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THE SIX-MINUTE WALK DISTANCE: LONG-TERM FOLLOW UP IN PATIENTS WITH COPD

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ABSTRACT

The 6-minute walk distance (6MWD) test is used in clinical practice and research of patients with chronic obstructive pulmonary disease (COPD). However, little is known about its natural long-term change. At baseline and then yearly during five years we measured the 6MWD in meters (m) in 294 patients with COPD and determined its annual rate of decline. We also measured FEV_1 to explore the relation between changes in both markers. At baseline, the median 6MWD was 380 m (range 160-600) and it declined by 19% (16 m/yr, p=0.006) compared with baseline in patients with ATS-ERS stage III (FEV_1<50 but >30 % predicted) and by 26% (15 m/yr, p=0.005) in patients with stage IV (FEV_1<30% predicted). Over 5 yr follow-up time the proportion of patients with a minimal clinical significant decline of 54 m increased with the severity of the disease. It was 24% in stage II, 45% in stage III, and 63% in stage IV (p=0.025). In contrast, the FEV_1 rate of decline was greater in patients with milder airflow obstruction and lesser in patients with lower FEV_1 values. The 6MWD test provides increasingly useful information as the severity of patients with COPD worsens.

Abstract word count: 194

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Key words: COPD; 6-minute walking distance;

INTRODUCTION

The 6-minute walking distance (6MWD) test has gained importance in the assessment of functional exercise capacity in patients with chronic obstructive pulmonary disease (COPD) (1, 2) and other respiratory diseases such as pulmonary hypertension (3), interstitial lung disease (4), cystic fibrosis (5) and post-acute respiratory distress syndrome (6). This test evaluates the global and integrated responses of the pulmonary, cardiovascular and muscular component and reflects the functional exercise level for daily physical activities (7).

Introduced in 1976 as a 12-min walk test to measure exercise capacity for patients with COPD, the abbreviated 6MWD has proved to be reliable, inexpensive, safe and easy to apply (7-10). Also, it correlates well with other important outcomes in COPD patients such as dyspnea, airway obstruction and lung hyperinflation (11). In addition, this test has been shown to be an important prognostic factor for outcome independent of the FEV_1 (12). The 6MWD is a submaximal excersise test, but it has a good correlation with the maximal cardiopulmonary exercise test (13-15) and appears to be better tolerated and more reflective of activities of daily living than other walks tests (16, 17).

In contrast to our knowledge regarding the natural history of FEV_1 over time, we have very little information about the temporal behaviour of the 6MWD. This is very important because the 6MWD test is frequently used to evaluate the long-term impact of interventions.. The change of 6MWD over time has been addressed in only one study from our group (12) but it was limited to patients with severe COPD, the follow up time was relatively short (1 yr) and the decline trend was established with only 2 measurements.

As part of the large BODE cohort, we have systematically evaluated the 6MWD as one of several variables included in the evaluation of the patients. Thus, we planned this study to determine the long-term follow-up and longitudinal changes of the 6MWD with a wide range of severity of COPD. We expressed our results as absolute change and with the reference equations derived for 6MWD in healthy populations (18, 19).

METHODS

A total of 294 outpatients with COPD from the BODE original cohort (1) and wide range of airflow obstruction from clinics in the United States (BayPines VA Medical Center, Florida), Spain (Hospital Universitario La Candelaria, Tenerife, and Hospital Miguel Servet, Zaragoza), and Venezuela (Hospital Jose I Baldo, Caracas) participated in the study, approved by the human review boards at each centre. Patients were enrolled from December 1995 to September 2004 and had to have at least 3 years of follow-up time. After those initial three years the cohort was followed up to five years. Deaths occurring during this time were confirmed by review of the records. COPD was defined by smoking of more than 20 pack-years history and a post-bronchodilator FEV_1/FVC less than 0.7. Patients were clinically stable for at least 6 weeks and receiving optimal medical therapy according to current guidelines. Exclusion criteria were: uncontrolled co-morbidities likely to affect mortality within 3 years such as malignant disorders or cardiovascular disease, history of asthma, inability to perform the lung function and six-minute walk tests and patients involved in pulmonary rehabilitation.

After at least 6 weeks of clinical stability the patients were tested with pulmonary function tests, spirometry and lung volumes according to ATS guidelines (20). The severity of the obstruction was classified using the GOLD/ATS-ERS classification. All patients had an FEV_1/FVC <0.7. Patients in stage I have an FEV_1>80% predicted; Stage II, FEV_1 of 50 to 80% predicted; Stage III, FEV_1 of 30 to 49% predicted and Stage IV, FEV_1<30% predicted.

