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Title:

Phenotypic characteristics associated with slow gait speed in Idiopathic Pulmonary Fibrosis

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Summary at a Glance:

We evaluated the 4 metre gait speed (4MGS), a simple functional performance test, in people with stable IPF. We found 4MGS a reliable, valid and responsive measure that can detect a patient phenotype with worse dyspnoea, exercise performance, quality of life and prognostic risk.

ABSTRACT

Background and objective: Usual gait speed over four metres (4MGS) is an established functional performance measure in older adults that consistently predicts adverse health outcomes, but few data exist in idiopathic pulmonary fibrosis (IPF). We assessed the reliability of 4MGS, its relationship with established outcome measures, and its responsiveness to pulmonary rehabilitation.

Methods: In four prospective IPF cohorts, 4MGS inter-observer (n=46) and test-retest (n=46) reliability, concurrent validity (n=65 and n=62) and responsiveness (n=60) were determined. The phenotypic characteristics of all patients stratified according to slow 4MGS (<0.8ms^{-1}) were compared, including lung function parameters, high-resolution computed tomography (HRCT) of the chest, six minute walk test distance (6MWD), Medical Respiratory Council (MRC) Dyspnoea score, King's Brief Interstitial Lung Disease (KBILD) questionnaire and Gender Age Physiology (GAP) prognostic index.

Results: Intra-class correlation coefficients for inter-observer and test-retest reliability were 0.996 and 0.983 respectively. There was a strong association between 4MGS and 6MWD (r=0.76; p<0.0001) and moderate correlations with MRC (r=-0.56), KBILD (r=0.44) and GAP index (r=-0.41); all p<0.005. 4MGS improved significantly with pulmonary rehabilitation (mean (95% confidence interval) change: 0.16 (0.12 to 0.20) ms^{-1}, effect size 0.65. Patients with slow 4MGS had significantly worse exercise performance (6MWD: -167 (-220 to -133)m), dyspnoea, health status and prognosis index than those with preserved 4MGS, despite similar lung function and HRCT parameters.

Conclusion: 4MGS is a simple, reliable, valid and responsive tool that may detect a patient phenotype with worse exercise performance, dyspnoea, health status and prognosis index in stable IPF.

Key words:

Idiopathic Pulmonary Fibrosis, gait, outcome assessment, phenotype, walking speed.

Short title:

Slow gait speed in IPF

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), a disease of older people, is a progressive fibrosing lung condition with a median survival of 2.8 to 4.2 years.[1] It is increasingly recognised that ageing and related extra-pulmonary manifestations, such as muscle dysfunction, depression and cardiovascular disease, contribute to morbidity in IPF.[2] There is growing interest in assessment tools outside of lung function and thoracic imaging that reflect these aspects. Due to the progressive nature of IPF, these tools should be feasible and reproducible in relevant healthcare environments, from the clinic to the hospital bedside, home and palliative care settings, and acceptable to those with severe exertional dyspnoea.

4 metre gait speed (4MGS), a measure of usual walking speed, is widely used in gerontology as a measure of functional and lower limb performance,[3] and a surrogate marker of sarcopenia and frailty.[4] It has been consistently shown to be an independent predictor of physical and cognitive disability, falls, hospitalisation and mortality in community-dwelling elders,[3, 5, 6] and is often described as a 'vital sign' or indicator of 'multi-system well-being'.[5, 7] 4MGS has been shown to be feasible in home,[8] acute hospital,[9] and outpatient settings.[10] In older adults, slow gait speed is defined as <0.8 ms^{-1},[11, 12] corresponding to a reduction in median life expectancy.[12]

The relevance of 4MGS to chronic respiratory disease has not been fully realised, with studies largely confined to chronic obstructive pulmonary disease[9, 10, 13, 14] or acute respiratory distress syndrome.[15] To date no studies have examined 4MGS in an IPF-specific population, but three have evaluated gait speed in interstitial lung disease (ILD) patients.[16-18] Significant associations between 4MGS and measures of dyspnoea and exercise capacity were reported in people with chronic lung disease (n=55 ILD)[16] and ILD,[18] and 4MGS was shown figuratively to improve post-pulmonary rehabilitation (PR) in ILD patients but absolute data was not reported which renders interpretation difficult.[18] Furthermore, in one study gait speed was measured over 2.4 metres[17] a

distance which is not sufficiently long to ensure measurement accuracy or satisfactory test-retest reliability.[19, 20] Accordingly, we hypothesised that 4MGS may be a useful assessment tool in IPF. The aims of the study were to: 1) determine the reliability, concurrent validity and responsiveness of 4MGS in IPF; 2) describe the phenotypic characteristics of IPF patients and "slow" 4MGS.

