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Validation and comparison of reference equations for the 6-min walk distance test

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ABSTRACT: Exercise impairment as measured by the 6-min walk distance (6MWD) test afflicts many patients with chronic obstructive pulmonary disease (COPD) and is known to predict mortality. Reference equations for the 6MWD in adults have been published but not yet validated.

The present authors prospectively followed 1,379 COPD patients for 55±30 months and tested the predictive value of the baseline 6MWD in metres, the 6MWD work (kg·m^{-1}) and as a percentage of predicted values the 6MWD in meters according to two reference equations. All-cause mortality was the validating outcome. The best threshold values were identified for each of the tests using receiver operating characteristic (ROC) curves.

The threshold values obtained were: 350 m for the 6MWD, 25,000 kg·m^{-1} for the 6MWD work, and 67 and 54% predicted for the two reference equations. All modalities of the testing were similar at predicting COPD mortality and correlated well with the 6MWD test.

In conclusion, all modalities of testing predict mortality in chronic obstructive pulmonary disease equally well. In the 6-min walk distance test, a value <350 m is associated with increased mortality and should be regarded as abnormal.

KEYWORDS: Chronic obstructive pulmonary disease, 6-min walk distance test, mortality, reference equations

Chronic obstructive pulmonary disease (COPD) ranks as one of the leading causes of mortality and is predicted to become the number one cause of respiratory-related disability in the world by 2020 [1–3]. The inability to perform everyday activities due to exercise intolerance affects many COPD patients and is associated with poor health-related quality of life [4, 5] and decreased survival [6, 7]. Targeting disability has become one of the main goals of the comprehensive management of COPD through interventions that improve the functional status of patients with this disease [3, 8].

The impairment in functional status affecting COPD patients is likely multifactorial, probably reflecting respiratory and nonrespiratory expressions of the disease. However, it is clear, that impaired exercise capacity better reflects the overall compromise of patients with COPD than markers that only reflect the physiological impairment of lung function, including the forced expiratory volume in one second (FEV_1) in particular, as disease severity increases. CASANOVA *et al.* [9] have recently demonstrated that in advanced Global initiative for chronic Lung Disease (GOLD) stages of COPD, patients show a greater loss in exercise capacity than on FEV_1 % predicted. Indeed, several studies [6, 10, 11] have described a better association between exercise performance and mortality than with FEV_1 in this disease.

The utility of the 6-min walk distance (6MWD) test to assess the functional status of patients with COPD is well established. Since its introduction [12], this test has proved to be easy to perform, reliable, inexpensive and amenable to standardisation [13, 14]. Several reference equations have been developed for healthy adults in an attempt to determine normal values for this test [15, 16]. CARTER *et al.* have also proposed using 6MWD work (6MWDW) as an improved outcome measure for the 6MWD test. The 6MWDW is the product of the distance walked by patients and their body weight in kg. The application of the two most widely used of these equations (one from USA and one from Europe), as well as the proposed method by CARTER *et al.* [17], to a large population of patients with COPD, and their validation using mortality as the main outcome became the purpose of the present study. The present authors aimed to compare all tests and aimed to identify the critical threshold values for the different methods of expressing the aforementioned 6MWD results, which have a close association with mortality.

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TABLE 1 Baseline patient characteristics shown by sex at the time of entry into the study