The 6MWD was measured using the best of two 6-minute walk distance tests separated by at least 30 minutes (1, 7, 21). The 6MWD was expressed in

absolute values and as percent of predicted using two published reference values: Enright et al (18) and Trooster and co-workers (19). We calculated BMI as kg/m^2. We used the inspiratory fraction or ratio between IC and total lung capacity (IC/TLC) as a measure of the static lung hyperinflation (11). The combined Charlson index was used to determine the degree of co-morbidity (22). Patients were re-evaluated every 12 months and for a minimum of three years.

Statistical analysis:

Qualitative variables are expressed as relative frequencies of its categories. Numerical values are expressed as median and 5th–95th percentile because of their skewed distribution. Differences between groups were tested by chi-squared test for categorical variables or Mann-Whitney U test for numerical ones. Correlations were estimated using Spearman´s rank coefficient. The slopes of 6MWD decline were estimated by means trend modelling based in median annual values with its confidence intervals (lower, upper). To estimate possible differences in progression due to the differential loss between patients who dropped out and those who remained between years 3 and 5, we performed General Linear Modelling (GLIM) for repeated measures. Significance was defined as a two tailed p value lower than 0.05. The calculations were made with SPSS 12.0 of SPSS Inc. ©, Chicago, Illinois, U.S.A.

RESULTS

The cohort of 294 patients was distributed as follows: 200 (68%) from the United States, 84 (29%) from Spain (56 from Tenerife; 28 from Zaragoza) and the rest from Venezuela. The patients' characteristic including anthropometric data, FEV_1, 6MWD and Charlson index are presented in Table 1. The age was 66 (51-79) years, and most (97%) were men. At entry time their GOLD/ATS-ERS severity stage had the following distribution: 4 (1%) Mild or Stage I (FEV_1% ≥80), 81 (28%) Moderate or Stage II (FEV_1% from 50 to 79), 136 (46%) Severe or Stage III (FEV_1% from 30 to 49) and 73 (25%) very severe or Stage IV (FEV_1% <30).

After the initial 3 years and during the follow up period of the study we lost 194 patients. Of these, 69 were due to deaths and 125 due to other causes. We did not find any statistical significant difference in the 6MWD decline progression between those patients lost from the study and those who remained: at 3 years (131 vs 163 patients) and 4 yrs follow up time (63 vs 100 patients). However, when we analyzed those that died and compared them with the survivors, they did have a steeper 6MWD decline of 25 (CI:10,40) m/yr.

The median 6MWD was 388 (160-600) m and declined 12.5 (CI:8,17) m/yr for up to five years (p=0.001) (Figure 1). The baseline 6MWD expressed as percent of predicted using Enright and co-workers and Troosters et al. were 75 (47-99) %, and 58 (39-77) % (Figure 2). Of note, the 6MWD has a significant decline only in patients with FEV_1 <50% (Figure 3). Patients with GOLD/ATS-ERS stage III decreased by 19% compared to baseline; 16 (CI:8,24) m/yr, p <0.006 and patients with stage IV decreased by 26% compared with baseline; 15 (CI:7,22) m/yr, p=0.005. The decline did not reach statistical significance in

patients with moderate obstruction: stage II 2% compared with baseline, 6 (CI:-4,16) m/yr, p=0.16 (Figure 4).

The rate of decline was not influenced by the age of the patients (14 m/yr in patients older than 65 years and 13 m/yr in patients younger than that age). The rate of decline was greater in patients from the United States 14 (CI:6,21) m/yr, p=0.008 compared with that of patients from the other regions 7 (CI:0,15) m/yr, p=0.05. This is in agreement with the fact that they had more obstruction and co-morbidity score.

The proportion of patients with a minimal clinical significant decline (≥54 m) increased with the severity of the disease stage: II 24%, III 45%, IV 63% (p=0.025).

The post-bronchodilator FEV_1 values declined significantly, with a yearly mean rate of decline of 23 (CI:14,32) ml/yr (p=0.002). However the decline differed by disease stage and in exactly the opposite way to the 6MWD. The FEV_1 declined in stage II by 40 (CI:20,70) ml/yr (p=0.011), whereas the value was less in patients with stage III, 10 (CI:4,20) ml/yr (p=0.017) and did not decline in patients with stage IV COPD (p=0.73) (Figure 4). These differences were similar when we only included the patients that had been followed for five years (n: 99): stage II 46 (CI:22,70) ml/yr (p=0.006), stage III 31 (CI:-18,80) ml/yr (p=0.158) and stage IV 27 (CI:1,53) ml/yr (p=0.047).

The IC/TLC did not significantly change over the period of study. There were no significant differences in the co-morbidity in the different GOLD ATS/ERS stages: II: 4 (1-8); III: 4 (1-8); IV: 4 (1-7). However, over time there was some worsening of co-morbidity with the Charlson score increasing from 4 (1-7) to 5 (2-12), p <0.001.