METHODS

Study participants

Participants were prospectively recruited from outpatient respiratory, ambulatory oxygen and PR clinics at the Royal Brompton and Harefield Hospitals, UK between January and December 2015. We included people diagnosed with IPF by a specialist ILD multidisciplinary team according to international guidelines,[1] and excluded those with co-morbidities that would make exercise unsafe (e.g. unstable ischemic heart disease). All participants provided informed written consent and the studies were approved by the London-Riverside Research Ethics Committee (14/LO/2248, 14/LO/2247, 15/LO/0015) and registered on clinicaltrials.gov (NCT02445157, NCT02436278, NCT02530736).

Measurements

4MGS was measured on a flat, 4-metre course with a standing start with patients walking at their usual speed as previously described.[10] The assessment was undertaken by trained research staff and physiotherapy assistants who followed a standard operating procedure. Two tests were performed with minimal rest and the faster of the two, measured by stopwatch, was used to calculate gait speed. Further details are available at www.healthmeasures.net.

Pulmonary function tests included spirometry (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC)) and diffusion capacity for carbon monoxide (DL_{CO}) (Jaeger Master screen PFT, Carefusion Ltd., UK).[21] The composite physiologic index (CPI)[22] and the gender, age and physiology (GAP) index, a prognostic staging system[23] were calculated as previously described. High resolution Computed Tomography (HRCT) scans were obtained using a 64-slice multiple detector scanner (Somatom Sensation 64, Siemens, Germany) and visually scored by two sub-specialist, experienced, thoracic radiologists (DMH, JJ) for the extent of ILD (to the nearest 5%) as described previously.[24] The six minute walk distance (6MWD) was conducted on a 30-metre course according to the international guidelines.[25] The incremental shuttle walk (ISW) was conducted on a 10-metre course, as previously described.[26] Health status was measured using the King's Brief Interstitial Lung Disease (KBILD) questionnaire.[27] The Medical Research Council Dyspnoea scale (MRC)[28] was used to assess dyspnoea and respiratory disability, whilst co-morbidity burden was quantified using the age-adjusted Charlson Co-morbidity Index.[29]

Reliability, validity and stratification

To evaluate test-retest and inter-observer reliability, participants performed the 4MGS test on two separate occasions 7-14 days apart in a clinic consultation room. On the first occasion, two observers measured 4MGS simultaneously.

The concurrent validity of 4MGS was assessed using a prospective study comprising two independent cohorts. The main cohort was recruited from a specialist ILD clinic at the Royal Brompton Hospital. Measurements included 4MGS, pulmonary function tests (calculated CPI and GAP index), HRCT, 6MWD, KBILD and MRC. A second validation cohort was recruited from an ambulatory oxygen assessment clinic; patients underwent 4MGS, spirometry, 6MWD, and MRC.

Patients in the main cohort were stratified according to the gait speed prognostic cut-point recommended by expert consensus groups (slow gait speed: $<0.8ms^{-1}$; preserved gait speed: $\geq 0.8ms^{-1}$),[11, 12] and differences in phenotypic characteristics compared between groups.

Response to Pulmonary Rehabilitation

IPF patients were prospectively recruited from the Harefield PR Unit, UK and underwent a multidisciplinary, outpatient 8-week PR programme as previously described.[30] 4MGS, MRC, ISW, and KBILD were recorded before and after the programme.