Variable	All	Male	Female	p-value#
Subjects n	1379	1221	158	
Age yrs	66±9	66.5±9	62.6±10	<0.0001
Weight kg	78.7±18	80.4±18	65.6±16	<0.0001
Height cm	171.7±9	173±8	159±8	<0.0001
6MWD m	365.9±133	363±135	388±116	<0.02
Enright				
m pred	523±71	528±70	488±67	<0.0001
% pred	71.2±27	70±28	79±23	<0.0001
Troosters				
m pred	653±66	662±61	582±68	<0.0001
% pred	56.6±21	55±21	66.6±20	<0.0001
6MWD work m·kg^{-1}	28783±1240	29183±1265	25304±9673	<0.0001
Current smoking %	32	31	41	<0.009
Ejection fraction %	55.9±11	55.9±10	57.6±8.7	>0.05
Charlson comorbidity points	4.15±2.7	4.34±2.7	2.7±2.3	<0.0001
FEV_1				
L	1.28±0.6	1.30±0.59	1.13±0.46	<0.009
% pred	43.8±18	42.8±17	50.3±20	<0.0001
MMRC dyspnoea scale points	2.3±1	2.32±1.08	2.14±1	<0.044
BMI kg·m^{-2}	26.6±5.6	26.7±5.6	25.7±6	<0.049
BODE index points	4.1±2.4	4.2±2.46	3.52±2.24	<0.0004
FVC				
L	2.77±1.91	2.85±2	2.19±0.7	<0.0001
% pred	72.7±21	72±20	78.8±23	<0.003
FEV_1/FVC %	46±18	45.9±19	48.8±12	<0.009
IC L	2.04±0.6	2.09±0.69	1.67±0.4	<0.0001
TLC				
L	7.14±1.7	7.33±1.6	5.73±1.21	<0.0001
% pred	116±25	116±25	120±22	>0.05
IC/TLC %	0.30±0.1	0.30±0.11	0.30±0.1	>0.05
FRC				
L	5.1±1.7	5.24±1.6	4.20±1.3	<0.0001
% pred	147±44	146±44	154±47	>0.05
RV				
L	4.4±1.6	4.48±1.6	3.65±1.2	<0.0001
% pred	184±68	184±68	189±67	>0.05
$D_{L,CO}$				
L	11.5±5.1	11.7±5.1	8.52±3.7	<0.0001
% pred	52±20	53±20	44±16	<0.0001
RV/TLC %	59±12	59.6±12	61±10	>0.05

Data are presented as mean±SD unless otherwise stated. 6MWD: 6-min walk distance; % pred: % predicted; FEV_1: forced expiratory volume in one second; MMRC: Modified Medical Research Council; BMI: body mass index; BODE: Body mass index, Obstruction, Dyspnoea, Exercise capacity; FVC: forced vital capacity; IC: inspiratory capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. #: p-value between males and females.

METHODS

Patients

A total of 1,379 patients with a wide range of COPD stages, as accepted by the American Thoracic Society (ATS) [18], were recruited into an observational study between January 1997 and September 2004, and followed until July 2007 at several of the BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index) study sites. Inclusion/exclusion criteria have been previously published [19]. The protocol was approved by the institutional review board of each institution and all patients signed a consent form. Patients completed an evaluation within 6 weeks of enrolment and continued to be followed thereafter at 6-month intervals until July 2007 or until death. Data for mortality was confirmed by reviewing the medical records and by contacting patients' next of kin in every site.

TABLE 2 Causes of death and performance in the 6-min walk distance (6MWD) test

	Patients' 6MWD group		
	<350 m	>350 m	All patients
Subjects n	559	820	1379
6MWD m	233±85	457±70	366±134
Mortality	369 (66)	254 (31)	623 (45)
Causes of death			
COPD	222 (60)	94 (37)	316 (51)
Lung cancer	42 (11)	50 (20)	92 (15)
Other	105 (28)	110 (43)	215 (34)

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease.

Measurements

Demographic information and smoking history were collected. Pulmonary function tests were obtained according to ATS guidelines [20]. Spirometry, lung volumes and diffusing capacity were also measured. The 6MWD was performed following ATS guidelines [14] and the 6MWD % pred was calculated by using the reference equations provided by ENRIGHT and SHERRILL [15] and TROOSTERS *et al.* [16] for males and females. In order to calculate the 6MWDW, the distance walked by the patient in metres was multiplied by the weight of the patient in kg [17]. Dyspnoea was assessed using the Modified Medical Research Council (MMRC) dyspnoea scale [21]. To determine the degree of comorbidity the validated Charlson's index [22] was used.

Reference equations

The reference equations for males (1) and females (2), respectively, provided by ENRIGHT and SHERILL [15] are:

$$6MWD=(7.57\times height(cm))-(5.02\times age(yrs))-(1.76\times weight(kg))-309m \quad (1)$$

$$6MWD=(2.11\times height(cm))-(5.78\times age(yrs))-(2.29\times weight(kg))-667m \quad (2)$$

and the reference equation for males and females by TROOSTERS *et al.* [16] is:

$$6MWD\ pred=218+(5.14\times height(cm)-5.32\times age(yrs))-(1.8\times height(cm))+(51.31\times sex) \quad (3)$$

where sex=1 for males and 0 for females.