The characteristic of the cohort according to regions are presented in Table 2. The COPD patients from Spain walked more (463, 336-635 m) than those from the United States (350, 146-503 m). The FEV_1 was slightly lower and the co-morbidity was higher among patients in the United States than in Spain. These variables explained partially the differences in the 6MWD (r^2 = 0.36, p <0.001). There was no difference in the 6MWD between the patients from Tenerife, Zaragoza and Venezuela.

DISCUSSION

To our knowledge, this is the first prospective large long-term cohort study evaluating the temporal change of 6MWD in patients with COPD and a wide range of airflow obstruction. The most important finding is that the 6MWD declines over time but the decline is really significant only in patients with severe airflow limitation (FEV_1 <50% predicted). In addition, the decline worsened with disease severity, a finding that contrasted with the FEV_1 loss over time, which showed lesser rate of decline at the more severe stages of the disease.

Currently, the impairment of patients with COPD is more comprehensibly described if pulmonary function tests are complemented with an evaluation of exercise performance (2). The latter is usually determined by the use of a cardiopulmonary test in a specialized laboratory or more commonly in the field, using a timed walk test. Because of its ease of administration and value as a predictor of functional capacity and mortality, the 6MWD has gained wide acceptance (12, 23). Surprisingly, compared to the FEV_1 (24, 25) there is very little information regarding the natural evolution of exercise capacity in general or the 6MWD more specifically, probably reflecting the belief that the degree of airflow represents the most important determinant of the natural history of COPD. Recently, Oga et al studying patients with COPD (26) have shown a progressive deterioration in exercise capacity over time when evaluated by peak VO_2 during maximal cycle ergometry. These authors described a weak correlation between peak VO_2 with the decline in FEV_1. Interestingly, they observed a stronger correlation of peak VO_2 with the dynamic ventilatory constraints of dynamic hyperinflation which in their patients progressed over

time. The authors speculated that hyperinflation contributed to the longitudinal decline in exercise capacity. However, in that study there was no adjustment for co-morbidity and therefore, other organs involvement could have influenced their overall results. Similar to the findings of Oga et al. we did not observe associations between the 6MWD decline and the FEV_1. On the other hand, we failed to detect a change in the static hyperinflation estimated by the rate of change of IC/TLC in our patients over the 5 years of the study. The differences between the two studies may relate to the methodology as Oga et al used symptoms limited exercise test and dynamic hyperinflation whereas we used the 6MWD and static hyperinflation. More studies using similar methodology may help resolve these differences.

After short term interventions, such as 3 months of pulmonary rehabilitation, the estimated threshold for clinical significant change in the 6 MWD is though to be around 50 m (27), but there is very limited information about of the predicted decline over a longer time-line in COPD (12). Our results show that the 6MWD annual decline is relatively small 12.5 m/yr. The decline was low in patients with moderate obstruction. However, the change was larger in patients with FEV_1 <50%. In this group the proportion of patients with values higher than the minimal clinical important difference increased with increasing airflow obstruction (figure 4). This has significant relevance because at that level of disease severity, the FEV_1 behaves as a more rigid and less sensitive parameter to detect clinical changes. Indeed, our results can help find an adequate positioning of the 6MWD in the long term evaluation of patients with COPD. According to these results, the 6MWD could be of most help when evaluating patients with FEV_1 <50%.

Why is the decline of the 6MWD more manifest in patients with more severe airflow limitation is highly speculative. It could simply relate to the deconditioning brought about by a more sedentary lifestyle as more severe COPD is associated with more dyspnea. However, it is also possible that the decline results from the development of more advanced systemic involvement from COPD (28). This hypothesis is further supported by the observations of Agusti and co-workers (29) who showed worsening apoptosis in muscle biopsies of patients with COPD and by Montes de Oca et al (30) who described increased levels of markers of oxidative stress and infiltration by macrophages in patients with severe COPD compared with controls. In addition, the worsening Charlson co-morbidity score over time suggest a possible role for increasing co-morbidity as the population aged. Taken together, these findings can be clinically important as the therapy could change depending upon the reason for the decline.

The mean annual decline of the 6MWD in our study is lower than that reported by Pinto-Plata et al from our group (26 m/yr). These differences may be explained by the fact that in our study we excluded patients who did not complete the first three years of follow up.. The differences therefore are more likely due to the fact that in the study reported by Pinto-Plata and co-workers, the decline was evaluated, in a population of severe COPD patients with a very low baseline 6MWD and high co-morbidity as supported by their high short term mortality (27%). This is supported by the finding in our study that patients followed for three years that subsequently died in the follow up period had a steeper rate of decline of 25 m/yr, very close to that observed by Pinto and co-workers. Taken together, the results of both studies indicate that steep declines

in the 6MWD are indicative of poor prognosis and should raise concern regarding the well being of the patient.

