Gait speed and adverse outcomes following hospitalised exacerbation of COPD

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TAKE HOME MESSAGE

Usual gait speed measured at hospital discharge is independently associated with adverse outcomes in COPD. Given the simplicity of this test, it should be considered for identification of at-risk patients to enable planning of post-discharge care.

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ABSTRACT

Four-metre gait speed (4MGS) is a simple physical performance measure and surrogate marker of frailty that is associated with adverse outcomes in older adults. We aimed to assess the ability of 4MGS to predict prognosis in patients hospitalised with acute exacerbations of COPD (AECOPD).

213 participants hospitalised with AECOPD (52% male, mean age and FEV_1, 72 years and 35% predicted) were enrolled. 4MGS and baseline demographics were recorded at hospital discharge. All-cause readmission and mortality were collected for one year after discharge, and multivariable Cox-proportional hazards regression were performed. Kaplan-Meier and Competing risk analysis was conducted comparing time to all-cause readmission and mortality between 4MGS quartiles.

111 participants (52%) were readmitted, and 35 (16%) died during the follow-up period. 4MGS was associated with all-cause readmission, with an adjusted subdistribution hazard ratio of 0.868 (95% CI 0.797 to 0.945; p=0.001) per 0.1m/s increase in gait speed, and with all-cause mortality with an adjusted subdistribution hazard ratio of 0.747 (95% CI: 0.622 to 0.898; p=0.002) per 0.1m/s increase in gait speed. Readmission and mortality models incorporating 4MGS had higher discrimination than age or FEV_1 % predicted alone, with areas under the receiver operator characteristic curves of 0.73 and 0.80 respectively. Kaplan-Meier and Competing Risk curves demonstrated that those in slower gait speed quartiles had reduced time to readmission and mortality (log rank both p<0.001).

4MGS provides a simple means of identifying at-risk patients with COPD at hospital discharge.

This provides valuable information to plan post-discharge care and support.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are one of the commonest reasons for emergency hospital admission in higher income countries and a major contributor to healthcare costs in COPD (1). For the individual, hospitalisation for AECOPD represents a major life event with significant impacts on physical functioning and health-related quality of life (2), as well as an increased risk of hospital readmission and mortality (3, 4).

Prognostic tools are of interest as they help risk stratify patients at the healthcare system level, as well as providing additional information that might help the clinician individualise post-discharge management. In a recent systematic review, 408 prognostic models were identified in COPD, including 155 models from the acute hospital setting (5). Many models comprised retrospective analysis of routinely collected data such as baseline demographics, baseline severity of disease or indices of hospital admission severity. A limitation is the most frequently included variables in these prognostic models are non-modifiable (age and sex) or have limited potential to improve (forced expiratory volume in 1 second (FEV_1)), and therefore do not inform clinicians on how prognostic risk might be influenced. (5)

There is growing interest in the prognostic role of simple functional tests in COPD as deterioration in functional capacity represents a common pathway that integrates the multisystem consequences of the disease (6). Functional performance may also be amenable to exercise-based interventions such as pulmonary rehabilitation (PR). The four metre gait speed (4MGS) is a measure of a patient's usual walking speed (7), and has been widely used as a simple functional performance measure and surrogate marker of frailty in older adults.

It has been consistently shown to be a strong predictor of adverse events in community-dwelling older adults (8, 9). Gait speed has also been shown to be of prognostic value in stable chronic respiratory conditions, such as COPD (10), idiopathic pulmonary fibrosis (IPF) (11) and acute respiratory distress syndrome (ARDS) survivors (12). Importantly gait speed has been shown to be modifiable, particularly by exercise based interventions in both community dwelling older adults (13), neurological conditions (14, 15) and in chronic respiratory disease (16, 17).

Due to its simplicity and need for little space, the 4MGS is feasible in most clinical settings, including the acute hospital setting. Walking speed is associated with increased length of hospital admission (18, 19) and increased risk of not being discharged home (18) in hospitalised older adults. In a hospitalised cohort of patients with AECOPD followed up for 90 days after discharge, we have previously demonstrated that 4MGS was an independent predictor of hospital readmission (10), and in a cohort surviving acute hypercapnic respiratory failure in intensive care, gait speed measured at hospital discharge was associated with 6 month readmission and death (20).

The aim of the current study was to evaluate the ability of 4MGS to independently predict prognosis in patients hospitalised with AECOPD. We hypothesised that patients with slower 4MGS at discharge would have increased risk of (and reduced time to) all-cause mortality and hospital readmission.

