SUPPLEMENTARY MATERIAL

HOSPITAL ADMISSIONS AND EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

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METHODS – COMPLETE VERSION

Study Design and Ethics

The "Phenotype and Course of COPD (PAC-COPD)" Study is a prospective cohort study described elsewhere [E1]. Briefly, COPD patients were recruited during their first hospitalization due to a COPD exacerbation, in nine teaching hospitals in Spain between January 2004, and March 2006, as published before [E2, E3]. Patients were evaluated three months after discharge, when clinically stable, at what constituted the baseline assessment. Eighteen to 24 months afterwards, patients were invited to participate in a second visit for follow-up assessment. The study was approved by the Clinical Research Ethical Committee of all participating hospitals and written informed consent was obtained from all participants.

Patients

The diagnosis of COPD was confirmed by spirometry (post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV1/FVC) $\leq$0.70) [E4]. The current analysis includes only those patients recruited into the PAC-COPD study who had exercise capacity measures in the two evaluation visits. Of the 342 patients originally recruited into the PAC-COPD study [E2], 19 died before the second visit, 32 refused to continue, 13 could not be contacted, 27 were excluded because of appearance of severe co-morbidities, and for 25 the exercise capacity test could not be conducted at follow-up, providing a total of 226 (66%) patients with repeated measures of exercise capacity (Figure E1). Subjects who died or were lost to follow-up during the study period were older, had more co-morbidities and lower FEV_1 than those who completed the study (Tables E1 and E2).

Measurements

Exercise capacity

Exercise capacity was assessed using the six-minute walk test (6MWT) according to published recommendations [E5, E6], and the six-minute walk distance (6MWD) was determined for each patient. In the baseline assessment, patients completed two 6MWT with at least a 30-min rest between, and the longer of the two distances was used for analysis. Only one test was conducted in the second evaluation. The annual rate of change in exercise capacity was defined as the difference between the 6MWD at the second evaluation minus the baseline 6MWD, divided by follow-up time for each subject. Patients were classified according to what is considered a Minimal Clinically Important Difference (MCID) for exercise capacity decline [E7], as having a clinically significant loss (≥35 m/year), or a less than clinically significant decline (<35 m/yr).

Hospital admissions

Information on hospital admissions, including dates and causes, from first to second assessment was obtained from the Minimum Basic Dataset (CMBD), a national administrative database. Hospitalization rate was defined as the number of hospitalizations (all-causes) during follow-up divided by follow-up time in each subject. Causes of admission were classified according to the International Classification of Diseases, 9th revision. Because some patients suffered more than one hospital admission during follow-up, the association between admissions and exercise capacity change according to causes could not be performed at a "single causes" level, but at the patients' level. Thus, to study the specific role of COPD admissions, patients were classified in two main groups: (i) patients with "only COPD" hospitalizations, due exclusively to a COPD exacerbation (primary cause of admission at discharge ICD-9 codes 490-496, or primary cause ICD-9 466 or 518.81 if second cause was

ICD-9 491.21), and (ii) patients with "non-Respiratory" hospitalizations, due to causes unrelated to respiratory conditions (primary cause different than ICD-9 460-519). A third group of patients combining respiratory and non-respiratory admissions was labelled as "mixed cause" hospitalizations, and used only for descriptive purposes. In patients who required hospitalization at least once during follow-up, we computed the cumulative hospital stay as defined by the total number of days of admission (all-cause admissions) during follow-up, and the time from the last discharge to the second evaluation.

Additional measurements

Detailed information about the methods, questionnaires, standardization of the tests, and fieldwork supervision has been previously reported [E1]. Briefly, during the baseline assessment all participants answered an epidemiological questionnaire that included socio-demographic data, life-style information, a previously validated 122-item food frequency questionnaire (FFQ) [E8] to asses dietary habits, the modified Medical Research Council (mMRC) scale for the assessment of dyspnoea [E9], the validated Spanish-language version [E10] of the St George's Respiratory Questionnaire (SGRQ) [E11] to measure health-related quality of life, and the validated Spanish-language version [E12] of the Hospital Anxiety and Depression Scale (HAD) [E13]. The Charlson index of comorbidity [E14] was calculated from doctor diagnosis of co-morbid conditions. Physical activity was assessed using the validated Spanish version of the Yale Physical Activity Questionnaire (YPAS) [E15] validated for COPD patients [E16]. In addition to forced spirometry (before and after bronchodilator), static lung volumes by whole-body plethysmography (residual volume (RV), total lung capacity (TLC)), diffusing capacity for carbon monoxide (DLco) and arterial blood gases (arterial oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$)) were determined. Likewise, weight and height were measured and the body mass index (BMI) was calculated