The current study also observed important variability in the expression of the results as percent of the predicted values derived from standard equations for healthy individuals (18, 19). This may be due to differences among the studies that generated the predictive equations in use. Enright generated the predicted equation, using the values from only one 6MWD and subjects were instructed to walk at their own pace and not as quickly as possible (18). On the other hand the studies by Troosters et al was based on a smaller size of healthy subjects and may not represent the general population at large (18, 19). This suggests a need to develop new reference values with larger numbers and standard methodology.

The present study has some limitations. First, few women were included. This was not by design, because we offered the opportunity to join the study independent of gender. On the other hand, the large proportion of men may be seen as lending more validity to our findings because they can't be attributed to gender bias. Second, our results do not totally address the issue of individual patient variability since we interpreted the 6MWD annual decline as a mean value of the group. The actual change for an individual may be less or more than the mean here reported and it is importance can only be judged in the context of the specific situation in which it is measured.

In summary, this study shows that the 6MWD decline over time is most important in patients with more severe obstruction. This contrasted with the lesser changes in the FEV_1 observed in those patients. Our results also suggest that in the regular evaluation of patients with severe obstruction (FEV_1),

repeated measures of the 6MWD can help describe clinical changes that can not be easily detected in the sequential evaluation of pulmonary impairment. These findings have to be taken into account when planning studies using the 6MWD changes over time. In addition, the current study suggests that the 6MWD is of most help in the evaluation of patients with severe airflow limitation.

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Figure Legends

Figure 1. The median 6 minute walk distance (6MWD) was 388 (range of 161 – 600) m and declined 12.5 (CI:8,17) m/yr for up to five years (p =0.001). The continuous line represents the median and the stippled lines the 5th–95th percentile interval.

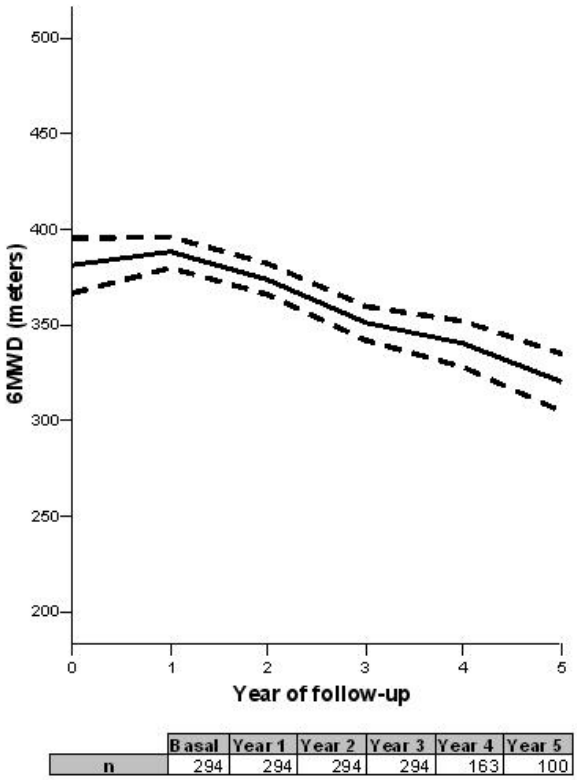
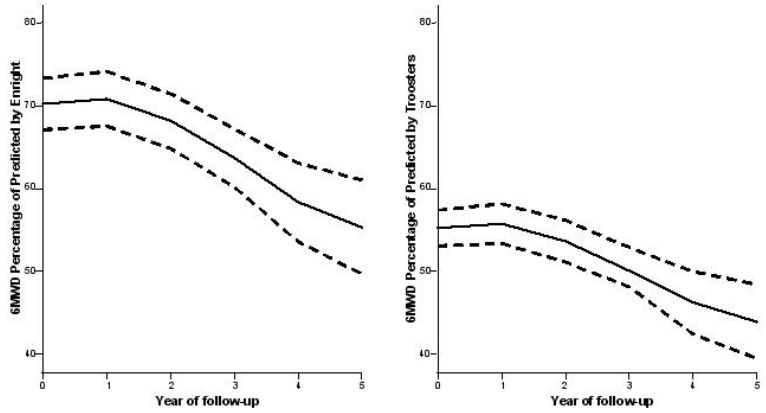


Figure 2. The change in the 6 minute walk distance (6MWD) over time as a function of the predicted values as reported by Enright and co-workers (left panel), Troosters et al (right panel). The decline was 2.1 (CI:1.6,2.7) %/yr (p <0.001), and 1.6 (CI:1.1,2.1) %/yr (p <0.001). The continuous line represents the median and the stippled lines the 5th–95th percentile interval. The decline is expressed as a function of the baseline value.