METHODS

The current study was a planned secondary analysis of a prospective cohort study (10). Ethical approval was obtained from the London-Dulwich Research Ethics Committee (11/LO/1250) and registered on UK Clinical Research Network Portfolio (ID: 11212) and ClinicalTrials.gov (NCT01507415). All participants provided written informed consent.

Full details of the study design, eligibility criteria and inpatient care have previously been described (10). In summary, participants were recruited at discharge following hospitalisation for a primary diagnosis of acute exacerbation of COPD, age over 35 years and residing in the London Borough of Hillingdon. They had to be ambulatory at discharge (defined as being able to walk five metres unassisted). Exclusion criteria included cardiac instability, a predominant neurological or orthopaedic limitation to walking and severe cognitive dysfunction. A study flow chart is shown in Figure 1.

Measurements:

All the measurements were collected within 24 hours before hospital discharge. The 4MGS was conducted as described previously (7). Other measurements included smoking history, body mass index (BMI), FEV_1 (21), self-reported hospital admissions in previous year, length of hospital stay, respiratory disability (Medical Research Council (MRC) dyspnoea score (22)), co-morbidity burden (Charlson co-morbidity index (23)), the DECAF Score (extended MRC Dyspnoea Score, Eosinopenia, Consolidation, Acidaemia, atrial Fibrillation (24)), health-related quality of life (St George's Respiratory Disease Questionnaire (SGRQ) (25)), independence in activities of daily living (KATZ index (26)), self-reported physical activity (modified Minnesota Leisure-time Physical Activity Questionnaires (27)), and previous participation in pulmonary rehabilitation. Participants were followed up for 12 months after

hospital discharge. All-cause hospital readmissions were determined using patient recall, hospital databases and General Practitioner health records. Survival status was collected using central NHS database and General Practitioner health records.

Sample size:

The required sample size for the primary outcome (readmission at 90 days) has been previously described (10), with a recruitment target of 225 patients, accounting for 10% loss to follow-up. Assuming a 50% readmission rate at one year (one non-admitted control for every admitted case), this sample size would have more than 99% power to show that a multivariable model incorporating 4MGS would demonstrate an area under the curve (AUC) of a receiver operating characteristic (ROC) analysis of 0.70 compared with the null hypothesis of 0.50. This sample size would also have more than 95% power to demonstrate that a multivariable model incorporating 4MGS would demonstrate an AUC of 0.70 compared with the null hypothesis of 0.50, assuming a mortality rate of 20% at one year (one death for every four survivors).

Analysis:

Participants' baseline characteristics were analysed using descriptive statistics, and stratified according to 4MGS quartiles (Q1 <0.40 m/s, Q2 0.4-0.59 m/s, Q3 0.60-0.79 m/s, Q4 $\geq$0.80 m/s) (10). One-way ANOVA, Kruskal-Wallis or Chi-squared test for trend was used to compare gait speed quartiles, as appropriate. Kaplan-Meier analysis was performed to compare time to all-cause readmission and mortality between gait speed quartiles and compared using the log-rank test.

Univariable Cox proportional hazard regression was performed to determine the association between 4MGS, and potential confounding variables, with all-cause hospital readmission. Collinearity was determined by showing a statistically significant correlation between the variables of interest ($p<0.05$) with a Rho of greater than >0.4.

Variables with $p<0.20$ on univariable analysis were entered into a multivariable Cox proportional hazard regression model and a backward stepwise method was used. Variables were retained in the final model if $p<0.20$. Interaction between gait speed and age was investigated and added to the final model with a subgroup analysis performed if interaction term was found to be significant. Model goodness of fit was assessed by the Hosmer-Lemeshow test.

Univariable Cox proportional hazards regression was performed to test the association between 4MGS (as a continuous variable and stratified by quartile) and potential confounding variables, and all-cause mortality at one year. Collinearity was assessed as per method described above. Variables with a $p\leq0.20$ were entered into a multivariable model. Using a backward stepwise method, variables were retained in the model if $p \leq0.05$. This stricter criteria for inclusion into the multivariable model was due to the small number of events, and so to lessen the likelihood of over-fitting.

Data were analysed to take into account that death and readmission are competing risks. We used the Fine and Gray regression model to calculate the subdistribution hazard ratio (SHR) for the occurrence of death or readmission. We also used both the Kaplan-Meier (KM) estimator and the cumulative incidence competing risk (CICR) method to calculate the

cumulative incidence of death based on whether the subject had a readmission or not, and the cumulative incidence of readmission based on whether the subject died or not.