and the fat free mass index (FFMI) was measured by bioimpedance. A hand dynamometer was used to measure peripheral muscle function. Respiratory muscle strength was tested using the maximum inspiratory (MIP) and expiratory pressures (MEP) and reference values were used [E17]. Serum inflammatory biomarkers (Tumour Necrosis Factor alpha) were also assessed at baseline. Finally, participation in pulmonary rehabilitation programs during follow-up was recorded.

Statistical analysis

Given that the 34% of patients without repeated measures of exercise capacity exhibited some differences in age, FEV_1 and comorbidities compared with the remaning patients (Tables E1 and E2 in the Online supplementary material), and that selective attrition is known to introduce bias into analysis if using a complete case strategy [E18], we used multiple imputation to compensate for the underrepresentation of the older, more severe population. Moreover, other variables had a small proportion (<15%) of missing values that, assuming ignorability holds, were considered either completely at random or at random [E19]. Thus, multiple imputation through chained equations was used, replacing missing values by imputations drawn from the predictive distribution of each variable [E20], which was obtained from a regression model (logistic, lineal, or politomous depending on the type of variable), where variables that were associated with the quantities of main interest and variables that were associated with the probability of missingness were used as covariates (age, sex, Charlson index of comorbidity, mMRC dyspnoea score, SGRQ total score, YPAS physical activity index, BMI, FFMI, FEV_1, RV/TLC, DL_{CO}, PaO_2, MIP, handgrip muscle force, baseline 6MWD and hospitalization rate). To account for the additional uncertainty produced by the fact that missing values are substituted by estimates [E21], we imputed

missing values 20 times. Table E3 in the Online supplementary material shows the descriptive characteristics of both the real population and the imputed population.

Provided sample size was fixed by the primary scientific objectives of the PAC-COPD Study [E3], prior to any analysis we calculated whether the available number of patients would allow for identification of significant differences in 6MWD decline between groups (admitted *vs*. non-admitted during follow-up). Calculations using the program GRANMO 5.2 [E22] showed that, assuming a standard deviation of 100 meters in the 6MWD [E23, E24], a 1:2 ratio of hospitalized: not hospitalized [E3], a correlation between first and second measurements of 0.84 [E25], and accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided contrast, a sample size of 342 patients allows for a 20 meter or more difference in the 6MWD decline between groups to be identified as statistically significant. This difference is lower than the test's minimal important difference [E7], suggesting the sample has sufficient power to provide clinically meaningful results.

The bivariate association between hospitalization and the annual rate of change in the 6MWD was analyzed using either unpaired t-test, analysis of variance, Chi-square, or Fischer's exact tests, as appropriate. As the annual rate of 6MWD change was normally distributed (Figure E2), multivariate linear regression models were used to assess the effect of hospitalizations as the exposure and adjusting for baseline 6MWD. Age, sex, smoking history, working status, daily physical activity, daily consumption of processed meats, vegetables and fruits, Charlson index of comorbidity, BMI, mMRC dyspnoea scale, SGRQ scores, HAD depression scale, severity of airflow limitation (FEV_1), gas trapping (RV/TLC), pulmonary diffusion impairment (DL_{co}), arterial oxygenation (PaO_2), muscle force (handgrip, MIP and MEP), serum TNFα, inhaled corticosteroids use, and participation in pulmonary rehabilitation

programs, were tested as potential confounders and included in the final model if (i) related to both the exposure and the outcome, (ii) modified (>10% change in regression coefficient) the estimates of the remaining variables, or (iii) there is consistent evidence in the literature on their association with exercise capacity. To assess whether exercise capacity exhibits different decline depending on the causes of hospitalization, linear regression models were stratified according the main cause of the hospitalization. Further stratification analyses according to sex, age, BMI, daily physical activity, FEV_1 and muscle force (handgrip, MIP and MEP) were conducted in order to study possible interactions, using the median as cut off point for continuous variables. Goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Sensitivity analysis was conducted (i) using the cutoff point of 26 meters/yr as the clinically significant threshold of exercise capacity decline [E26], (ii) excluding subjects who participated in any pulmonary rehabilitation program during follow-up, and (iii) using a complete case analysis.