	Basal	Year 1	Year 2	Year 3	Year 4	Year 5
n	294	294	294	294	163	100

Figure 3. The 6 minute walk distance (6MWD) has a significant decline only in patients with FEV_1 <50%: 15.3 (CI:9.1,21.4) m/yr (p =0.002).

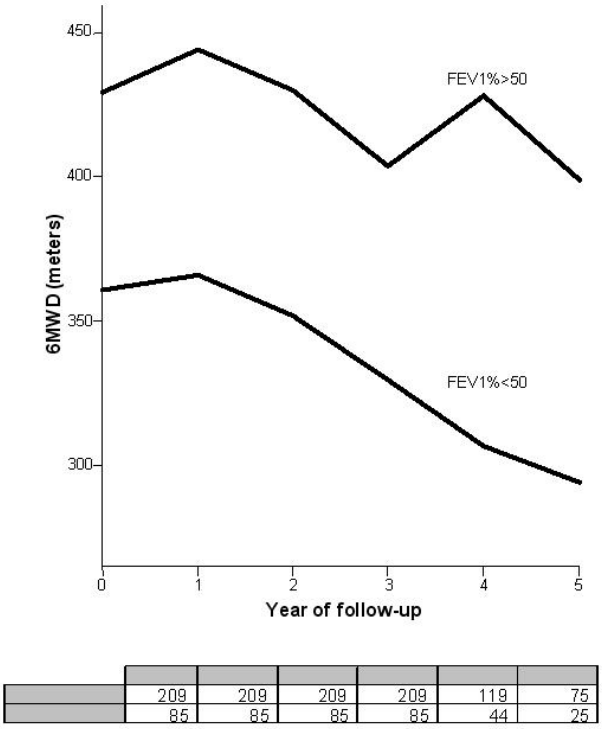


Figure 4. The decline of the 6 minute walk distance (open circles) was greater in patients with more severe airflow obstruction as determined by the GOLD/ATS-ERS staging criteria. In contrast the FEV_1 (closed circles) changed less in those patients with more severe airflow limitation.

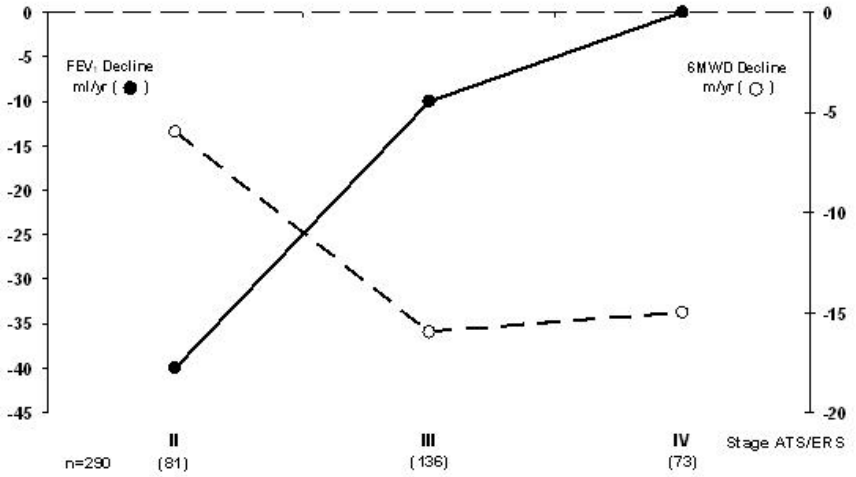


Table 1. Baseline characteristic of the Patients.

	Value* n: 294 patients (range)
Gender, M/F	285 / 9
Age, yr	66 (51 – 79)
Current smokers %	18
BMI, kg/m^2	27 (19 – 36)
6MWD, m	388 (160 – 600)

FEV_1, L	1.13 (0.64 – 2.22)
FEV_1 %	39 (20 – 70)
ATS-ERS staging	
Mild (FEV_1 ≥80%)	4 (1%)
Moderate (FEV_1 50-79%)	81 (28%)
Severe (FEV_1 30- 49%)	136 (46%)
Very Severe (FEV_1 <30%)	73 (25%)
IC/TLC	0.28 (0.16 – 0.42)
Charlson Index	4 (1 – 7)