A significance level of $p<0.05$ was defined for all analyses. Analysis was performed using a combination of SPSS version 22 (IBM, USA), GraphPad Prism 8 (GraphPad Software, USA) and Stata 16,1 (StataCorp, College Station, Texas).

RESULTS

A study flow chart is shown in Figure 1. Of 311 eligible participants, 226 consented, with baseline data collected in 213 participants. Hospital readmission and mortality data in the one year period following hospital discharge were available for all 213 participants.

Baseline characteristics for the whole cohort and each gait speed quartile are presented in Table S1 in the online supplement (10). Overall, 111 participants (52%) were readmitted, with 35 (16%) dead at twelve months. The risk of hospital readmission over the 12-month period decreased with increasing 4MGS at hospital discharge (Q1 (slowest): 70%, Q2: 60%, Q3: 48%, Q4 (fastest): 29%; $p=0.001$). Similarly, the risk of death over the 12-month period decreased with increasing 4MGS at hospital discharge (Q1 (slowest): 32%, Q2: 21%, Q3: 9%, Q4 (fastest): 4%; $p<0.001$).

Hospital readmissions

Baseline characteristics of those readmitted and those who were not are reported in the online supplement (Table S2). Results of the univariable Cox proportional hazard regression are presented in Table 1. Faster 4MGS, both as a continuous measure and as quartiles, was

associated with reduced risk of hospital readmission. With multivariable Cox proportional hazard regression analysis, the final model comprised 4MGS, age, number of exacerbations in the past year and Charlson co-morbidity index (Table 2). 4MGS was an independent predictor of all-cause readmission with an adjusted Cause specific hazard ratio of 0.868 (95% CI: 0.799 to 0.943; p=0.001) and Subdistribution hazard ratio of 0.868 (95% CI: 0.797 to 0.945; p=0.001) per 0.1 m/s increase in gait speed (Table 2a). The Hosmer-Lemeshow test was not significant (p=0.900) demonstrating adequate model fit. An interaction term of age and gait speed was added to the final model; this was not significant (p=0.286) so no subgroup analysis was performed.

When 4MGS was considered as quartiles, the slowest quartile (Q1) had significantly higher hazard ratios compared to those in the fastest quartile (Q4). The final model is presented in Table 2b. The AUC of the ROC was 0.73, demonstrating acceptable discrimination (Figure 2a). When compared to univariable models, the multivariable model outperformed age (AUC = 0.63) or FEV_1 alone (AUC = 0.52) (Figure 2a). Figure 3 demonstrates the Kaplan Meier (Figure 3a) and Competing Risk Survival (Figure 3b) curves for readmission according to 4MGS quartiles; log rank p<0.001.

Mortality risk

Baseline characteristics stratified by survival status at 12 months post-discharge are presented in the online supplement (Table S3). Univariable Cox proportional hazard regression results are presented in Table 3. 4MGS as a continuous measure had an unadjusted cause specific hazard ratio of 0.773 (95% CI: 0.669 to 0.892; p<0.001) and subdistribution hazard ratio of 0.773 (95% CI: 0.665 to 0.899; p=0.001) per 0.1 m/s increase in gait speed.

When stratified as quartiles, those in Q1 (slowest) and Q2 had significantly higher unadjusted hazard ratio compared with those in Q4 (fastest). Following multivariable analysis, the final model consisted of 4MGS, age, sex, BMI and FEV_1 percent predicted and number of exacerbations in the previous year (Table 4) with 4MGS remaining an independent predictor of mortality at 1-year with an adjusted cause specific hazard ratio of 0.740 (95% CI: 0.623 to 0.880; p=0.001) and subdistribution hazard ratio of 0.747 (95% CI: 0.622 to 0.898; p=0.002) per 0.1 m/s increase in gait speed (Table 4a). When considered as quartiles, those in the slowest gait speed quartile (Q1) had a significantly higher adjusted hazard ratio compared to those in the fastest quartile (Q4) (Table 4b). The AUC for the final model was 0.80 (Figure 2b), suggesting superior discrimination to age (AUC=0.65) or FEV_1 alone (AUC=0.58). Kaplan-Meier (Figure 4a) and Competing Risk survival (Figure 4b) curves demonstrated that those in slower gait speed quartiles had reduced time to death; log rank p<0.001.

