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ORIGINAL RESEARCH

Baseline Exercise Tolerance and Perceived Dyspnea to Identify the Ideal Candidate to Pulmonary Rehabilitation: A Risk Chart in COPD Patients

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Stefania Costi[1]
Ernesto Crisafulli[2]
Ludovico Trianni[3]
Bianca Beghè[4]
Silvia Faverzani[5]
Giuseppe Scopelliti[5]
Alfredo Chetta[5]
Enrico Clini[4]

[1]Department of Surgical, Medical and Dental Department of Morphological Sciences Related to Transplants Oncology and Regenerative Medicine-University of Modena and Reggio Emilia and Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy; [2]Department of Medicine, Respiratory Medicine Unit and Section of Internal Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [3]Rehabilitation Unit-Hospital Villa Pineta, Pavullo Nel Frignano, Modena, Italy; [4]Department of Medical and Surgical Sciences-University of Modena and Reggio Emilia and University Hospital of Modena Policlinico, Modena, Italy; [5]Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy

Background: The appropriate criteria for patient selection are still a key issue in the clinical management of patients referred to pulmonary rehabilitation (PR).

Methods: We retrospectively analyzed the records of a wide population of 1470 outpatient or inpatients with chronic obstructive pulmonary disease (COPD) referred to standard PR at two specialized Italian centers. Two models of multivariate logistic regression were developed to test the predictive powers of baseline exercise tolerance, namely the distance walked in 6 mins (6MWD), and of baseline dyspnea on exertion, measured by the modified Medical Research Council scale (mMRC), versus the minimal clinically important difference (MCID) for the same outcomes.

Results: Compared to the category of individuals with 6MWD >350 meters, those patients with 201–350 meters and ≤200 meters showed a higher probability ($p<0.001$) of predicting a MCID change. Compared to the category of individuals with mMRC 0-1point, all the other categories (2, 3, and 4) also showed a higher probability ($p<0.001$) of predicting a MCID change. The incorporation of baseline categories of 6MWD and mMRC in a risk chart showed that the percentage of patients reaching MCID in both variables increased as the baseline level of 6MWD decreased and of mMRC increased.

Conclusion: This study demonstrates that lower levels of exercise tolerance and greater perceived dyspnea on exertion predict achieving clinically meaningful changes for both these treatment outcomes following PR. A specific risk chart that integrates these two variables may help clinicians to select ideal candidates and best responders to PR.

Keywords: chronic obstructive pulmonary disease, pulmonary rehabilitation, patient selection, minimal clinically important difference, exercise tolerance, dyspnea

Introduction

Pulmonary rehabilitation (PR) is a comprehensive and tailored intervention recommended to patients with chronic obstructive pulmonary disease (COPD).[1] In the context of patient selection, PR provides benefits independently of baseline characteristics and others such as age,[2] functional stages,[3] comorbidities,[4,5] and physical frailty.[6] Even in cachectic COPD patients, a PR effect on physical capacity and on muscle remodeling has been proven.[7]

Although, at least theoretically, all COPD patients are potential candidates to PR based on the occurrence and persistence of symptoms and disability, it has been shown that different multidimensional profiles,[8] disability level at baseline,[5] and dyspnea perception may affect the response to PR and predict its likely effectiveness.[9] Specific

Correspondence: Ernesto Crisafulli
Department of Medicine, Respiratory Medicine Unit and Section of Internal Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
Email ernesto.crisafulli@univr.it

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determinants of PR success concerning the degree of breathlessness, body weight, or gas exchange have been thus identified.[10] Walking limitation and perceived dyspnea, however, represent two common, easy-to-measure characteristics of disabled COPD patients.[1]

In clinical practice around the world, the main factors that impede the actual delivery of PR services to suitable patients[11] are related to limited funding and reimbursement, lack of healthcare professionals and expertise,[12] poor patient awareness, and/or additional patient-related barriers.[11] Since PR is a challenging intervention for individuals and given the current need to allocate the available resources properly, referring clinicians should improve their ability to better screen eligible patients. This would help to identify those individuals that would benefit most from PR.

