 (4.4)	−0.1 (−0.4 to 0.3)	0.69
FVC: L	2.65 (0.66)	−0.16 (−0.24 to −0.09)	<0.001
FVC % predicted	77.6 (17.7)	−3.9 (−6.0 to −1.8)	<0.001
DL_{CO}: mL/min/kPa	3.31 (2.78, 4.11)	−0.14 (−0.80, 0.18)	0.02
DL_{CO} % predicted	41.1 (34.7, 50.3)	−2.20 (−7.08, 2.63)	0.10
CPI	49.2 (12.8)	1.2 (−2.8 to 5.2)	0.55
GAP index	4.3 (1.2)	0.1 (−0.2 to 0.3)	0.68
6MWD: m	378 (121)	−15 (−33 to 2)	0.08
KBILD-Total score	57.4 (11.6)	−0.5 (−3.1 to 2.0)	0.68

Note: Baseline data reported as mean (standard deviation) or median (25th, 75th centile) unless stated otherwise. Change data reported as mean (lower and upper 95% confidence limit) change or median (25th, 75th centile) change.

Abbreviations: 4MGS, four-metre gait speed; 6MWD, Six-Minute Walk Test; CPI, Composite Physiologic Index; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GAP, gender age and lung physiology; KBILD, King's Brief Interstitial Lung Disease questionnaire; MRC, Medical Research Council Dyspnoea score.

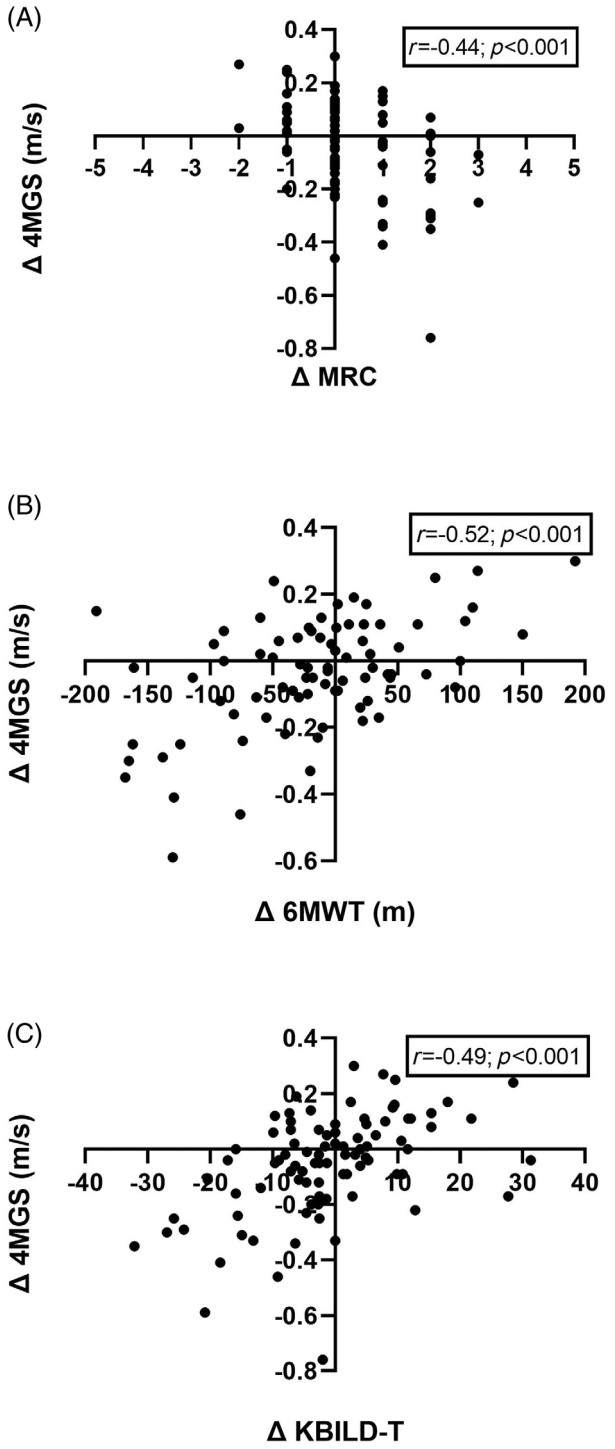

FIGURE 2 Relationship between change in 4MGS and change in (A) MRC, (B) 6MWD, and (C) KBILD-T. 4MGS, four-metre gait speed; 6MWD, Six-Minute Walk Test; KBILD-T, Kings Brief Interstitial Lung Disease-Total; MRC, Medical Research Council.