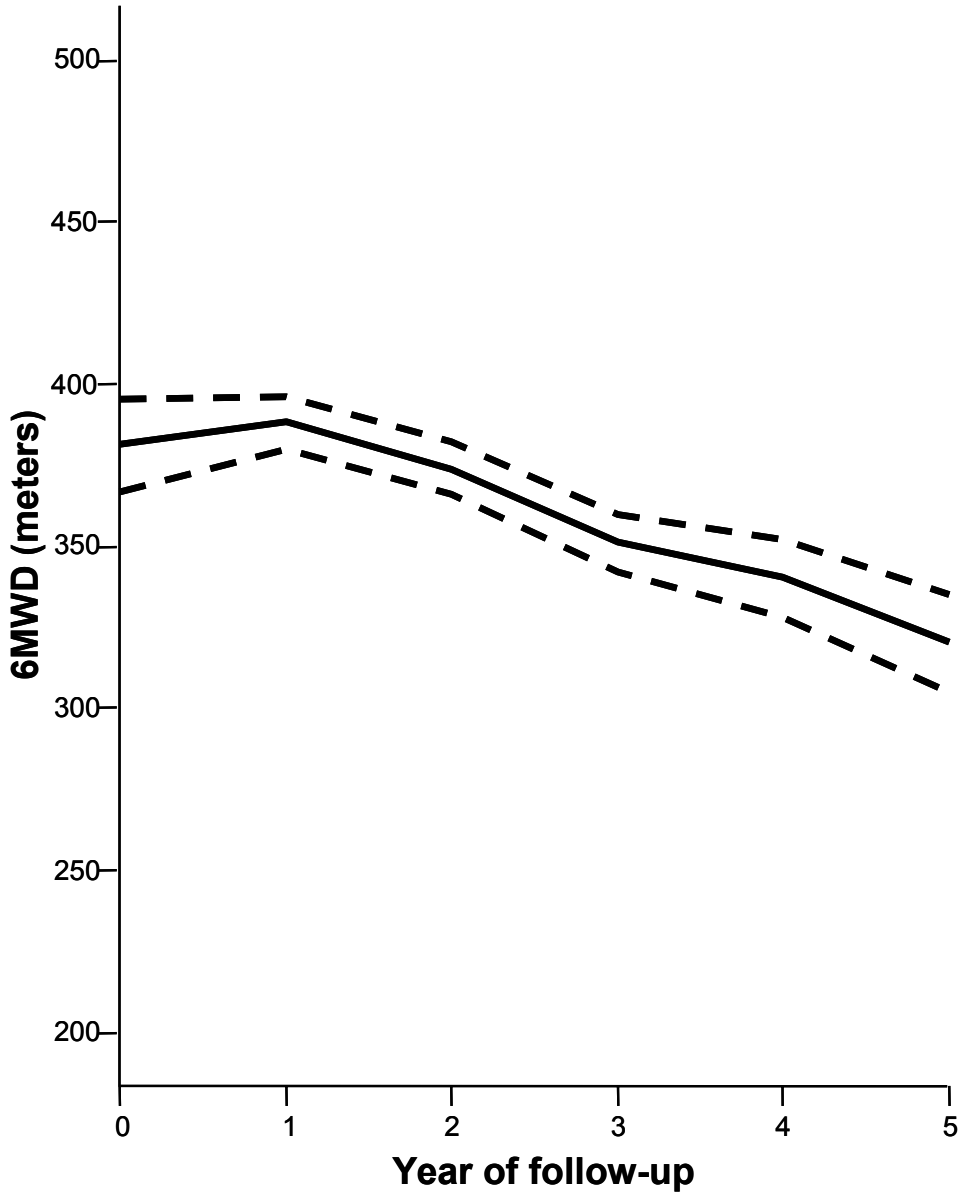
* Frecuency, median (5^{th}-95^{th} percentiles) or percentage.

Table 2. Characteristic of the Cohort According to Country.

	USA (n = 200)	Spain (n = 84)	p Value
Gender, M/F	193 / 7	83 / 1	0.443
Age, yr	66 (51 – 79)	67 (47 – 76)	0.461
BMI, kg/m^2	27 (18 – 37)	27 (19 – 36)	0.658
6MWD, m	350 (146 – 503)	463 (336 – 635)	<0.001
FEV_1, L	1.20 (0.6 – 2.1)	1.15 (0.6 – 2.3)	0.946
FEV_1 %	37 (19 – 67)	43 (21 – 75)	0.014
IC/TLC	0.29 (0.14 – 0.42)	0.28 (0.13 – 0.44)	0.385
Charlson Index	4 (2 – 8)	2 (1 – 6)	<0.001