Statistical analysis

For the reliability analysis, assuming a 5% significance level and 80% power with two observations, a minimum of 39 patients would be needed to show an intra-class correlation co-efficient (ICC) >0.6 when the true coefficient is 0.8.[31] For the validity study, to demonstrate a moderate strength correlation (r>0.4) between 4MGS and 6MWD against the null hypothesis (r=0) with 90% power at a p-value threshold of 0.05 would require a minimum of 62 patients. For the responsiveness study, previous data indicated that the difference in the response of matched pairs is normally distributed with a standard deviation of $0.13ms^{-1}$.[13] If the true difference in the mean response of matched pairs is $0.08ms^{-1}$, a minimum 30 pairs of patients would be needed with 90% power at 5% significance level to reject the null hypothesis that this response difference is zero.
Data analyses were performed using GraphPad Prism 6 (GraphPad Software, USA) and SPSS version 22 (IBM, USA). Single measure ICCs of consistency and random effect were calculated with 95% confidence intervals (95%CI) to examine inter-observer and test-retest reliability. Measurement variability was determined by calculating the standard error of measurement (SEM)

and percentages of SEM (SEM%). Bland–Altman plots were plotted to demonstrate the 95% limits of agreement. Pearson's correlation co-efficient (Spearman's rank for non-parametric data) was used to quantify the correlation between 4MGS and other measures. Multivariable regression was used to investigate determinants of 4MGS. 6MWD, MRC, GAP index, FVC %predicted, body mass index, age-adjusted Charlson Co-morbidity Index and KBILD-T were considered as independent variables. Age, sex and DL_{CO} %predicted were not considered as they are components of the GAP index. After checking for co-linearity between independent variables ($r < 0.5$), a stepwise approach was used to retain or remove them from the model; entry criterion $p < 0.05$, removal criterion $p \geq 0.10$. Between-group differences were assessed using unpaired t-tests (Mann Whitney U test for nonparametric data). Paired t-tests (Wilcoxon Signed Rank test for nonparametric data) were used to compare outcomes before and after PR and the effect size was calculated using Cohen's d. Statistical significance was considered to be $p<0.05$.

RESULTS

Reliability

Sixty patients were approached: 13 declined to participate and one did not meet the inclusion criteria. The baseline characteristics of the recruited 46 patients were: 33 (72%) male; mean (standard deviation) age 75 (7.6) years; body mass index 27.1 (5.8)kg/m^2; 4MGS 0.94 (0.25)ms^{-1}; FVC 71.9 (20.8)%predicted; DL_{CO} 47.4 (21.3)%predicted.

4MGS showed high inter-observer and test-retest reliability with ICC values (95%CI) of 0.996 (0.992 to 0.998) and 0.983 (0.970 to 0.991) respectively. The mean differences between test occasions and observers were 0.001ms^{-1} and 0.01ms^{-1} respectively with no significant change in gait speed between the two occasions (p=0.85) or between observer values (p=0.42). Measurement variability was low with SEM and SEM% values of 0.002 and 0.16% for inter-observer and 0.0002

and 0.65% for test-retest reliability respectively. Narrow limits of agreement between observers (0.05 to -0.04) and occasions (0.09 to -0.09) were demonstrated in the Bland Altman plots.

Validity and stratification

For the main cohort, we approached 87 patients: 17 declined to participate and five did not meet the inclusion criteria. The baseline characteristics of the 65 recruited patients and the relationship between 4MGS and other outcome measures are reported in Table 1. Seven patients used a walking aid whilst seven other patients were prescribed ambulatory oxygen. 4MGS was strongly correlated with 6MWD ($r=0.76$, $p<0.001$), and had a moderately strong relationship with health status, (KBILD total: $r=0.44$, $p=0.0003$), and a negative correlation with MRC ($r=-0.56$, $p<0.0001$) and GAP index ($r=-0.41$; $p=0.002$). No significant relationships were seen between 4MGS and HRCT extent of disease, nor with lung function parameters such as FVC or DL_{CO} %predicted.

The independent validation cohort (n=62) undergoing ambulatory oxygen assessment had the following baseline characteristics: 46 (74%) men; mean (standard deviation) age 74 (8) years; FVC 69 (22)%predicted; 4MGS 0.87 (0.25)ms^{-1}; MRC 3(1); 6MWD 229 (103)m; ISW 246 (131)m. Similar to the main cohort, 4MGS correlated strongly with 6MWD ($r=0.85$, $p<0.0001$), and negatively with MRC ($r=-0.59$, $p=0.0002$).