Data analysis was conducted using Stata 9.1 (StataCorp, College Station, TX, USA).

Table E1. Comparison between participants with repeated measures of exercise capacity and patients lost to follow-up.

	Participants (n=226)	**Lost to follow up (n=91)**	**p**
Sex: Males, n (%)	209 (9)	85 (93)	0.773
Age (years), mean ± SD	67.4 ± 8.3	67.9 ± 9.4	0.658
Smoking: current smoker, n (%)	78 (35)	35 (38)	0.507
YPAS index (score 0 to 137), median (P25-P75)	36 (23-53)	31 (18-49)	0.139
Co-morbidities: Charslon index ≥2, n (%)	115(51)	61 (67)	0.009
Charlson Co-morbidities, n (%)			
Myocardial infarction	19 (8)	12 (14)	0.163
Congestive heart failure	11 (5)	7 (8)	0.290
Peripheral vascular disease	20 (9)	14 (16)	0.071
Cerebrovascular disease	8 (4)	4 (5)	0.745
Connective tissue disease	3 (1)	3 (3)	0.355
Ulcer disease	23 (10)	14 (16)	0.137
Mild liver disease	13 (6)	6 (7)	0.722
Moderate or severe liver disease	1 (0.4)	2 (2)	
Diabetes	38 (17)	21 (24)	0.151
Hemiplegia	0	2 (2)	0.078
Moderate or severe renal disease	11(5)	8 (9)	0.159
Diabetes with end organ damage	3 (1)	3 (3)	0.355
Any malignancy	25 (11)	10 (11)	0.939
Cancer	0	0	
AIDS	0	0	
Self- reported comorbidities, n (%)			
Arthrosis or rheumatism	79 (35)	28 (31)	0.466
Paralysis	5 (2)	2 (2)	0.994
Chronic Back-Ache	49 (22)	15 (16)	0.289
Varices	56 (25)	23 (25)	0.943
Cataracts	61 (27)	24 (26)	0.911
Blindness	4 (2)	3 (3)	0.403
BMI kg/m^2, mean (SD)	28.2 ± 4.6	27.7 ± 4.8	0.307
FFMI kg/m^2, mean (SD)	19.8 ± 3.2	19.0 ± 2.7	0.063
Significant dyspnoea (mMRC ≥2), n (%)	95 (42)	48 (53)	0.083
PostBD FEV_1 (% pred), m ± SD	54 ± 17	49 ± 16	0.019
PostBD FEV_1/FVC (%), m ± SD	54 ± 12	52 ± 12	0.099
COPD severity, n (%)[#]			
I: Mild (FEV_1 ≥80%)	15 (7)	4 (4)	0.289
II: Moderate (FEV_1 ≥50%, <80%)	111 (49)	37 (41)	
III: Severe (FEV_1 ≥30%, <50%)	85 (37)	40 (44)	
IV: Very severe (FEV_1 <30%)	15 (7)	10 (11)	
RV (% pred) , mean ± SD	155.3 ± 46.6	157.6 ± 54.7	0.723
TLC (% pred) , mean ± SD	101.3 ± 17.8	100.3 ±20.0	0.674
RV/TLC (%), mean ± SD	55.1 ± 10.1	56.5 ± 10.1	0.298
DLco (% pred) , mean ± SD	66.5 ± 20.7	62.8 ± 19.9	0.189
PaO_2 (mmHg) , mean ± SD	74.9 ± 11.2	72.6 ± 9.4	0.094
Handgrip muscle force (Kg) , mean ± SD	31.3 ± 8.3	29.1 ± 8.1	0.043
Baseline 6MWD (meters)[¶], mean ± SD	444 ± 83	411 ± 107	0.066

Definition of abbreviations: mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced espiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= Residual Volume/Total Lung Capacity; DLCo= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension.

[#]According to the American Thoracic Society/European Respiratory Society criteria [E4]

[¶]The best of two six-minute walk distance tests separated by ≥30 min.

Table E2. Comparison between participants with repeated measures of six minute walk distance (6MWD) and subjects without repeated measures.