Accordingly, we investigated the predictive role of both the baseline distance walked (6MWD) and the mMRC (Modified Medical Research Council) Dyspnea Scale score on successful PR, as defined by clinically meaningful changes in these two relevant measurements. Thus, in a population of COPD patients with different categories of baseline disability referring to these two outcome measures, we tested the probability of achieving the minimal clinically important difference (MCID) for both these patient-centered outcomes following PR.

Methods

Study Sample

This retrospective study analyzed stable COPD patients admitted to a pulmonary rehabilitation program. The institutional review board and ethical committee of each hospital approved the study, conducted according to the Declaration of Helsinki. Patient data were treated confidentially and patients' consent to review their medical records was not required.

Patients were cared for by the Rehabilitation Unit of Villa Pineta Hospital (Pavullo n/F (MO), Italy) from 2002 to 2010 (n=1394) or by the Respiratory Disease and Lung Function Unit (Parma, Italy) from 2016 to 2018 (n=76). The primary diagnosis of COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease criteria.[13] We excluded COPD patients: a) with an acute event in the 4 weeks prior to enrollment; b) with a coexisting diagnosis of asthma or any other pulmonary disease; c) with any comorbidity affecting exercise performance (anemia, disabling neuromuscular conditions, acute cardiac failure, malignancies); d) with cognitive impairments that might have interfered with the adherence to the rehabilitation program; e) who withdrew from the PR for any cause or patients in whom it was not possible to obtain the measures of exercise tolerance or dyspnea perception at discharge. Data on all patients were analyzed and reported anonymously. No extramural funding was used to support the study.

General Measurements

Age, sex, and body mass index-BMI were recorded at enrolment. Lung function was measured at baseline by means of standard spirometry, performed according to international recommendations.[14] Arterial blood samples were taken for gas analysis. Concomitant chronic diseases were assessed by the self-reported Charlson Comorbidity Index, which assigns to each disease a score that is proportional to the related risk of death.[15] The self-reported prevalence of some chronic diseases (arterial hypertension, diabetes, coronary disease, chronic heart failure, dyslipidemia, and osteoporosis) was collected.

Rehabilitation Program and Outcomes

Patients included were treated on an inpatient or outpatient basis, depending on the individual's level of functional limitations, and the patient's preference. The rehabilitation program consisted of 21 consecutive 3 hr sessions and included in each session standard activities (peripheral limb training, respiratory muscle training, chest physiotherapy), and psychological and nutritional counselling when indicated. The program was conducted in the same way at the two facilities, as previously reported.[4] Physiotherapists involved were previously instructed to homogenize the type and duration of all activities.[4]

The outcomes were analyzed as pre-to-post PR change in exercise tolerance by the 6 min walking distance test (6MWD) and perceived dyspnea on exertion by the modified Medical Research Council Dyspnea Scale (mMRC). The 6MWD was performed according to the international recommendations,[16] and repeated twice to limit the leaning effect; the best distance was recorded. The daily living activities-related dyspnea was evaluated with the Italian version of the MRC modified by the American Thoracic Society.[17]

Statistical Analysis

Categorical variables are reported as number or percentage, whereas continuous variables are indicated as medians

(interquartile range) due to a non-normal distribution and are then compared using the non-parametric Mann–Whitney test.

Two models of multivariate logistic regression were developed to test the predictive power of baseline 6MWD and mMRC score versus the relative predefined post-PR change (i.e. the minimal clinically important difference-MCID) in both walking capacity (6MWD ≥30 meters)[18] and dyspnea score (mMRC −1 point)[19] (as the dependent variables).

In the first model, we used baseline values of 6MWD and mMRC as continuous variables. To explore the role of these variables as outcomes, we retrieved the predicted probability of reaching the MCID in both 6MWD and mMRC for each patient from the final model and plotted it against the respective absolute baseline values. In the second model, we used categorical variables of baseline 6MWD (≤200 meters, 201–350 meters, >350 meters) and mMRC (0–1 points, 2 points, 3 points, 4 points). The choice of these categories was based on the possibility of distinguishing between patients with less impairment and fewer symptoms (6MWD >350 meters and mMRC 0–1 points) and those who are more compromised (6MWD ≤200 meters and mMRC 4 points). The value limits of the three 6MWD categories refer to the greatest, average, or least performance[20] and to the prognostic indication of each in terms of mortality risk,[21–23] as previously reported in the literature. Both models were adjusted for age, sex, comorbidities (Charlson index ≥ the median value of 2), severity of airflow obstruction (forced expiratory volume at 1st second – FEV_1 ≤ 50% pred.), and clinical setting (outpatient/inpatient). We then calculated the odds ratios (ORs) and 95% confidence intervals (CI), and the calibration ability with the Hosmer-Lemeshow goodness-of-fit test.