Using a stepwise multivariable linear regression model to describe 4MGS, 6MWD alone explains 57% of the variance in 4MGS (Table 3, Model 1). However the addition of GAP index explained 67% of the variance in 4MGS (Table 3, Model 3). The equation to predict 4MGS is: mean (95% confidence interval) 4MGS = 0.001 (0.001 to 0.002) * 6MWT -0.040 (-0.078 to -0.002) * GAP index + 0.586 (0.356 to 0.817) ms^{-1}, $r^2=0.67$, $p<0.0001$.

In the main cohort, 24 (37%) participants had a "slow 4MGS" and 63% had preserved 4MGS. Those with slow 4MGS were older, but there were no differences in sex distribution, lung function parameters or radiological quantification of ILD. However large deficits in exercise capacity, respiratory disability, health status and multi-dimensional prognostic index were observed in the slow 4MGS group (Table 2 and Figure 1). For example, there was a mean (95%CI) 6MWD difference of 167 (133 to 220)m between the slow and preserved gait speed groups.

Response to Pulmonary Rehabilitation

Of 79 IPF patients referred to the Harefield PR Unit, nine declined to participate, three did not meet the inclusion criteria, and seven failed to complete PR. The baseline characteristics and response to PR of these patients are in Table 4. 4MGS was strongly correlated with ISW (r=0.74; p=<0.0001). Mean (95%CI) change in 4MGS was 0.16 (0.12 to 0.20)ms^{-1} with effect size of 0.65. There was no significant correlation between change in and baseline 4MGS (r=-0.23; p=0.08).

DISCUSSION

This study determines the reliability, validity and responsiveness of 4MGS in an IPF-specific population. We demonstrated high inter-observer and test-retest reliability and in two independent cohorts, 4MGS correlated strongly with 6MWD (the best characterised field walking test in IPF) and moderately with measures of dyspnoea, health status and a multi-dimension prognostic index. When used to stratify participants according to slow gait speed, 4MGS could identify differences in phenotypic characteristics such as exercise capacity, health status, dyspnoea and prognosis index despite similar lung function and radiological parameters. We propose 4MGS has potential as a simple tool in the assessment and stratification of patients with IPF.

There is a paucity of data on 4MGS in this population. In earlier work, DePew *et al* studied 70 people with chronic lung disease (n=55 ILD – IPF data not reported) and demonstrated, like our study, a strong correlation between 4MGS and 6MWD (r=0.70) and a significant negative correlation with MRC (r=-0.44) in the whole group.[16] Mendes *et al* measured the short physical performance battery (SPPB) (a component of which is usual gait speed measured over 2.4 metres) in 26 advanced ILD patients (n=23 IPF) listed for lung transplantation, and demonstrated lower SPPB scores compared with 12 age-matched controls.[17] Absolute gait speed values were not reported, and the relationship between gait speed and measures of functional status were not presented. Furthermore, 2.4 metres may not be sufficiently long to ensure measurement accuracy[19] and has worse test-retest reliability compared to using 4 metres.[20] In a study involving 52 ILD patients (n=20 IPF), Ryerson *et al* reported a weak but significant relationship between gait speed and measures of dyspnoea (Baseline Dyspnoea Index: r=-0.36; University of California San Diego Shortness of Breath Questionnaire: r=0.37).[32] They also showed figuratively that 4MGS improved with a 6 to 9 week outpatient PR programme in 54 ILD patients (n=22 IPF) (p=0.01), but neither absolute values nor effect size were reported leading to difficulty with data interpretation.[18] To our knowledge, our study is the first to report the reliability of 4MGS, provide evidence to support its validity as a measure of functional status, and demonstrate its responsiveness to PR in adequately powered IPF-specific cohorts.