Statistical analysis

Normally distributed variables are reported as mean±SD. The differences in physical characteristics, pulmonary function test and exercise parameters were evaluated using unpaired t-tests. Comparison of 6MWD between patients with terminal COPD and those dying from other terminal diseases was performed using ANOVA. Pearson's correlation coefficients were obtained between different variables and mortality and between 6MWD, and 6MWDW and % pred by ENRIGHT and SHERRILL [15] and TROOSTERS *et al.* [16]. For diagnostic analysis of the different modalities of testing, receiver operating characteristic (ROC) curves were used in order to assess the thresholds with the best sensitivity and specificity to predict mortality.

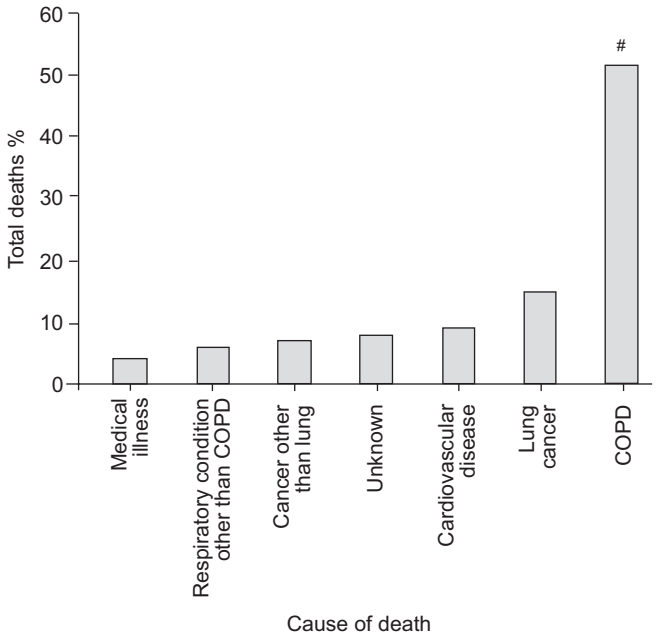

FIGURE 1. Mortality outcomes over the study period. COPD: chronic obstructive pulmonary disease. The 6-min walk distance (6MWD; mean±SD) at entry into the study for each cause of death were: 353±109 m for medical illness; 359±129 m for respiratory disease other than COPD; 349±124 m for cancer other than lung; 326±116 m for unknown reasons; 328±106 m for cardiovascular disease; 366±130 m for lung cancer; and 268±136 m for COPD. #: 6MWD was significantly different ($p<0.00005$) to other causes of death.

RESULTS

A total of 1,379 patients with COPD aged 39–91 yrs were included in the present study. Patients were followed for 55±29 months (range 1–150 months) or until death. The majority of patients had symptomatic COPD. FEV_1 % pred ranged 9–93% and FEV_1/forced vital capacity (FVC) from 16–70%. In total <4% of the patients were in stage I COPD according to the ATS/European Respiratory Society/GOLD guidelines, 30% were in stage II, 41% were in stage III and 25% were in stage IV. Their 6MWD ranged 24–771 m. The baseline characteristics are shown in table 1.

Mortality

There were 623 deaths. In total 316 (51%) of deaths were directly related to COPD, 40 (6.4%) were of respiratory origin other than COPD, 92 (14.7%) were due to lung cancer, 56 (8.9%) to cardiovascular disease, 44 (7%) to malignancies other than lung cancer, 27 (4.3%) to various medical illnesses and in 48 (7.7%) cases, the cause of death could not be determined. The mortality rates and the different causes of death are shown in table 2 with patients classified into two groups according to 6MWD > or <350 m. COPD mortality was much higher for patients walking <350 m. Non-COPD causes of death were higher among patients with preserved exercise capacity. Using ANOVA for inter-group comparisons, the mean 6MWD of patients who died as a result of COPD (268±136 m) was

TABLE 3 Receiver operating curve analysis for the best sensitivity and specificity thresholds of the tests to predict survival

Test	Threshold value	Specificity %	Sensitivity %	AUC
6MWD m	350	70.3	68.3	0.754
6MWD work m·kg^{-1}	25000	69.9	69.5	0.771
Enright % pred	67	67.1	67.1	0.745
Troosters % pred	54	69.1	67.5	0.753

AUC: area under the curve; 6MWD: 6-min walk distance; % pred: % predicted.

significantly different from that of patients dying from any other cause (348±121 m) as shown in figure 1.

Receiver operating characteristic curves

Using ROCs, the threshold values with the best specificity and sensitivity to predict mortality were determined for the reference equations, 6MWDW and 6MWD test. The results are shown in table 3. The area under the curve was very similar for all four modalities of testing. Values below the thresholds were considered as abnormal.