DISCUSSION

This prospective study demonstrates that slower 4MGS at hospital discharge, a simple physical performance measure and surrogate marker of frailty, independently predicts increased risk of readmission and mortality over 12 months. 4MGS may have value in the risk stratification of patients surviving a hospitalisation for AECOPD.

Prognostic value of Gait Speed

The 4MGS is a simple functional performance measure and a surrogate marker of frailty and sarcopenia (28, 29) that has been validated and widely used in gerontology populations. It has been consistently associated with poor prognosis in older adults; for example, in a pooled analysis of nine cohort studies comprising 34485 older adults, Studenski and colleagues demonstrated an association between gait speed and survival after adjusting for gender, BMI, smoking or medical history (30).

Recent studies have shown the 4MGS might be relevant in chronic respiratory disease populations. In COPD, the 4MGS shows excellent test-retest and inter-occasion reliability and correlates with exercise capacity and health related quality of life (7, 17). Nolan *et al* demonstrated that 4MGS was an independent predictor of all-cause mortality (HR=0.03, 95% CI=0.01 to 0.31) and all-cause hospitalisation (HR=0.02, 95% CI=0.01 to 0.14) in idiopathic pulmonary fibrosis (11), whilst Chan and colleagues have shown that 4MGS predicts mortality and hospitalisations at 12 -months in survivors of acute respiratory distress syndrome (12).

In the acute setting, the 4MGS has suitable properties as a functional measure. It requires minimal space (therefore feasible at the bedside) and is quick to perform (less than two

minutes). It does not require expensive equipment and can be performed by non-specialist healthcare staff in a variety of settings. The primary analysis of the current dataset has previously shown that measuring 4MGS in patients with COPD at hospital discharge is feasible, and that slow 4MGS is associated with 90-day readmission, especially in older patients (10).

We extend these findings with a planned secondary analysis of adverse outcomes, namely hospital readmission and deaths, in the year after the index admission. Our results show that 4MGS is an independent predictor of both one-year all-cause readmission and mortality. When 4MGS is stratified by quartiles, the Kaplan-Meier plots (Figures 3 and 4a) show that there is differentiation between the curves early in the follow-up period (within the first 90 days) that persists across 12-months. Interestingly, 34 of the 35 deaths in the follow-up period occurred during or just after a hospital readmission, suggesting that the mortality signal may be driven by the ability of the 4MGS to stratify risk for readmission.

Clinical implications

Hospitalised AECOPD are not only associated with inpatient mortality, but for survivors, there remains an increased risk of hospital readmission and mortality following discharge. Risk stratification is of interest due to the financial implications and burden on healthcare systems from unscheduled hospitalisation and increased health resource usage. It may also impact on treatment decisions (e.g., such as prioritisation of palliative or supportive care) (31) or identify populations suitable for targeted interventions.

Outcomes from a hospitalised AECOPD will be partly determined by the severity of the acute event and the underlying pre-morbid condition of the individual. Previous systematic reviews examining prognostic models for AECOPD admissions (5, 32) have identified common predictors that are related to pre-morbid baseline characteristics such as age, sex, FEV1 % predicted, the presence of comorbidities such as heart failure, or physiological status at the time of the index admission such as blood gas derangements (32). These studies were often retrospective and may have limited utility for planning post-hospital care for survivors as identified factors were not easily amenable to intervention after discharge.

4MGS, at the time of discharge, may provide a simple integrated measure of the multisystem consequences of the hospitalisation and comorbidities upon the pre-morbid condition, and identify a phenotype associated with increased healthcare usage. 4MGS is already well established as a surrogate marker of frailty (28, 33) and sarcopenia (29, 34), and there are recent data supporting the relevance of gait speed in acute cardiac syndromes (35) and hypercapnic respiratory failure (20).

The use of 4MGS as a risk stratification tool may assist healthcare and social support systems to shift to a more preventative strategy, including the identification of individuals who require increased support. Unlike many other previously identified predictors, 4MGS is amenable to intervention, particularly exercise-based interventions, both in non-respiratory and respiratory populations (16, 17). Demonstrating the association between 4MGS and increased readmission risk may encourage clinicians to recommend and refer for physical interventions such as pulmonary rehabilitation, which is associated with improved survival in the post-hospitalisation period (36). Notably, only 7% of our cohort completed post-

hospitalisation pulmonary rehabilitation. Individuals with slow 4MGS may need additional support to attend such interventions (37) as frailty has been identified as an independent risk factor for non-completion of pulmonary rehabilitation (33).