There are some limitations to 4MGS and our study. First, there is a recognised "ceiling effect" associated with 4MGS,[13] and therefore it may have more value as an outcome or stratification tool in poorly functioning individuals than in those with well-preserved functional status. Second, 4MGS is not a measure of peak exercise capacity,[33] but an indicator of functional impairment, particularly in frail older patients, and has been previously used as a functional outcome measure in interventional pharmacological trials.[34] Third, as the study participants were primarily outpatients attending specialist ILD clinics at a tertiary centre, our data need to be corroborated in

other IPF populations and settings. Fourth, we were unable to comment on the longitudinal validity of 4MGS in IPF, particularly with regards to prognostic value. Given the prognostic value of the 6MWD and the GAP index in IPF, and the relationships observed between 4MGS and these prognostic indices in our study, we hypothesise that 4MGS will help predict mortality in IPF, as has been consistently observed in community-dwelling elders.[12] Future longitudinal studies are required to confirm this hypothesis. Fifth, 4MGS showed no relationship with lung function or HRCT parameters, which arguably are a more precise reflection of lung disease severity. Therefore we do not envisage a role for 4MGS as a primary outcome measure in trials of anti-fibrotic drugs, but it may have value in stratifying IPF patients. We demonstrated that the "slow gait speed" clinical phenotype exhibited significantly reduced exercise capacity, increased dyspnoea and poor health status in comparison to those with preserved gait speed. However, despite large differences between slow and preserved gait speed groups, there was no significant difference in lung function or HRCT results, suggesting that extra-pulmonary factors such as ageing, skeletal muscle manifestations, and frailty[35, 36] may contribute significantly to morbidity and perhaps prognosis. This is corroborated by data from a recent trial of anti-fibrotic medication that showed little impact on health status.[37]

4MGS has several attractive properties. It is cheap and quick to perform, and requires little space. As walking is familiar to the vast majority of adults, the test is easy to understand and has been shown to be reliable even in people with cognitive dysfunction.[38] These properties mean that 4MGS could be adopted in almost any clinical environment including the home[19] or hospital bedside.[9] We believe that 4MGS may play a particular role in measuring functional performance in advanced IPF when measuring exercise capacity with field walking tests like the 6MWTmight become less acceptable to patients with severe ventilatory limitation or dyspnoea,[39] leading to missing data in research and clinical settings. Additionally, the 6MWT requires a 30 metre course

which may limit its applicability in many settings compared to 4MGS.. In this study, we demonstrated that 4MGS was responsive to PR, and as responsive as the ISW, an established field walking test widely used by the PR community.[13] However, future research is needed to evaluate the feasibility and potential function of longitudinal measurements of 4MGS.

Conclusion

4MGS, a simple functional performance measure used in gerontology, is reliable, valid and responsive in IPF. Compared to those with preserved gait speed, the "slow gait speed" phenotype is characterised by significantly reduced exercise capacity, increased dyspnoea and impaired health status despite comparable lung function and HRCT abnormalities.

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REFERENCES 50 ALLOWED – all at the end of the manuscript – will rearrange when text has been amended.

TABLES

TABLE 1: Baseline characteristics and relationship (r value) between 4MGS and other outcome measures in the first validity cohort (n=65)

Variable (n=65)	Baseline	r value	p value
Sex (male: n (%))	58 (89)	-	-
Age (years)	72 (7)	-0.35 (-0.54 to -0.11)	0.0049
MRC	3 (1)	-0.56 (-0.71 to -0.36)	<0.0001
BMI (kg/m^2)	27.3 (4.4)	-0.01 (-0.26 to 0.23)	0.91
Age-adjusted Charlson Co-morbidity Index	0 (0, 5)	-0.13 (-0.37 to 0.13)	0.31
FVC (L)	2.6 (0.7)	0.14 (-0.10 to 0.37)	0.25
FVC (% predicted)	73.2 (16.5)	0.15 (-0.10 to 0.38)	0.24
FEV_1/FVC	81.2 (6.8)	0.12 (-0.13 to 0.35)	0.35
DL_{CO} (% predicted)	43.8 (14.3)	0.13 (-0.14 to 0.38)	0.35
CPI	49.7 (10.8)	-0.13 (-0.38 to 0.14)	0.35
GAP index			
Stage 1 (%)	22	-	-
Stage 2 (%)	67	-	-
Stage 3 (%)	11	-	-
GAP score	4 (1)	-0.41 (-0.61 to -0.16)	0.002
4MGS (ms^{-1})	0.89 (0.25)	-	-
6MWD (m)	355 (132)	0.76 (0.63 to 0.85)	<0.0001
KBILD – Psychological	60.4 (22.1)	0.34 (0.11 to 0.54)	0.006
KBILD – Breathlessness and activities	40.9 (19.2)	0.45 (0.23 to 0.62)	0.0002
KBILD – Chest symptoms	66.7 (24.0)	0.42 (0.19 to 0.60)	0.0006
KBILD – Total	56.7 (13.8)	0.44 (0.22 to 0.62)	0.0003
Total lung ILD extent on HRCT (%)	33.6 (13.6)	-0.05 (-0.30 to 0.21)	0.71