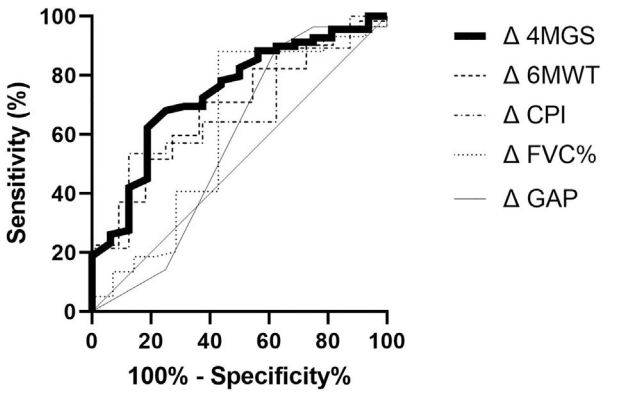

FIGURE 3 Receiver Operating Characteristic plot of change in 4MGS; 6MWD; CPI; FVC %predicted and GAP for all-cause non-elective hospitalization or death at 6 months. 4MGS, four-metre gait speed; 6MWD, Six-Minute Walk Test; FVC, forced vital capacity.

Studies investigating the relationship between change in gait speed and prognosis have focused on community-dwelling elders. These have consistently demonstrated either reduced risk of mortality with improving gait speed,[25,30] or increased mortality with the reduction in gait speed.[25,27,28,31] There is limited data evaluating the association between change in gait speed and hospitalization. Purser et al. demonstrated that for each annual 0.10 m/s increase in gait speed there were fewer inpatient hospitalization days (β [95% CI]) 2.3 (1.3–3.3) in elderly veterans.[32]

Our study is the first to explore the relationship between longitudinal decline in gait speed and adverse outcome in a respiratory population. Our findings are comparable to other populations as both complete case and multiple imputation analyses demonstrated that 4MGS deterioration over 6 months was independently associated with hospitalization or death in people with IPF. Furthermore, in people with IPF, we were able to identify a clinically significant change in 4MGS (greater than 0.07 m/s decline) that was associated with these adverse clinical outcomes. Our change threshold, as would be expected, was greater than previous estimates of minimum important difference for gait speed. For example, Perera et al., using both distribution- and anchor-based methods, estimated a small but meaningful change in gait speed to be close to 0.05 m/s for gait speed.[26] In the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study, Kwon and colleagues estimated the minimal magnitude of meaningful change in 4MGS to be 0.03–0.05 m/s and a substantial change to be a decline of 0.08 m/s.[33]

Whilst most experts believe that all-cause mortality and all-cause non-elective hospitalization best meet clinically meaningful end-point criteria,[34] others have argued that using mortality as a primary endpoint would be unacceptable to many symptomatic trial participants and make clinical trials unfeasible.[2] For example, in order for a 25% reduction in mortality to be statistically significant in a placebo-controlled trial of people with IPF, the enrolment of 2600 patients and 5 years of follow-up would be required.[35]

The most commonly used surrogate endpoint is FVC. FVC is valid and responsive, FVC change is associated with mortality[5] and regulatory approvals of both pirfenidone and nintedanib were based on their effect on FVC change. It is worth noting that these medications, despite slowing FVC, have little impact on health-related quality of life.[6,36]