Although our data shows 4MGS is an independent predictor of adverse events, the simple composite model produced provides a stronger means of risk stratification. These composite models require validation and calibration. As measures included in both our readmission and mortality composite models are easily or routinely collected in clinical practice, there is potential to produce prognostic indices that are easily implemented into clinical practice.

Strengths and limitations

A strength of our study is that it is one of the few prospective studies to examine the association between objectively measured functional status at hospital discharge and outcomes. We were able to conduct a comprehensive assessment at discharge allowing us to determine the relevance of potential confounding factors. Reliable follow-up data on hospital admissions and deaths in the twelve months after the index admission were collected from medical and central records.

There were limitations to our study. This was a single centre study and our models need to be validated in independent COPD cohorts from other healthcare systems with differing models of inpatient care and post-discharge follow-up. However, our findings are consistent with previous gait speed studies in acute setting cohorts (12, 20, 35) and outpatient respiratory populations (11). There was a relatively low number of mortality events in the cohort. This has implications for multivariable modelling; however we took guidance from

Vittinghoff and McCullogh who argued for a relaxation of the 10 events per variable rule, with 5-9 events per variable generally comparable to 10-16 events per variable (38). We also only measured 4MGS at one time-point (hospital discharge); demonstrating an association between change in 4MGS and outcomes would further corroborate the prognostic value of 4MGS in COPD. For example, Volpato *et al* showed that those with a decline in the short physical performance battery (which incorporates 4MGS as one of three domains) was associated with a threefold increase in risk of readmission or death in the year following discharge in hospitalised older patients (39).

Future research

In order to support our findings, internal and external validation of the risk models described in this study is needed. After validation and appropriate adjustment of our models, development of a simple scoring index similar to DECAF (24) or BODE (40) might facilitate implementation into clinical practice, providing real-time feedback on patient risk profiles. Another potential area amenable to further research is to explore whether regular measurement of 4MGS during a hospital admission could influence medical decision-making around timing of discharge.

In summary, 4MGS is an independent risk factor for both 1-year all-cause readmission and mortality. As the measure is simple, cheap and quick, we propose that routine measurement at hospital discharge would provide clinicians with valuable information to plan post-discharge care and support.

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Competing interests:

JAW, REB, SSCK, BMH, SEJ, SP, OP, WB, PC, report no conflicts of interest; CMN reports personal fees from Novartis, outside the submitted work; MIP reports personal fees from Philips and JFD, grants from GlaxoSmithKline, outside the submitted work; WD-CM reports grants from Medical Research Council UK, during the conduct of the study, grants from National Institute for Health Research, British Lung Foundation and Pfizer, personal fees from Jazz Pharmaceuticals, Mundipharma and Novartis, non-financial support from GlaxoSmithKline, outside the submitted work.

TABLE 1. Univariable Cox proportional hazard regression predicting all-cause readmission at 1-year post discharge

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed by Quartiles				
Quartile 4	*Reference*			
Quartile 3	1.886 (0.999 to 3.562)	0.050	1.886 (1.010 to 3.524)	0.047
Quartile 2	2.601 (1.407 to 4.805)	0.002	2.601 (1.426 to 4.743)	0.002
Quartile 1	3.961 (2.175 to 7.214)	<0.0001	3.961 (2.152 to 7.291)	<0.0001
Gait speed per 0.1 m/s increase	0.823 (0.761 to 0.891)	<0.0001	0.823 (0.758 to 0.894)	<0.0001
Age	1.030 (1.012 t0 1.049)	0.001	1.030 (1.013 to 1.048)	0.001
Sex (male)	1.104 (0.760 to 1.602)	0.604	1.104 (0.762 to 1.599)	0.602
BMI	0.994 (0.966 to 1.024)	0.712	0.994 (0.965 to 1.025)	0.717
FEV_1 (% predicted)	0.996 (0.986 to 1.005)	0.379	0.996 (0.987 to 1.005)	0.356
MRC Dyspnoea score	1.217 (1.018 to 1.456)	0.031	1.217 (1.021 to 1.451)	0.027
Bed days during admission	1.054 (1.020 to 1.090)	0.002	1.054 (1.019 to 1.091)	0.002
Exacerbations in last year	1.118 (1.042 to 1.199)	0.002	1.118 (1.036 to 1.206)	0.004
Charlson co-morbidity index	1.339 (1.162 to 1.541)	<0.0001	1.339 (1.172 to 3.528)	<0.0001

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second;; HR, hazard ratio; MRC, Medical Research Council; SHR, Subdistribution hazard ratio.