All analyses were performed using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

Our study cohort considered 1470 symptomatic COPD patients who were elderly males with a moderate to severe airflow obstruction, moderate number of comorbidities (principally arterial hypertension), moderate walking ability and dyspnea perception. Data on body weight and gas exchange were reported and then collected from a small proportion of individuals (13% and 19%, respectively). Chronic respiratory failure was present in 17% of the total sample. General characteristics of our study sample are reported in Table 1.

Figure 1 illustrates the linear regression analyses exploring the predictive power of continuous baseline 6MWD and mMRC versus each respective MCID. The risk of reaching the MCID increased for the 6MWD and for the mMRC score in patients with a lower walking capacity [odds ratio-OR 0.995 (95% confidence interval-CI 0.993–0.998)] and a higher dyspnea level [OR 4.52 (95% CI 3.35–6.10)], respectively.

Figure 2 shows the significant distribution of pre-to-post change in 6MWD (left panel) and mMRC (right panel) according to the baseline categories. Patients with a worse walking distance (6WMD ≤200 meters) and perceived dyspnea (mMRC 3–4 points) had greater improvement post-rehabilitation ($p < 0.001$ between each category considered).

Table 2 reports the multivariate regression analyses that explored the probability of achieving the MCID in both 6MWD and mMRC, based on their baseline categorical variables. Compared to the category of individuals walking >350 meters, the categories of both those performing 201–350 meters [OR 1.9 (95% CI 1.2–2.8)] and those performing ≤200 meters [OR 1.5 (95% CI 0.86–2.8)]

Table 1 General Characteristics of Study Cohort (n=1470)

Variables	n	Value
Age, years	1463	71 [10]
Male, %	1470	75
BMI, kg/m^2	185	26.7 [5.5]
FEV_1, % pred.	1443	50 [23]
PaO_2, mmHg	273	70 [12.9]
$PaCO_2$, mmHg	274	40.9 [6.7]
Chronic respiratory failure, %	1470	17
Charlson index	1135	2 [1]
Hypertension, %	1277	30
Diabetes, %	1277	11
Coronary disease, %	1277	8
Chronic heart failure, %	1277	10
Dyslipidemia, %	1277	9
Osteoporosis, %	1277	5
6MWD, baseline	1467	360 [120]
mMRC, baseline	1174	2 [1]
SGRQ, baseline	569	40 [23]
Outpatients/Inpatients, %	1470	45/55

Notes: Data are shown as number of patients (%) or medians [interquartile range]. Percentages are calculated on non-missing data.

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume at 1st second; PaO_2, partial arterial oxygen pressure; $PaCO_2$, partial arterial carbon dioxide pressure; 6MWD, six-minute walking distance; mMRC, modified Medical Research Council Dyspnea Scale; SGRQ, St. George's Respiratory Questionnaire.