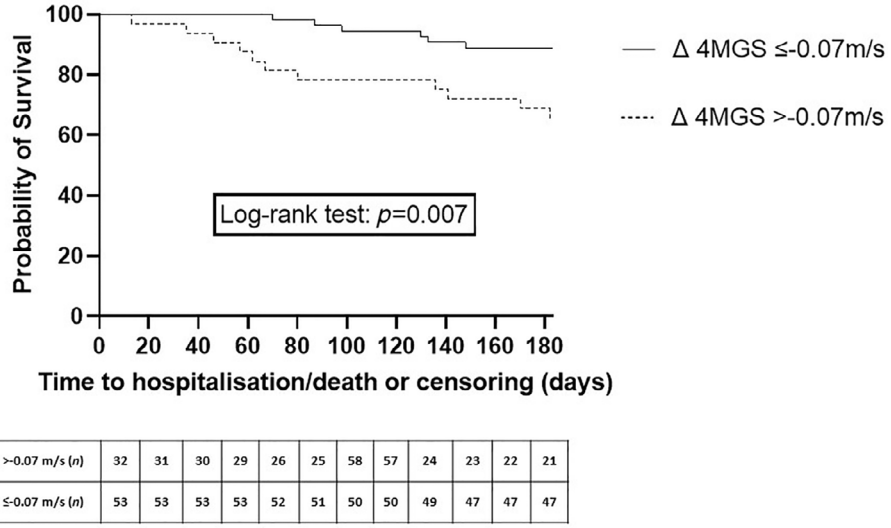

FIGURE 4 Kaplan–Meier curve demonstrating time to all-cause non-elective hospitalization or death at 6 months according to change in 4MGS ≤−0.07 m/s versus >−0.07 m/s. 4MGS, four-metre gait speed.

TABLE 3 Univariable and multivariable Cox proportional regression analysis for time to all-cause hospitalization or death.

	Univariable	Adjusted model[a]	
	HR (95% CI)	HR (95% CI)	*p*-value
Complete case analysis (n = 85)			
Change in 4MGS (categorical)			
Minor decline/improvers (decline 0.07 m/s or less)	1 (ref)	1 (ref)	0.017
Substantial decline (decline 0.07 m/s or more)	3.40 (1.24–9.37)	4.61 (1.234–15.83)	
Change in 4MGS (continuous: 0.1 m/s decrease)	1.48 (1.18–1.85)	2.29 (1.43–3.69)	0.001
Multiple imputation (n = 111)			
Change in 4MGS (categorical)			
Minor decline/improvers (decline 0.07 m/s or less)	1 (ref)	1 (ref)	0.009
Substantial decline (decline 0.07 m/s or more)	2.93 (1.013–7.74)	4.83 (1.49–15.69)	
Change in 4MGS (continuous: 0.1 m/s decrease)	1.47 (1.18, 1.82)	2.08 (1.43–3.02)	<0.001

[a]Adjusted for age (years), sex, BMI (<25, 25–30, >30 kg/m^2), FVC (% predicted), baseline 4MGS, DL_{CO} %predicted, prescribed anti-fibrotic therapy before visit 2 (yes/no).
Abbreviations: 4MGS, four-metre gait speed; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; Ref, reference.

Additional limitations include measurement variation of 5%–9% between readings of FVC[37] which impacts validity. Missing values also occur because of inability to perform the test due to cough, dyspnoea or infection[7] and a proportion who die from IPF have stable FVC prior to death.[7] Although there is evidence to show that 6MWD is associated with mortality in select individuals (FVC >55% predicted),[9] there are some limitations associated with 6MWD as a surrogate endpoint. From a practical basis, the 6MWD requires a straight, 30-metre course and sufficient time to perform a practice test with 30 min rest between testing[8] which may limit feasibility in some settings. Prognostic validity has not been demonstrated in individuals with more severe disease,[9,10] partly because of missing values due to the inability to perform sequential tests.

We have previously demonstrated that 4MGS measured at time of diagnosis is an independent predictor of all-cause mortality and non-elective hospitalization.[18] Additionally, stratification according to slow 4MGS identified significant impairments in exercise capacity, health status, dyspnoea and composite prognostic indices score despite similar lung function and radiological parameters.[17] The definition of a surrogate endpoint includes demonstrating that changes in the measure is associated with subsequent concordant changes in clinically relevant outcomes.[38] Therefore the current study extends the findings from previous validation studies by demonstrating that the decline in 4MGS is associated with non-elective all-cause hospitalization or death, and provides further evidence to support the potential value of 4MGS as a surrogate endpoint in IPF. Of note, the predictive value of change in 4MGS alone (AUC 0.74) was as least as good as established prognostic markers and indices for example, change in 6MWD (AUC 0.69), FVC % predicted (AUC 0.62), (CPI [AUC 0.67] and GAP [AUC 0.57]). Furthermore, from a purely practical perspective, the 4MGS is quicker to perform than either FVC or 6MWD. Although it is worth noting that the 6MWD is a

validated field walking test that can provide information on the presence of exercise-induced oxygen desaturation.