TABLE 2a. Multivariable Cox proportional hazard regression predicting all-cause readmission at 1-year post discharge according to gait speed as a continuous variable – final model

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed per 0.1 m/s increase	0.868 (0.799 to 0.943)	0.001	0.868 (0.797 to 0.945)	0.001
Age	1.023 (1.004 to 1.043)	0.019	1.023 (1.005 to 1.043)	0.014
Exacerbations in last year	1.148 (1.062 to 1.240)	<0.0001	1.148 (1.057 to 1.246)	0.001
Charlson co-morbidity index	1.267 (1.092 to 1.471)	0.002	1.267 (1.095 to 1.466)	0.001

Data expressed as hazard ratio (95% confidence interval)

Abbreviations: HR, hazard ratio; SHR, Subdistribution hazard ratio.

TABLE 2b. Multivariable Cox proportional hazard regression predicting all-cause readmission at 1-year post discharge according to gait speed by quartiles – final model

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed by Quartiles				
Quartile 4	*Reference*			
Quartile 3				
Quartile 2				
Quartile 1	1.802 (1.209 to 2.685)	0.004	1.802 (1.181 to 2.750)	0.006
Age	1.026 (1.006 to 1.046)	0.009	1.026 (1.007 to 1.046)	0.008
Bed days during admission	1.041 (1.001 to 1.081)	0.042	1.041 (1.007 to 1.076)	0.019
Exacerbations in last year	1.164 (1.078 to 1.257)	<0.0001	1.164 (1.074 to 1.262)	<0.0001
Charlson Co-morbidity index	1.274 (1.095 to 1.484)	0.002	1.274 (1.092 to 1.487)	0.002

Data expressed as hazard ratio (95% confidence interval).

Abbreviations: HR, hazard ratio; SHR, Subdistribution hazard ratio.

TABLE 3. Univariable Cox proportional hazard regression predicting all-cause mortality at 1-year post discharge

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed by Quartiles				
Quartile 4	*Reference*			
Quartile 3	2.445 (0.747 to 12.601)	0.285	2.445 (0.467 to 12.789)	0.290
Quartile 2	5.722 (1.268 to 25.819)	0.023	5.722 (1.250 to 26.199)	0.025
Quartile 1	9.608 (2.219 to 41.600)	0.002	9.608 (2.171 to 42.522)	0.003
Gait speed per 0.1 m/s increase	0.773 (0.669 to 0.892)	<0.001	0.773 (0.665 to 0.899)	0.001
Age	1.050 (1.014 to 1.088)	0.006	1.050 (1.021 to 1.080)	0.001
Sex (male)	1.834 (0.912 to 3.686)	0.089	1.834 (0.912 to 3.688)	0.089
BMI	0.907 (0.850 to 0.968)	0.003	0.907 (0.846 to 0.972)	0.005
FEV_1 (% predicted)	0.982 (0.962, 1.003)	0.088	0.982 (0.963 to 1.001)	0.069
MRC Dyspnoea score	1.679 (1.127 to 2.501)	0.011	1.679 (1.162 to 2.427)	0.006
Bed days during admission	1.074 (1.028 to 1.124)	0.002	1.074 (1.041 to 1.109)	<0.0001
One or more admissions in last year	1.470 (0.756 to 2.860)	0.256	1.470 (0.758 to 2.853)	0.254
Exacerbations in last year	1.104 (0.979 to 1.244)	0.106	1.104 (0.981 to 1.242)	0.102
Charlson co-morbidity index	1.436 (1.155 to 1.786)	0.001	1.436 (1.163 to 1.773)	0.001

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; MRC, Medical Research Council; SHR, Subdistribution hazard ratio.

TABLE 4a. Multivariable Cox proportional-hazards regression predicting all-cause mortality at 1-year post discharge according to gait speed as a continuous variable – final model

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed per 0.1 m/s increase	0.740 (0.623 to 0.880)	0.001	0.747 (0.622 to 0.898)	0.002
Age	1.042 (1.001 to 1.086)	0.046		NS
Sex (male)	2.104 (1.011 to 4.380)	0.047		NS
BMI	0.899 (0.840 to 0.961)	0.002	0.896 (0.839 to 0.956)	0.001
FEV_1 (% predicted)	0.977 (0.954 to 1.000)	0.046	0.976 (0.956 to 0.997)	0.023
Exacerbations in last year	1.160 (1.009 to 1.334)	0.037		NS
Charlson Co-morbidity index		NS	1.312 (1.062 to 1.621)	0.012

Data expressed as hazard ratio (95% confidence interval).