Enright's reference equation

The threshold value for the Enright's equation was 67%. A total of 560 (40.6%) patients were below this threshold, 612 (44.3%) fell between 67–100% of normal and 206 (15%) patients exceeded 100% of their predicted walk. Overall mortality of patients below the critical threshold was 64.2% (n=360). A total of 212 (37.7%) deaths were due to COPD. Conversely, 263 (31.7%) deaths were seen in patients above the critical threshold and, of these, 103 (12.4%) deaths were due to COPD.

Troosters' reference equation

The threshold value for Troosters' equation was 54%. In total, 563 (40.5%) patients were below this level, 612 (58%) patients fell between 54–100% pred and only 10 (0.7%) patients exceeded 100% of their predicted walk. The mortality in patients below the critical threshold was 65.7% (n=370). A total of 218 (38.7%) patients died from COPD. Among the 816 (58.7%) patients with normal exercise capacity there were 253 (31%) deaths and 98 (12%) were due to COPD.

6MWD work

The threshold valued identified for the 6MWD work was 25,000 kg·m^{-1}. Using this value, 545 (39.2%) patients were below the critical threshold. All cause mortality among these patients was 65.5% (n=357) and COPD mortality was 40.5% (n=221). Overall mortality among the 844 patients with values above the threshold was 31.5% (n=266). A total of 95 (11.2%) patients died from COPD.

6MWD test

The threshold value for the 6MWD test was 350 m. A total of 559 (40.2%) patients were below this threshold and the observed mortality among these patients was 66% (n=369). COPD mortality was 39.7% (n=222). Mortality in patients above the critical threshold was 30.6% (n=254), and 94 (11.3%) patients died from COPD.

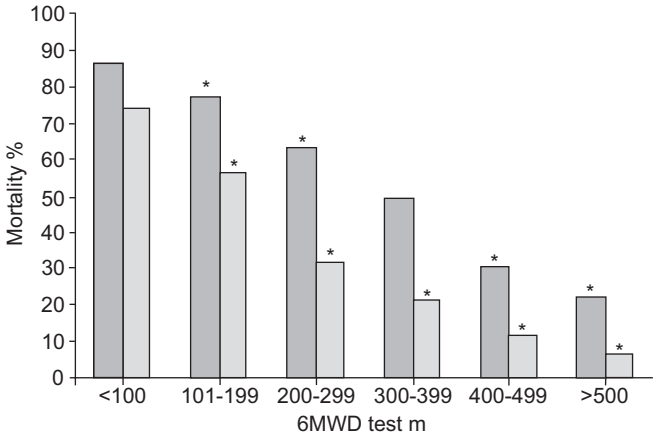

FIGURE 2. All-cause and chronic obstructive pulmonary disease (COPD) mortality in COPD patients stratified by 100 m in the performance of the 6-min walk distance (6MWD). ■: all-cause mortality; ■: COPD mortality. *: $p<0.05$.

Comparison of patients above and below the different thresholds are shown in table 2. An exponential increase was noted in all-cause mortality for every 100 m decrease in the 6MWD test. The results are shown in figure 2.

Correlations with mortality

Pearson's correlation coefficients were used to investigate the relationship between all-cause mortality and COPD mortality with exercise performance in all patients and according to sex. When all patients were included in the analysis, similar correlations between all-cause mortality and COPD mortality were found, with all type of evaluations. Higher correlations were seen between all-cause mortality and female sex for all modalities of testing. The results are shown in table 4.

Kaplan–Meier survival analysis is shown in figure 3. No significant differences between the tests was found. The best Chi-squared value was seen with the 6MWD work.

TABLE 4 Correlation coefficients for all-cause mortality and chronic obstructive pulmonary disease (COPD) mortality for all patients and according to sex

	Enright	Troosters	6MWD	6MWD work
All-cause mortality				
All	-0.358	-0.388	-0.396	-0.388
Males	-0.339	-0.358	-0.382	-0.412
Females	-0.496	-0.499	-0.495	-0.449
COPD mortality				
All	-0.378	-0.395	-0.398	-0.395
Males	-0.369	-0.386	-0.395	-0.411
Females	-0.412	-0.403	-0.394	-0.381

6MWD: 6-min walk distance test.