Importantly, the 4MGS appears to be responsive to both pharmacological and non-pharmacological intervention in IPF. Justice and colleagues reported a 0.12 m/s improvement in 4MGS following 3 weeks of intermittent senolytics (dasatinib plus quercetin),[39] whilst Nolan et al. demonstrated a significant improvement in 4MGS with pulmonary rehabilitation (mean [95% CI] change: 0.16 [0.12–0.20] m/s).[17] This corroborates recent work showing that improvement in functional capacity with pulmonary rehabilitation is associated with reduced mortality in IPF.[40]

This was a single-centre study, which may limit generalisability, and therefore our data need corroboration from other centres and cohorts. Although we did not validate our results in an external cohort, we specified an a priori hypothesis which partially mitigates against this concern. Furthermore, the prospective nature of our study compares favourably with the retrospective validation of established prognostic indices such as CPI[22] and GAP.[23] Given the consistent demonstration of the predictive ability of 4MGS in other populations,[13,14] the need for a validation cohort is less pronounced. In the literature, the 4MGS test has been predominantly evaluated in older populations. The mean age of our cohort was 72 years. Further research is needed to see whether our findings are generalizable to younger populations with IPF.

Only all-cause mortality and all-cause, non-elective hospitalization were reported. Neither the national database nor primary care records allowed the cause of death nor reason for hospitalization 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.[41,42] Nonetheless, identifying the cause of death or reason for hospitalization may have established whether 4MGS was a clinical indicator of multisystem wellbeing[11] or provided some measure of IPF severity.

Due to missing data, a complete case analysis could have biased the results and therefore, under the missing at random assumption, we imputed 4MGS change data. Although we included an auxiliary variable, used a robust method (multiple imputation by chained equations) and excluded those who died before follow-up, we cannot rule out that some of the information is actually missing not at random and therefore the results may still be biased. An assumption of missing at random is likely to make the imputation more conservative, but imputation will have assumed average outcomes.

Due to a small number of events, a composite outcome of all-cause hospitalization or all-cause death was chosen. Analyses whereby outcomes were looked as separately were also reported in the supplementary data, although events are small and therefore are likely underpowered.

In summary, in patients with a new diagnosis of IPF, 4MGS declines significantly over 6 months and those with a substantial decline (of more than 0.07 m/s) are at a higher risk of all-cause non-elective hospitalization or death over the subsequent 6 months. Further research is required to corroborate these findings but we propose that 4MGS may have potential as a surrogate endpoint of adverse outcomes in people with IPF.

AUTHOR CONTRIBUTION

Claire M Nolan: Conceptualization (equal); data curation (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); project administration (lead); resources (lead); supervision (equal); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Susie J Schofield:** Formal analysis (lead); validation (lead); visualization (supporting); writing – original draft (equal). **Matthew Maddocks:** Conceptualization (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Suhani Patel:** Data curation (supporting); writing – review and editing (supporting). **Ruth E Barker:** Data curation (supporting); writing – review and editing (supporting). **Jessica A. Walsh:** Data curation (supporting); writing – review and editing (supporting). **Oliver Polgar:** Data curation (supporting); writing – review and editing (supporting). **Peter M George:** Conceptualization (supporting); writing – review and editing (supporting). **Philip L Molyneaux:** Conceptualization (supporting); writing – review and editing (supporting). **Toby M Maher:** Funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Paul Cullinan:** Conceptualization (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **William D-C Man:** Conceptualization (lead); funding acquisition (equal); methodology (lead); project administration (equal); supervision (lead); writing – original draft (equal); writing – review and editing (equal).

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CONFLICTS OF INTEREST STATEMENT

Toby M. Maher is an Editorial Board member of Respirology and a co-author of this article. He was excluded from all editorial decision-making related to the acceptance of this article for publication.

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DATA AVAILABILITY STATEMENT

We did not obtain consent from participants to share their data outside of this study.

HUMAN ETHICS APPROVAL DECLARATION

All participants provided written informed consent and the study was approved by the London-Riverside Research Ethics Committee (15/LO/0015).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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