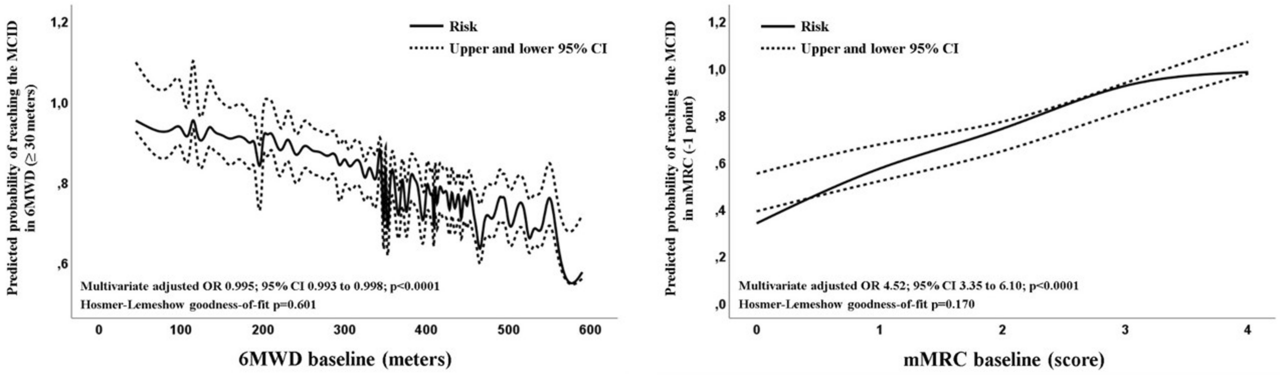

Figure 1 Multivariate adjusted linear regression model predicting the probability of reaching the MCID in 6MWD and mMRC.

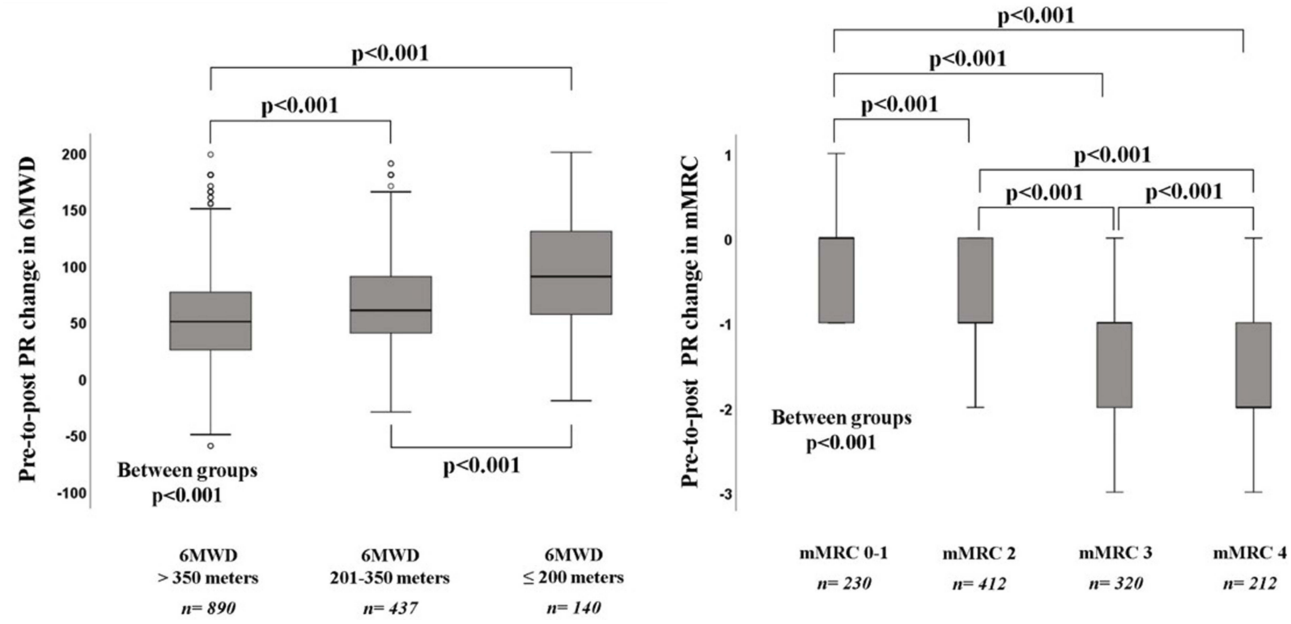

Figure 2 Distribution of pre-to-post PR changes in 6MWD and mMRC, according to the baseline categories.

showed a higher probability of predicting the achievement of the MCID for 6MWD, although the latter category was not statistically significant (p=0.141). Similarly, compared to the category of individuals with lower dyspnea on exertion (0–1 point at mMRC), the other 3 categories, representing progressively increasing levels of breathlessness, showed a higher probability of predicting the achievement of the MCID for the mMRC.

The incorporation of baseline categories of 6MWD and mMRC with the percentage of patients reaching the MCID in both outcomes (6MWD ≥30 meters and mMRC −1 point) into a risk chart is reported in Figure 3. This chart shows that few patients reached the MCID for both outcomes (0–30%, red box) if they had higher baseline exercise tolerance (6MWD >350 meters) and lower baseline dyspnea perception (mMRC 0–1), while the percentage of patients progressively increased (yellow and green boxes) according to the increase in mMRC categories and the decrease in baseline 6MWD.