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; NS, Not significant with p>0.20; SHR, Subdistribution hazard ratio.

TABLE 4b. Multivariable Cox proportional-hazards regression predicting all-cause mortality at 1-year post discharge according to gait speed by quartiles – final model

Variable	Cause specific hazard ratios model		Subdistribution hazards model	
	HR (95% confidence interval)	P value	SHR (95% confidence interval)	P value
Gait speed by Quartiles				
Quartile 4	*Reference*			
Quartile 3		NS		NS
Quartile 2		NS		NS
Quartile 1	1.802 (1.209 to 2.685)	0.004	1.802 (1.181 to 2.750)	0.006
Age	1.026 (1.006 to 1.046)	0.009	1.026 (1.007 to 1.046)	0.008
Bed days during admission	1.041 (1.001 to 1.081)	0.042	1.041 (1.007 to 1.076)	0.019
Exacerbations in last year	1.164 (1.078 to 1.257)	<0.0001	1.164 (1.074 to 1.262)	<0.0001
Charlson Co-morbidity index	1.274 (1.095 to 1.484)	0.002	1.274 (1.092 to 1.487)	0.002

Data expressed as hazard ratio (95% confidence interval).

Abbreviations: HR, hazard ratio; NS, not significant with p>0.20 not; SHR; Subdistribution hazard ratio.

FIGURE CAPTIONS

FIGURE 1. Study flow chart. Abbreviations: AECOPD, acute exacerbation of COPD

FIGURE 2. Receiver operator characteristic curves demonstrating the ability of univariate and multivariate models in predicting a) readmission at 1-year post discharge b) mortality at one-year post discharge. Abbreviations: 4MGS, 4 m gait speed; FEV_1, forced expiratory volume in 1 second

FIGURE 3. a) Kaplan–Meier curve and b) Competing risks survival curve demonstrating time to 1-year all-cause readmission according to 4MGS quartile (Q1≤0.40 m/s; Q2=0.40–0.59 m/s; Q3=0.60–0.79 m/s; Q4≥0.80 m/s). Abbreviations: 4MGS, 4 m gait speed

FIGURE 4. a) Kaplan–Meier curve and b) Competing risks survival curve demonstrating time to 1-year all-cause mortality according to 4MGS quartile (Q1≤0.40 m/s; Q2=0.40–0.59 m/s; Q3=0.60–0.79 m/s; Q4≥0.80 m/s). Abbreviations: 4MGS, 4 m gait speed

REFERENCES:

1. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. Respir Care. 2002;47(10):1184-99.
2. Jones SE, Barker RE, Nolan CM, Patel S, Maddocks M, Man WDC. Pulmonary rehabilitation in patients with an acute exacerbation of chronic obstructive pulmonary disease. J Thorac Dis. 2018;10(Suppl 12):S1390-S9.
3. Harries TH, Thornton H, Crichton S, Schofield P, Gilkes A, White PT. Hospital readmissions for COPD: a retrospective longitudinal study. NPJ Prim Care Respir Med. 2017;27(1):31.
4. Stone RA HBJ, Lowe D, McMillan V, Saleem Khan M, Searle L, Skipper E,, Welham S RC. COPD: Who cares when it matters most? National Chronic Obstructive Pulmonary Disease (COPD) Programme: Outcomes from the clinical audit of COPD exacerbations admitted to acute
units in England 2014. London: RCP; 2017.
5. Bellou V, Belbasis L, Konstantinidis AK, Tzoulaki I, Evangelou E. Prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease: systematic review and critical appraisal. Bmj. 2019;367:l5358.
6. Bui K-L, Nyberg A, Maltais F, Saey D. Functional Tests in Chronic Obstructive Pulmonary Disease, Part 1: Clinical Relevance and Links to the International Classification of Functioning, Disability, and Health. Annals of the American Thoracic Society. 2017;14(5):778-84.
7. Kon SS, Patel MS, Canavan JL, Clark AL, Jones SE, Nolan CM, et al. Reliability and validity of 4-metre gait speed in COPD. Eur Respir J. 2013;42(2):333-40.
8. Abellan van Kan G, Rolland Y, Andrieu S, Bauer J, Beauchet O, Bonnefoy M, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging. 2009;13(10):881-9.
9. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc. 2003;51(3):314-22.
10. Kon SSC, Jones SE, Schofield SJ, Banya W, Dickson MJ, Canavan JL, et al. Gait speed and readmission following hospitalisation for acute exacerbations of COPD: a prospective study. Thorax. 2015;70(12):1131-7.
11. Nolan CM, Maddocks M, Maher TM, Banya W, Patel S, Barker RE, et al. Gait speed and prognosis in patients with idiopathic pulmonary fibrosis: a prospective cohort study. European Respiratory Journal. 2019;53(2):1801186.
12. Chan KS, Aronson Friedman L, Dinglas VD, Hough CL, Shanholtz C, Ely EW, et al. Are physical measures related to patient-centred outcomes in ARDS survivors? Thorax. 2017;72(10):884-92.
13. Barthuly AM, Bohannon RW, Gorack W. Gait speed is a responsive measure of physical performance for patients undergoing short-term rehabilitation. Gait & Posture. 2012;36(1):61-4.
14. Salbach NM, Mayo NE, Higgins J, Ahmed S, Finch LE, Richards CL. Responsiveness and predictability of gait speed and other disability measures in acute stroke. Archives of Physical Medicine and Rehabilitation. 2001;82(9):1204-12.
15. Baert I, Freeman J, Smedal T, Dalgas U, Romberg A, Kalron A, et al. Responsiveness and clinically meaningful improvement, according to disability level, of five walking