Pearson's correlation coefficients revealed an excellent correlation between the 6MWD, Troosters % pred (r=0.96), Enright % pred (r=0.93), and a slightly less significant correlation with 6MWD work (r=0.83). ROC curves (fig. 4) showed all tests to have a similar discriminatory diagnostic capability for mortality in COPD patients. The area under the curve (AUC) for: 6MWD was 0.75; for 6MWD work, 0.77; for Enright % pred, 0.74; and for Troosters % pred, 0.75. The differences between groups were not statistically significant.

Discussion

The present study has several important findings. First, it has been found that the absolute value of 6MWD is as good a predictor of mortality in patients with COPD as values normalised by reference equations. Secondly, a 6MWD value of <350 m can be used as a threshold for poor prognosis. ROCs are considered the optimal method to determine the best performance for a diagnostic test, based on their best sensitivity and specificity. Threshold values of clinically significant abnormality were identified for published reference equations and for the 6MWD work and the 6MWD test and it was found that they predicted mortality in COPD in almost an identical way (table 3).

Thirdly, the present study has shown that there is an increased correlation between mortality and female sex for all tests, which suggests that poor exercise performance in females might carry an ominous prognosis. As seen in table 4, the correlation between 6MWD and mortality in females was r= -0.49, p<0.0001 *versus* r= -0.38, p<0.0001 in males. Sex-related differences in patients with COPD need closer consideration.

COPD is a disease that impairs functional capacity. However, the degree of exercise intolerance as measured by the 6MWD test varies widely even among patients with similar airflow limitation. This was evident in large clinical trials such as that of patients enrolled for lung volume reduction surgery [23], who by design had a narrow range of airflow limitation but a wide range of exercise performance. The exact reason for exercise limitation in COPD is not fully understood but appears to be somewhat independent of FEV_1. In the majority of patients with COPD, dyspnoea is a main limiting factor [24],