Discussion

This retrospective study on a large cohort of COPD patients admitted to a PR program provides two important conclusions. First, it demonstrates that patients' baseline assessment in terms of both the distance walked (6MWD) and their perceived dyspnea on exertion (mMRC) predicts post-rehabilitation clinically meaningful changes. Second, the risk chart integrating specific categories of these two baseline measures identifies those patients who have greater or lesser benefit from participating in PR, thus

Table 2 Multivariate Regression Analyses Predicting the Probability of Reaching the MCID in Exercise Tolerance and Dyspnea Perception

	Multivariate Adjusted*		
	OR	95% CI	p-value
Dependent variable: MCID in 6MWD (≥30 meters)			
Patients with baseline 6MWD >350 meters (n=890)	1	–	–
Patients with baseline 6MWD between 201–350 meters (n=437)	1.9	1.2–2.8	**0.003**
Patients with baseline 6MWD ≤200 meters (n=140)	1.5	0.86–2.8	0.141
Dependent variable: MCID in mMRC (−1 point)			
Patients with baseline mMRC 0–1 points (n=230)	1	–	–
Patients with baseline mMRC 2 points (n=412)	4.3	2.3–7.7	**<0.001**
Patients with baseline mMRC 3 points (n=320)	17.8	8.5–38.5	**<0.001**
Patients with baseline mMRC 4 points (n=212)	29.7	12.2–72.4	**<0.001**

Notes: *Adjusted for anthropometric characteristics, comorbidities, severity of airflow obstruction, and setting. Hosmer-Lemeshow goodness-of-fit p=0.744 and p=0.936 for models with dependent variable the MCID of 6MWD and mMRC, respectively. Bold data indicate statistical significance.

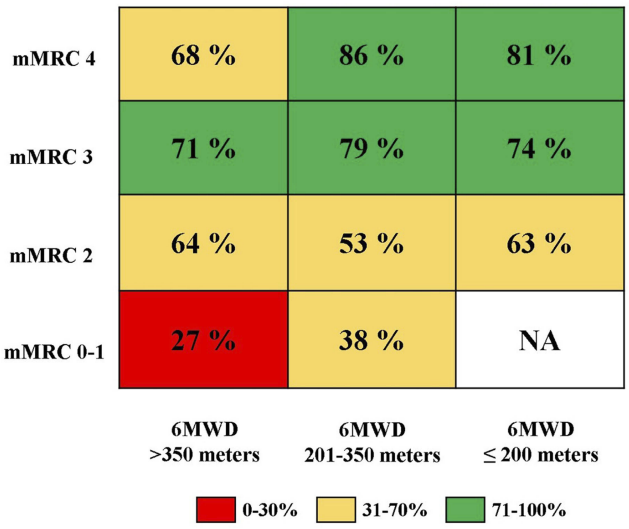

Figure 3 Risk chart integrating baseline categories of exercise tolerance and of dyspnea perception, with the percentage of patients reaching the MCID in both outcomes (6MWD ≥30 meters and mMRC −1 point).
Abbreviation: NA, indicates not applicable.

clarifying who is the best candidate in the selection of patients.

To date, there is much evidence proving the efficacy of a standard PR course in symptomatic COPD patients,[1,18,24] even in those complex individuals who were previously excluded from programs due to their physical frailty,[6] degree of comorbidities,[5] or cachexia.[7] Therefore, we now know that these complex patients[2,3,5–7] should not be excluded a priori from rehabilitation.

Predictors of improvement following PR might be seen on admission and include either degree of breathlessness, body weight, or gas exchange (i.e. arterial partial pressure of oxygen);[10] however, gains and benefits in patients treated with PR are not predictable by other usual measures such as sleep quality, social behaviors, and so on.[10]

To the best of our knowledge, this study is the first to adopt an aimed and pre-specified hypothesis to explore the role of two relevant and easy-to-collect outcome variables (6MWD and mMRC) as predictors of improvement up to MCID following a standard PR course.