measures after rehabilitation in multiple sclerosis: a European multicenter study. Neurorehabil Neural Repair. 2014;28(7):621-31.
16. Nolan CM, Maddocks M, Maher TM, Canavan JL, Jones SE, Barker RE, et al. Phenotypic characteristics associated with slow gait speed in idiopathic pulmonary fibrosis. Respirology. 2018;23(5):498-506.
17. Kon SSC, Canavan JL, Nolan CM, Clark AL, Jones SE, Cullinan P, et al. The 4-metre gait speed in COPD: responsiveness and minimal clinically important difference. European Respiratory Journal. 2014;43(5):1298-305.
18. Ostir GV, Berges I, Kuo YF, Goodwin JS, Ottenbacher KJ, Guralnik JM. Assessing gait speed in acutely ill older patients admitted to an acute care for elders hospital unit. Arch Intern Med. 2012;172(4):353-8.
19. Purser JL, Weinberger M, Cohen HJ, Pieper CF, Morey MC, Li T, et al. Walking speed predicts health status and hospital costs for frail elderly male veterans. J Rehabil Res Dev. 2005;42(4):535-46.
20. Karege G, Zekry D, Allali G, Adler D, Marti C. Gait speed is associated with death or readmission among patients surviving acute hypercapnic respiratory failure. BMJ Open Respir Res. 2020;7(1).
21. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. European Respiratory Journal. 2005;26(2):319-38.
22. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
24. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax. 2012;67(11):970-6.
25. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85 Suppl B:25-31; discussion 3-7.
26. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31(12):721-7.
27. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58(2):100-5.
28. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
29. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and Ageing. 2010;39(4):412-23.
30. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait Speed and Survival in Older Adults. JAMA. 2011;305(1):50-8.
31. Maddocks M, Lovell N, Booth S, Man WD, Higginson IJ. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. Lancet. 2017;390(10098):988-1002.
32. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2013;10(2):81-9.

33. Maddocks M, Kon SSC, Canavan JL, Jones SE, Nolan CM, Labey A, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax. 2016;71(11):988-95.
34. Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax. 2015;70(3):213-8.
35. Dodson JA, Arnold SV, Gosch KL, Gill TM, Spertus JA, Krumholz HM, et al. Slow Gait Speed and Risk of Mortality or Hospital Readmission After Myocardial Infarction in the Translational Research Investigating Underlying Disparities in Recovery from Acute Myocardial Infarction: Patients' Health Status Registry. Journal of the American Geriatrics Society. 2016;64(3):596-601.
36. Lindenauer PK, Stefan MS, Pekow PS, Mazor KM, Priya A, Spitzer KA, et al. Association Between Initiation of Pulmonary Rehabilitation After Hospitalization for COPD and 1-Year Survival Among Medicare Beneficiaries. JAMA. 2020;323(18):1813-23.
37. Brighton LJ, Bristowe K, Bayly J, Ogden M, Farquhar M, Evans CJ, et al. Experiences of Pulmonary Rehabilitation in People Living with COPD and Frailty: A Qualitative Interview Study. Ann Am Thorac Soc. 2020.
38. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-8.
39. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci. 2011;66(1):89-96.
40. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12.