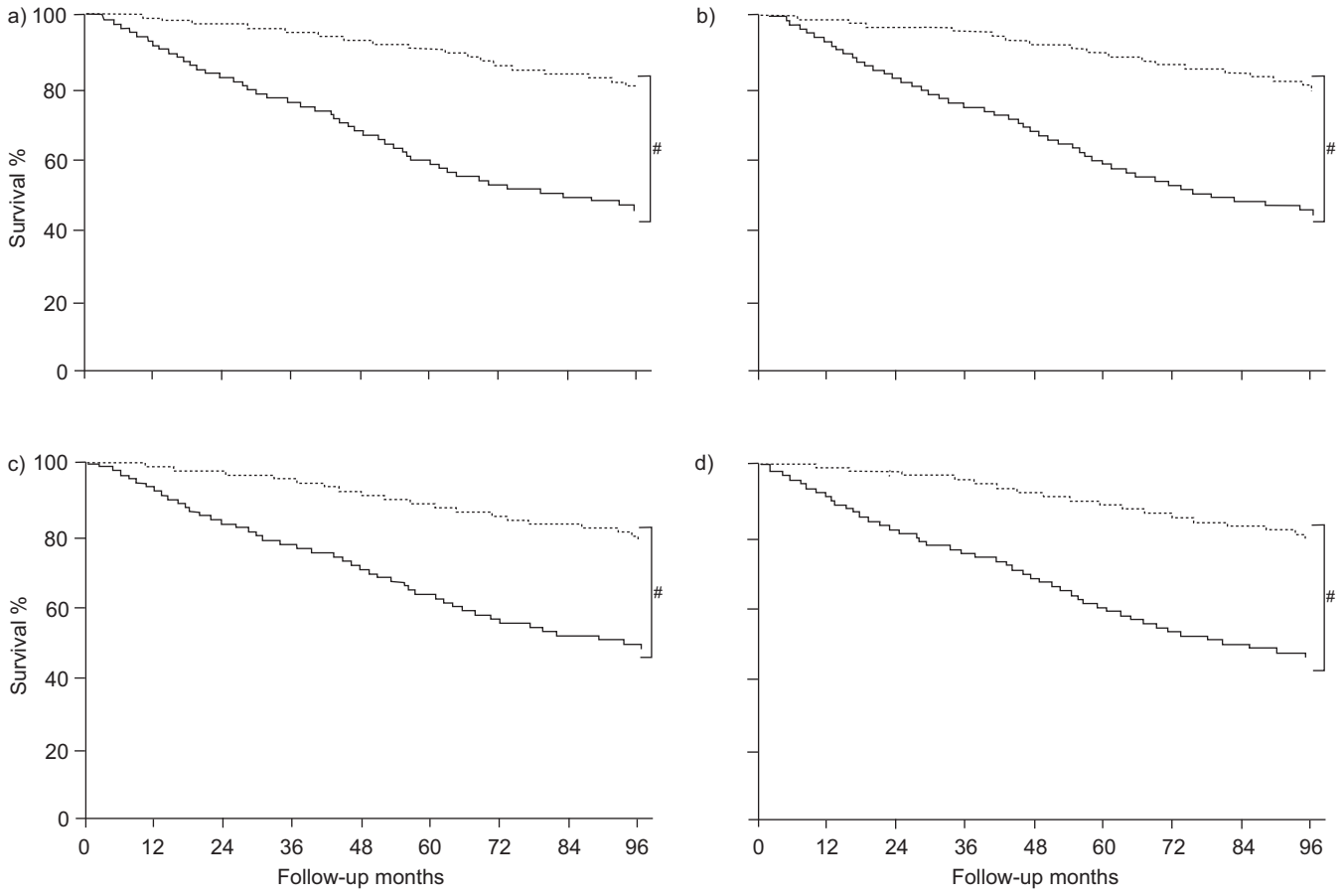

FIGURE 3. Kaplan–Meier survival analysis for a) 6-min walk distance (6MWD) test; b) 6MWD work; c) Enright % predicted; and d) Troosters % pred. Survival curves are shown for patients above (·····) and below (—) threshold values. Threshold values were: a) 350 m; b) 25,000 m·kg^{-1}; c) 67%; and d) 54%. Chi-squared values were 168.262, 181.233, 127.025 and 147.744 for 6MWD, 6MWD work, Enright % pred and Troosters % pred, respectively. Number of patients at months 0, 12, 24, 36, 48, 60, 72, 84 and 96 for: a) 6MWD <350 m were 559, 495, 415, 356, 293, 252, 221, 209, 199, and >350 m were 820, 797, 745, 712, 663, 621, 597, 579, 570; b) 6MWD work <25,000 m·kg^{-1} were 545, 485, 402, 340, 289, 247, 217, 205, 197, and >25,000m·kg^{-1} were 834, 808, 759, 729, 668, 627, 602, 584, 573; c) Enright % pred <67% were 560, 495, 416, 357, 302, 265, 232, 218, 209, and >67% were 819, 797, 744, 711, 654, 608, 586, 570, 560; and d) Troosters % pred <54% were 563, 497, 416, 355, 298, 259, 225, 211, 202, and >54% were 816, 795, 744, 713, 658, 614, 593, 577 and 567; respectively. #: p<0.00005.

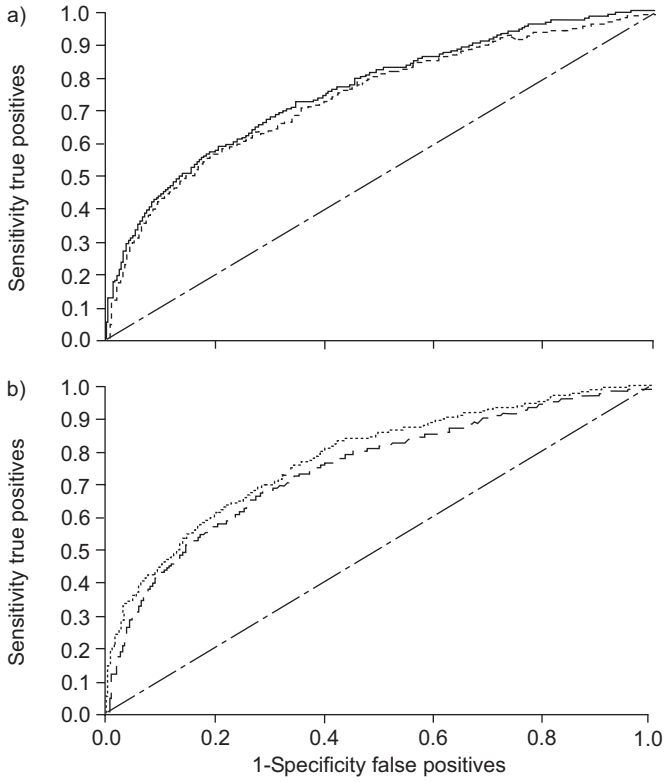

FIGURE 4. Receiver operating characteristic curves show great similarity between all modalities of testing. The best area under the curve was found with the 6-min walk distance (6MWD) test work, although there was no statistical significant difference between the groups. ——: Troosters % predicted; ----: Enright % pred; ·····: 6MWD work; — — —: 6MWD.