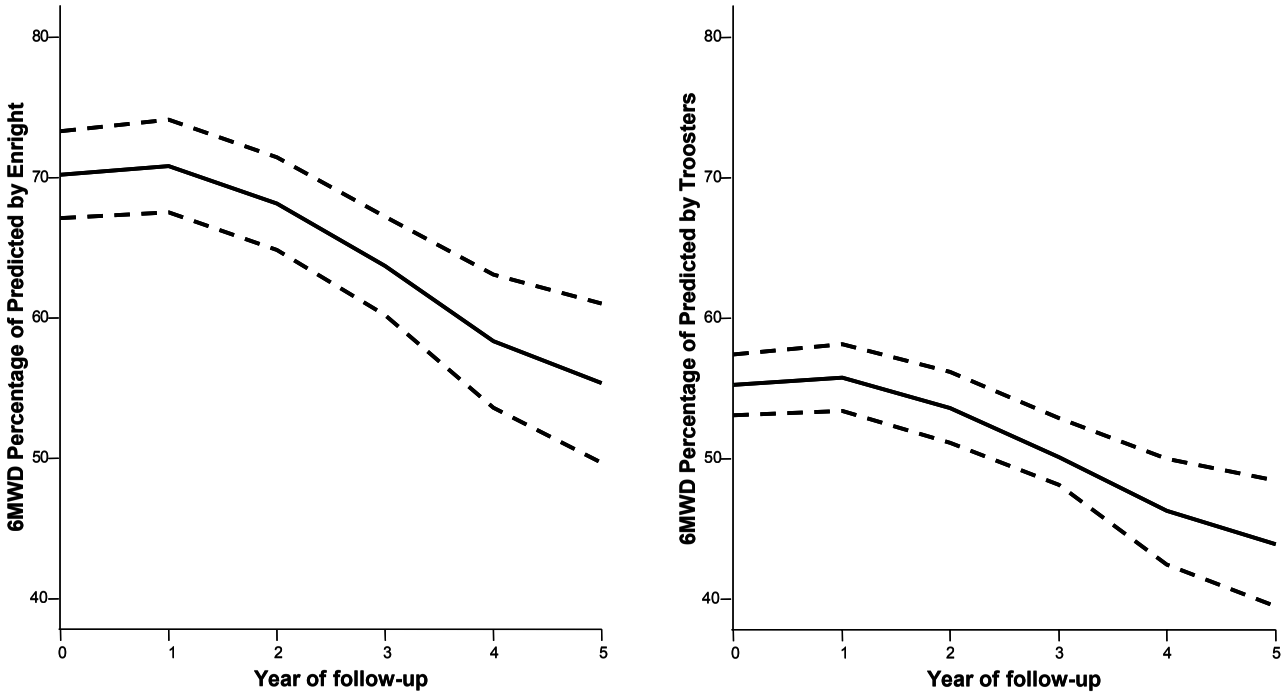
* Frecuency or median (5^{th}-95^{th} percentiles).