At baseline, it is very likely that both of these two outcome measures describe important characteristics of symptomatic COPD candidates to PR.[25,26] It is noteworthy that, a previous prospective observational study of over 300 complex comorbid COPD patients[5] showed the predictive role of baseline 6MWD and mMRC score on the efficacy of outpatient PR, compared to other outcomes. Nevertheless, the present analysis presents major differences compared to the study by Crisafulli et al,[5] namely 1) a stronger methodology to test the hypothesis, with two regression models exploring continuous and dichotomous variables of the outcomes considered (see Figure 1 and Table 2); 2) a large study cohort including more than 1400 candidates; 3) the assessment and analysis of patients referred to either outpatient or inpatient PR settings; 4) the adoption of updated criteria for the MCID in 6MWD (i.e. +30 meters), different from that previously defined by Redelmeier et al;[27] 5) a multiple adjustment of the regression models, which considered several variables connoting patient's complexity and lung impairment, thus extending its validity to the typical patients referred to a PR program in real life.

Our choice to categorize COPD patients by threshold limits of 6MWD, although perhaps apparently arbitrary, was in fact based on the previous literature[20–23] and related to the patients' different performance and prognosis. As for the well-known clinical and prognostic value of the different categories of the mMRC[17] that we also used in this study, we think that the categories here proposed for the 6MWD represent different levels of disability and might play a prognostic role similar to that of mMRC in accurately predicting a meaningful gain post-PR (Figure 2).

Since the response to PR may vary considerably among COPD patients,[10,28] as long as available resources are still limited,[11,12] it seems appropriate to implement a careful selection process of all potential candidates once they are referred to PR.[1,11] Notwithstanding a global call to implement and expand the referral to PR worldwide,[29] the selection process should inform the appropriate indication at the individual level, something that remains a cornerstone in this clinical field.

Our attempt to create an easy-to-interpret risk chart that incorporates the measures of exercise tolerance and of dyspnea perception on exertion (Figure 3) responds to the actual need to identify the good responder to PR (namely, the best candidate). Findings obtained with this tool are in line with those reported very recently, which show that different responses to PR in the COPD population substantially depend on patients' baseline profile, as defined by a multidimensional assessment.[8] In our study, very good responders to PR were indeed those individuals showing higher dyspnea and worse exercise tolerance at baseline.[8] Clearly, the identification of the best candidate in our risk chart is based on these two outcomes. Nonetheless, we cannot exclude that COPD patients may also improve according to other outcome measures (i.e. health status or health-related quality of life).[1,10]

Although COPD patients may show differential responses to PR when considering different outcome measures,[19] the chance to incorporate multiple patient domains into a single response to PR[8] still remains controversial and/or might be difficult to apply in different contexts and organizations worldwide.[30] Although the approach of a cluster analysis based on the patient's multidimensional response to PR represents a novel and intriguing opportunity for clinicians,[8] it does not substitute the need for a very simple criterion for users. For example, although cycle endurance time through a constant work-rate test may predict response to PR in terms of exercise tolerance, thus discriminating different categories of response, skills and technologies might be not accessible worldwide. In addition, there might also be other measures that, at baseline, are not predictors per se.[8] Therefore, in future, global perspective to implementing PR and to selecting ideal candidates, 6MWD and mMRC are still identifiable as key outcomes.[30] Indeed, our risk chart starts from both the easy-to-use and the easy-to-interpret concepts.

The strengths of this retrospective study are the large cohort of patients included, the strong methodology based on two different adjusted models of regression analysis, and the original proposal of a chart to implement in the selection process of candidates to PR. This latter might be translated into a simple, practical message to help physicians to prioritize resources, at least within the COPD population.

Despite this, we here recognize some important limitations that readers should also consider. First, the analysis was based on retrospective data; our results need to be confirmed prospectively. Second, we had limited access to data on other outcomes (e.g. perceived health-related quality of life) as well as on other COPD-related factors such as smoking status, long-term oxygen therapy, fat-free mass index, physical activity level, and exacerbation rates, which could not thus be integrated into the chart. Finally, our analyses were done on a prevalence of males and therefore need to be confirmed in a sample with more females.

In conclusion, our study demonstrates that the baseline levels of exercise tolerance and dyspnea on exertion, as measured by two simple and accessible outcomes (6MWD and mMRC) predict the COPD patient's response to PR. A risk chart incorporating these two variables may easily identify any ideal candidate and best responder to a standard PR course.

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Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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