likely related to hyperinflation [25, 26], airflow limitation [27] and impairment in diffusing capacity [28]. In addition, skeletal muscle dysfunction has also been implicated in the genesis of exercise limitation among patients with COPD [29]. The muscle of COPD patients shows structural and metabolic abnormalities, not seen in normal patients of similar age [30–32]. Whatever the exact reasons for exercise limitation, the evaluation of exercise capacity using the 6MWD in patients with COPD helps assess disease severity. Furthermore, identifying levels of exercise impairment helps with the characterisation of these patients and assists with the referral to programmes such as pulmonary rehabilitation, lung reduction surgery or lung transplantation.

Most authors agree that 6MWD is a practical field test but its correct interpretation is more debatable [33]. Studies have used the absolute value in metres to determine its prognostic ability or its responsiveness to pulmonary rehabilitation [7] or lung reduction surgery [23]. However, it is well known that the 6MWD is influenced by age, sex and height. Indeed, the two studies validated herein, have provided reference equations based on the testing of normal individuals and then expressed the observed results as a percentage of predicted normal [15, 16]. Interestingly, both reference values, although obtained through different methodologies, performed similarly at predicting mortality in COPD, indicating that at least for males, the equations have similar behaviour. Although the number of female patients in the present study was relatively small (n=158), they were found to have a higher 6MWD compared with males. The female patients were compared to an equal number of male patients (n=160), matched by FEV_1% (50±12) and age. Females walked 12–15% more according to reference equations and ~35 m more according to the 6MWD. This finding is similar to that found in the unmatched analysis (females n=158, males n=1221) but needs to be tested in a larger population of female patients with COPD. This finding may explain the lower mortality observed among females compared with males (all-cause mortality 22 *versus* 48%, $p<0.002$; COPD mortality 12 *versus* 24%, $p<0.007$). Conversely, the walking distance of males dying from COPD (252±131 m) was very similar to that of females dying from COPD (264±118 m). However, the observed per cent predicted by reference equations for males (Enright=48%, Troosters=38%) was significantly lower than the observed per cent predicted among females who died (Enright=54%, Troosters=45%). Taken together, these findings suggest that a lower 6MWD in females might confer a worse prognosis than in males.

The present authors believe that, this is the first large study of a well characterised population of patients with COPD that applies and validates reference equations, determines values of clinical significance and describes the association between the performance on these tests and mortality over a long observational period. Previous reports included a smaller number of patients and a shorter time of follow-up. In the present study, the value of the 6MWD as a surrogate for survival has been further demonstrated. The present study confirms the threshold of clinical relevance for the 6MWD, as described in the original BODE study [19]. As shown in table 3, this threshold has similar sensitivity and specificity for mortality as reference equations and 6MWD work, and an almost linear increase in mortality as the walking distance decreases by 100 m (fig. 2).

The present study has several limitations; the most important is the small number of females included in the study. Thus, the generalisation of these results to female patients with COPD may not fully apply and remains to be validated in studies including a much larger number of females. Additionally, the population included is primarily that of patients attending pulmonary clinics. This may bias toward patients with more symptomatic disease and it remains to be proven that the conclusions are extensive to the COPD population at large. Conversely, the long-term follow-up and the relatively large population included do suggest that the conclusions may be applicable to the majority of patients in whom an evaluation of exercise capacity may be of clinical value.

In summary, the present study shows that the distance walked during a 6-min walk distance test by patients with chronic obstructive pulmonary disease is as good a predictor of mortality as values normalised by reference equations and by the 6-min walk distance work. The present authors believe that the application of reference equations may be justified for the scientific interpretation of exercise performance. However, they add complexity to a test that remains grossly underutilised. Facilitating the interpretation of the test could influence implementation by the practitioner. The present authors believe that a 6-min walking distance test adds

important independent information to the routine evaluation of patients with symptomatic chronic obstructive pulmonary disease and should be incorporated in the regular evaluation of these patients. If the value is >350 m, there is less need for close observation. Conversely, a value lower than this threshold identifies patients at higher risk for death and therefore candidates for closer observation and for possible therapies, such as pulmonary rehabilitation or lung volume reduction.

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