Data are reported as mean (standard deviation) and r value (95% confidence interval) unless stated otherwise

Abbreviations: MRC: Medical Respiratory Council Dyspnoea score; BMI: Body Mass Index; Charlson: Charlson Co-morbidity index; FVC: Forced Vital Capacity; FEV_1/FVC: ratio of

Forced Expiratory Volume in 1 second and Forced Vital Capacity; DL_{CO}: Diffusing Capacity for Carbon Monoxide; CPI: Composite Physiologic Index; GAP: Gender, Age and Pulmonary Function index; 4MGS: 4 Metre Gait Speed; 6MWD: 6 Minute Walking Test distance; KBILD: King's Brief Interstitial Lung Disease questionnaire; HRCT: High resolution computed tomography

TABLE 2: Phenotypic characteristics and between group differences of patients with slow and preserved gait speed

Variable (n=65)	Slow gait speed <0.80ms^{-1} (n=24)	Preserved gait speed ≥0.80ms^{-1} (n=41)	Between group difference	p value
Sex (male: n (%))	24 (100)	34 (83)	-10 (-17)	0.03
Age (years)	75 (7)	71 (7)	-4 (-8 to -1)	0.02
MRC	3.4 (1.0)	2.7 (1.0)	-0.7 (-0.2 to -0.1)	0.01
BMI (kg/m^2)	27.2 (4.0)	27.3 (4.7)	0.1 (-2.2 to 2.4)	0.91
Age-adjusted Charlson Co-morbidity Index	0 (0, 5)	2 (0, 5)	2 (0, 2)	0.98
FVC (L)	2.6 (0.7)	2.6 (0.6)	0.01 (-0.33 to 0.35)	0.95
FVC (% predicted)	69.0 (14.9)	75.6 (17.0)	6.6 (-1.9 to 15.1)	0.12
FEV_1/FVC	80.4 (8.2)	81.7 (6.0)	1.3 (-2.2 to 4.8)	0.46
DL_{CO} (% predicted)	44.2 (16.7)	42.5 (14.3)	-1.7 (10.4 to 6.9)	0.69
CPI	50.4 (12.9)	49.3 (9.6)	-1.1 (-7.3 to 5.1)	0.73
GAP index	5 (1)	4 (1)	-0.8 (-1.4 to -0.2)	0.01
4MGS (ms^{-1})	0.64 (0.13)	1.04 (0.17)	0.40 (0.32 to 0.48)	<0.0001
6MWD (m)	250 (92)	416 (112)	167 (133 to 220)	<0.0001
KBILD - Psychological	52.7 (16.0)	65.0 (23.9)	12.3 (1.2 to 23.3)	0.03
KBILD – Breathlessness and activities	32.1 (16.0)	46.2 (19.2)	14.1 (4.8 to 23.5)	0.004
KBILD – Chest symptoms	56.7 (23.2)	72.8 (22.7)	16.1 (4.3 to 27.9)	0.01
KBILD - Total	50.8 (11.1)	60.2 (14.2)	9.4 (2.6 to 16.2)	0.007
Total lung ILD extent on HRCT (%)	33.2 (15.4)	33.9 (12.9)	0.7 (-6.9 to 8.2)	0.86

Data are reported as mean (standard deviation), median (25th, 75th centile), mean (95% confidence interval) change or median (25th, 75th centile) change unless stated otherwise