	Participants with repeated measures of 6MWD (n=226)	**Subjects without repeated measures of 6MWD (n=25)**	**p**
Sex: Males, n(%)	209 (92)	24 (96)	0.999
Age (years), mean ± SD	67.4 ± 8.3	72.5 ± 7.0	0.003
Smoking: current smoker, n (%)	78 (35)	7(28)	0.657
YPAS index (score 0 to 137), median (P25-P75)	36 (23-53)	29 (19–46)	0.260
Charslon index ≥2, n (%)	115(50.88)	18 (72)	0.045
Charslon Co-morbidities, n (%)			
Myocardial infarction	19 (8)	5 (29)	0.074
Congestive heart failure	11 (5)	3 (12)	0.152
Peripheral vascular disease	20 (9)	3 (12)	0.711
Cerebrovascular disease	8 (4)	0	1.000
Connective tissue disease	3 (1)	1 (4)	0.344
Ulcer disease	23 (10)	3 (12)	0.731
Mild liver disease	13 (6)	1 (4)	1.000
Moderate or severe liver disease	1 (0.4)	0	1.000
Diabetes	38 (17)	6 (24)	0.405
Hemiplegia	0	0	1.000
Moderate or severe renal disease	11(5)	2 (8)	0.625
Diabetes with end organ damage	3 (1)	1 (4)	0.344
Any malignancy	25 (11)	5 (20)	0.196
Cancer	0	0	
AIDS	0	0	
Self- reported comorbidities, n (%)			
Arthrosis or rheumatism	79 (35)	15 (60)	0.016
Paralysis	5 (2)	0	1.000
Chronic Back-Ache	49 (22)	9 (36)	0.133
Varices	56 (25)	5 (20)	0.806
Cataracts	61 (27)	11 (44)	0.074
Blindness	4 (2)	0	1.000
BMI (kg/m^2), mean ± SD	28.2 ± 4.6	29.5 ± 4.6	0.194
FFMI kg/m^2, mean ± SD	19.78 ± 3.2	20.6 ± 2.5	0.226
Significant dyspnoea (mMRC ≥2), n (%)	95 (42)	15 (60)	0.094
PostBD FEV_1 (% pred), m ± SD	54 ± 17	52 ± 12	0.648
PostBD FEV_1/FVC (%), m ± SD	54 ± 12	55 ± 11	0.798
COPD severity, n (%)[#]			
I: Mild (FEV_1 ≥80%)	15 (7)	0	0.379
II: Moderate (FEV_1 ≥50%, <80%)	111 (49)	16 (64)	
III: Severe (FEV_1 ≥30%, <50%)	85 (37)	7 (28)	
IV: Very severe (FEV_1 <30%)	15 (7)	2 (8)	
RV (% pred), m ± SD	155.3 ± 46.6	137.8 ± 38.6	0.083
TLC (% pred), m ± SD	101.3 ± 17.8	92.7 ± 17.0	0.027
RV/TLC (%), m ± SD	55.1 ± 10.1	55.7 ± 9.5	0.798
DLco (% pred),m ± SD	66.5 ± 20.7	61.2 ± 22.9	0.259
PaO_2 (mmHg), m ± SD	74.9 ± 11.2	74.6 ± 9.0	0.903
Handgrip muscle force (Kg), m ± SD	31.3 ± 8.3	28 ± 8.3	0.068
Baseline 6MWD (meters)[¶], mean ± SD	444 ± 83)	415 ± 98	0.251

Definition of abbreviations: mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced espiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= Residual Volume/Total Lung Capacity; DLCo= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension.

[#]According to the American Thoracic Society/European Respiratory Society criteria (E4)

[¶]The best of two six-minute walk distance tests separated by ≥30 min.

Table E3. Characteristics of study participants at baseline using complete cases and imputed datasets.