Figure 1



	Basal	Year 1	Year 2	Year 3	Year 4	Year 5
n	294	294	294	294	163	100

Figure 2



	Basal	Year 1	Year 2	Year 3	Year 4	Year 5
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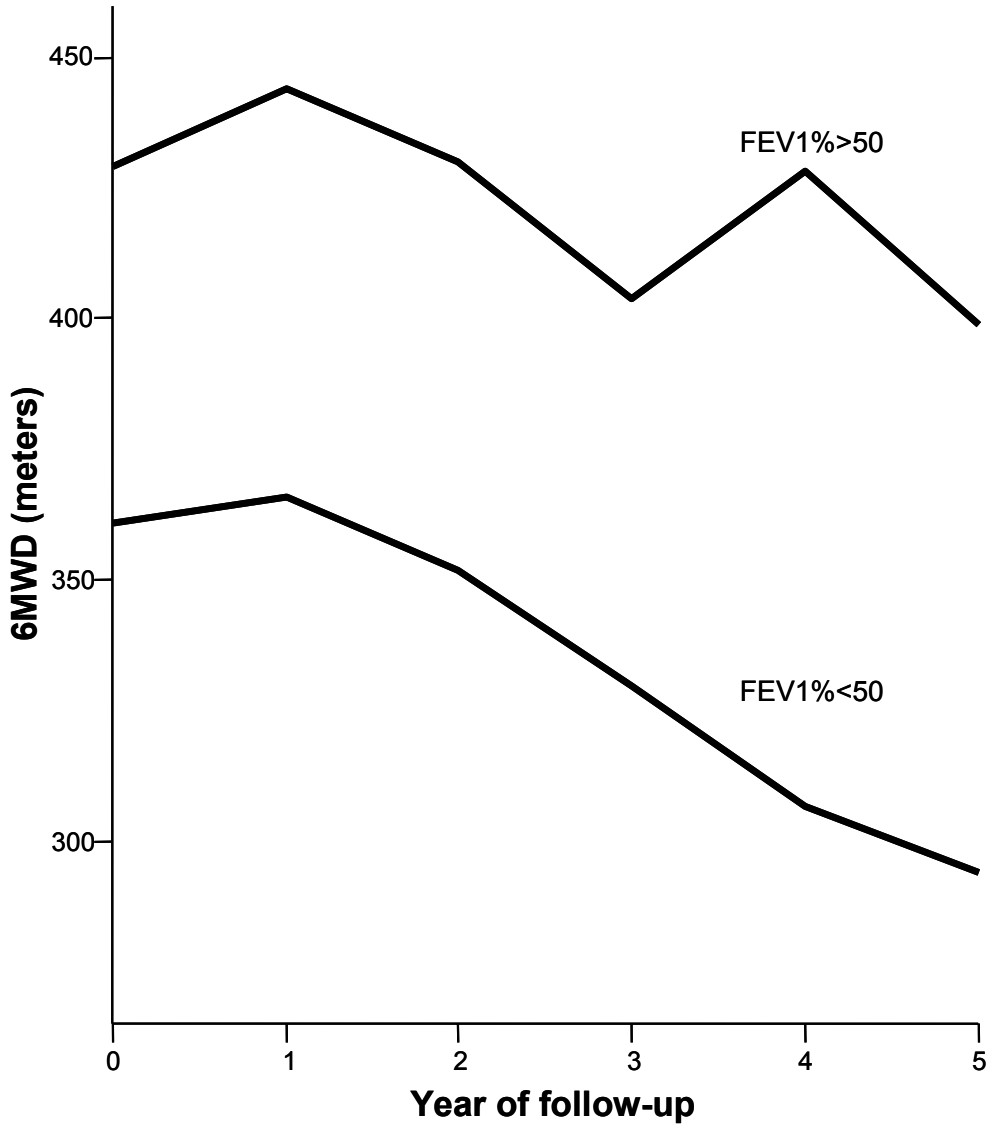
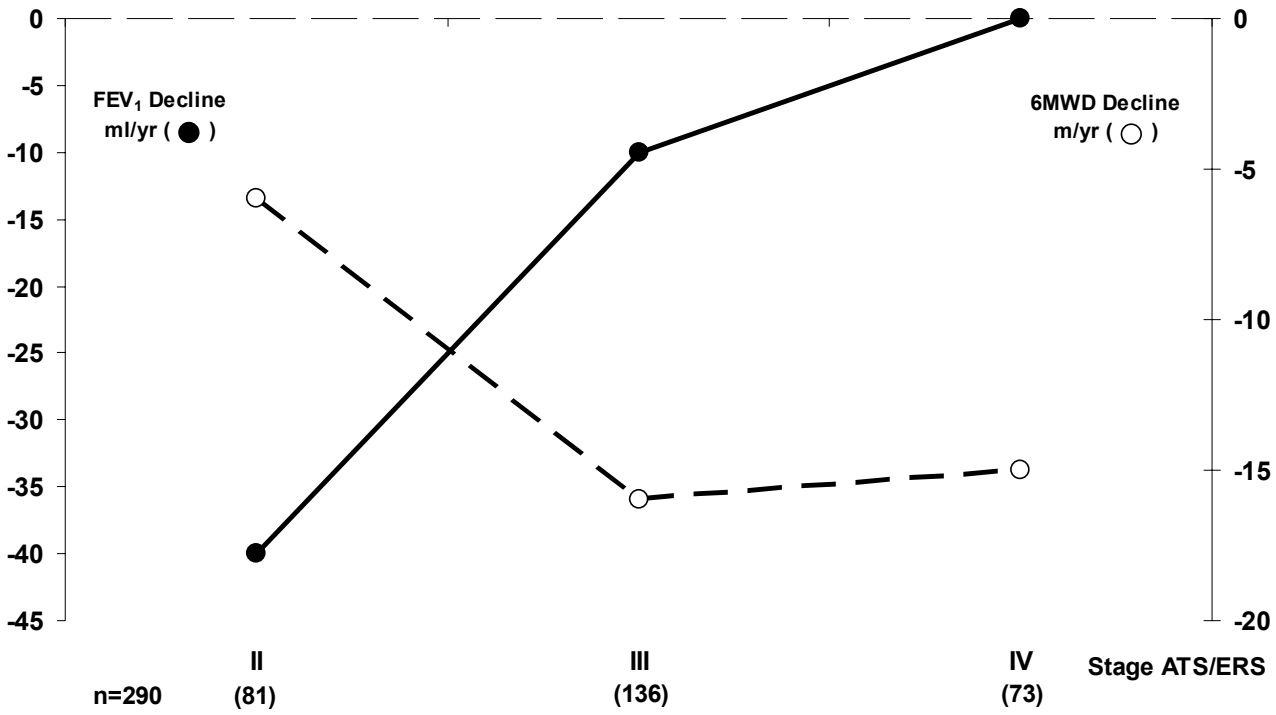
Figure 3



	Basal	Year 1	Year 2	Year 3	Year 4	Year 5
FEV1%<50	209	209	209	209	119	75
FEV1%>50	85	85	85	85	44	25

Figure 4


0
-5
-10
-15
-20
-25
-30
-35
-40
-45
FEV1 Decline
ml/yr (●)
6MWD Decline
m/yr (○)
0
-5
-10
-15
-20
n=290
II
(81)
III
(136)
IV
(73)
Stage ATS/ERS