Abbreviations: MRC: Medical Respiratory Council Dyspnoea score; BMI: Body Mass Index; Charlson: Charlson Co-morbidity index; FVC: Forced Vital Capacity; FEV_1/FVC: ratio of Forced Expiratory Volume in 1 second and Forced Vital Capacity; DL_{CO}: Diffusing Capacity for

Carbon Monoxide; CPI: Composite Physiologic Index; GAP: Gender, Age and lung Physiology; 4MGS: 4 Metre Gait Speed; 6MWD: 6 Minute Walking Test distance; KBILD: King's Brief Interstitial Lung Disease questionnaire; HRCT: High resolution computed tomography.

TABLE 3: Multivariable linear regression models to predict 4MGS

Model	***Covariate***	**β *co-efficient (95% CI)***	***p-value***	***Model r^2 (adjusted r^2)***
I	*6MWD*	*0.001 (0.001 to 0.002)*	*<0.0001*	*0.58 (0.57)*
II	*6MWD*	*0.001 (0.001 to 0.002)*	*<0.0001*	*0.59 (0.58)*
	MRC	*-0.038 (-0.088 to 0.011)*	*0.13*	
III	*6MWD*	*0.001 (0.001 to 0.002)*	*<0.0001*	*0.67 (0.66)*
	GAP index	*-0.040 (-0.078 to -0.002)*	*0.04*	

Abbreviations: 6MWD: 6 Minute Walking Test distance, MRC: Medical Research Council Dyspnoea score, GAP: Gender, Age and lung Physiology; CI: Confidence Interval

TABLE 4: Baseline characteristics and response to pulmonary rehabilitation

Variable (n=60)	**Baseline characteristics**	**Change following PR**	**p value**
Sex (male) (n (%))	43 (72)	-	-
Age (years)	74 (69, 79)	-	-
MRC	3 (1)	-0.7 (-0.5 to -0.9)	<0.001
BMI (kg/m^2)	27.7 (4.5)	0.1 (-0.5 to 0.6)	0.94
Age-adjusted Charlson	4 (0, 4)	-	-
FVC (%)	75 (21)	0.8 (-1.2, 2.8)	0.41
Walking aid (n (%))	-	-	-
Walking stick	1 (2)	-	-
LTOT (n (%))	4 (7)	-	-
ABOT (n (%))	8 (13)	-	-
Pirfenidone (n (%))	7 (12)	-	-
Nintedanib (n (%)	0 (0)	-	-
4MGS (ms^{-1})	0.95 (0.24)	0.16 (0.12 to 0.20)	<0.001
ISW (m)	296 (184)	50 (10, 80)	<0.001
KBILD-Psychological	62.1 (17.8)	6.0 (1.9 to 10.1)	<0.01
KBILD-Breathlessness and activities	41.9 (35.6, 52.5)	6.1 (0.01, 12.6)	<0.01
KBILD-Chest symptoms	69.2 (18.8)	4.6 (-1.0, 10.3)	0.11
KBILD-Total	58.3 (10.9)	4.6 (3.7 to 2.1)	<0.001

Data are reported as mean (standard deviation), median (25^{th}, 75^{th} centile), mean (95% confidence interval) change or median (25^{th}, 75^{th} centile) change unless stated otherwise

Abbreviations: MRC: Medical Respiratory Council Dyspnoea Score; BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV_1/FVC: ratio of Forced Expiratory Volume in 1 second and Forced Vital Capacity; LTOT: long-term oxygen therapy; ABOT: ambulatory oxygen therapy; 4MGS: 4 Metre Gait Speed; ISW: Incremental Shuttle Walk Test; CRQ: Chronic Respiratory Questionnaire; KBILD: King's Brief Interstitial Lung Disease questionnaire.

FIGURE LEGEND

- Figure 1: Slow and preserved gait speed in cohort 1 a) 6MWD; b) KBILD T; c) MRC Dyspnoea score; d) GAP index

  Abbreviations: 6MWD:6 minute walk distance; KBILD T: King's Brief Interstitial Lung Disease questionnaire – Total score; MRC: Medical Research Council; GAP: Gender, Age, Physiology.

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