	All patients n=342	
	Complete cases[#]	**Multiple imputation**
Anthropometric and clinical data		
Males, n (%)	314 (92)	314 (92)
Age (years)	67.9 ± 8.57	67.9 ± 8.57
Current smokers	120 (35)	120 (35)
YPAS physical activity index (score 0 to 137)	34 (20-53)	34 (20-53)
SGRQ total score (0-100)	33 (23-47)	33 (23-48)
Charlson index ≥2	194 (57)	194 (57)
Body mass index (kg/m^2)	28.2 ± 4.7	28.2 ± 4.7
Fat free mass index (kg/m^2)	19.7 ± 3.0	19.7 ± 3.1
Significant dyspnoea (mMRC ≥2)	158 (46)	158 (46)
Lung function		
Postbronchodilator FEV_1 (% pred)	54 ± 16	54 ± 17
COPD severity		
Stage I: Mild (FEV_1 ≥80%)	19 (6)	19 (6)
Stage II: Moderate (FEV_1 ≥50%, <80%)	164 (48)	164 (48)
Stage III: Severe (FEV_1 ≥30%, <50%)	132 (38)	132 (38)
Stage IV: Very severe (FEV_1 <30%)	27 (8)	27 (8)
RV/TLC(%)	55.5 ± 10.1	55.9 ± 10.5
DLco (% pred)	65.2 ± 20.7	64.4 ± 22.7
PaO_2 (mmHg)	74.3 ± 10.6	74.4 ± 10.9
Exercise capacity and muscle force		
6MWD at baseline (meters)	435 ± 90	433 ± 93
6MWD at follow-up visit (meters)	407 ± 94	396 ± 99
Annual change in 6MWD (meters/year)	-20.4 ± 39.2	-21.9 ± 51.0
Patients with clinically significant annual decline of 6MWD (≥ 35m/year)	65 (29)	113 (33)
Handgrip muscle force (Kg)	30.5 ± 8.3	30.5 ± 8.5
MIP (% pred)	68 ± 25	68 ± 27
Pulmonary Rehabilitation during follow-up, n (%)	13 (5)	13 (5)[¶]
Follow up time (years)	1.70 ± 0.34	1.70 ± 0.34

Definition of abbreviations: YPAS= Yale physical activity survey; SGRQ= Saint George's respiratory questionnaire; mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced espiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= residual volume/total lung Capacity; DLco= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension; MIP=maximum inspiratory pressure.

[#]Some variables had missing values: Fourteen in physical activity index, 4 in quality of life, 13 in fat free mass index, 27 in RV/TLC, 46 in DLco, 11 in PaO_2, 33 in baseline 6MWD, 107 in 6MWD at follow-up visit, 116 for annual change in 6MWD and for clinically significant annual decline of 6MWD, in 13 in handgrip muscle force, 43 in MIP, 91 in pulmonary rehabilitation during follow-up.

[¶]Variable not imputed.

Table E4. Adjusted association between hospitalization rate and annual change in the six-minute walk distance in 342 COPD patients followed during 1.7 years (linear regression model), using complete cases and imputed datasets.

	Complete cases (n=226)		**Multiple imputation (n=342)**	
	Coefficient[¶] (95%CI)	**p**	**Coefficient[¶] (95%CI)**	**p**
Constant[#]	-6.4 (-14.5; 1.6)	0.117	-7.3 (-15.8; 1.2)	0.088
Hospitalization Rate:				
0 per year	(*reference*)		*(reference)*	
>0 and ≤1 per year	-13.6 (-26.7; -0.5)	0.042	-7.4 (-19.1; 4.3)	0.211
>1 per year	-34.2 (-49.3; -19.1)	<0.001	-26.1 (-38.6; -13.1)	<0.001
Significant dyspnoea (mMRC ≥2) at baseline	-15.3 (-26.6; -4.1)	0.008	-17.2 (-27.8; -6.6)	0.002
Age at baseline (years)	-0.7 (-1.4; 0.02)	0.058	-0.6 (-1.3; 0.01)	0.057
Sex (women)	-12.8 (-33.0; 6.9)	0.198	-11.1 (-30.2; 7.9)	0.249
Baseline Body Mass Index (Kg/m^2)	-0.6 (-1.8; 0.7)	0.631	-0.3 (-1.5; 0.9)	0.664
Baseline RV/TLC (%)	-0.5 (-1.0; 0.1)	0.079	-0.5 (-1.0; 0.04)	0.069
Baseline PaO_2 (mmHg)	0.1 (-0.2; 0.4)	0.586	0.1 (-0.2; 0.4)	0.692
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.203*		*0.223*	

Definition of abbreviation: 95% CI = 95% confidence interval; mMRC = Modified Medical Research Council dyspnoea scale; RV/TLC= residual volume/total lung Capacity; PaO_2= arterial oxygen tension; 6MWD= six-minute walk distance.

[#]Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with 0 COPD hospitalizations/year, mMRC<2, male, and mean age, Body Mass Index, RV/TLC, PaO_2 and mean baseline six-minute walk distance. Negative values represent decline.

[¶]Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

FIGURE LEGENDS

Figure E1. Flow chart of patients enrolled in the PAC-COPD study (patients at first evaluation) participating in the current analysis.

Figure E2. Distribution of annual 6MWD change in 342 COPD patients followed over 1.7 years.

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