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Efficacy of standard rehabilitation in COPD outpatients with comorbidities

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ABSTRACT: A prospective study was performed to confirm the prevalence pattern of the most frequent co-morbidities and to evaluate whether characteristics of patients, specific comorbidities and increasing number of comorbidities are independently associated with poorer outcomes in a population with complex chronic obstructive pulmonary disease (COPD) submitted for pulmonary rehabilitation (PR).

316 outpatients (mean±SD age 68±7 yrs) were studied. The outcomes recorded were comorbidities and proportion of patients with a pre-defined minimally significant change in exercise tolerance (6-min walk distance (6MWD) +54 m), breathlessness (Medical Research Council (MRC) score -1 point) and quality of life (St George's Respiratory Questionnaire -4 points).

62% of patients reported comorbidities; systemic hypertension (35%), dyslipidaemia (13%), diabetes (12%) and coronary disease (11%) were the most frequent. Of these patients, >45% improved over the minimum clinically important difference in all the outcomes. In a logistic regression model, baseline 6MWD (OR 0.99, 95% CI 0.98–0.99; p=0.001), MRC score (OR 12.88, 95% CI 6.89–24.00; p=0.001) and arterial carbon dioxide tension (OR 1.08, 95% CI 1.00–1.15; p=0.034) correlated with the proportion of patients who improved 6MWD and MRC, respectively. Presence of osteoporosis reduced the success rate in 6MWD (OR 0.28, 95% CI 0.11–0.70; p=0.006).

A substantial prevalence of comorbidities in COPD outpatients referred for PR was confirmed. Only the individual's disability and the presence of osteoporosis were independently associated with poorer rehabilitation outcomes.

KEYWORDS: Comorbidities, minimum clinically important difference, outcomes, rehabilitation

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Comorbidities are usually defined as chronic clinical conditions associated with a disease process and are particularly relevant in elderly patients [1–4]. Chronic obstructive pulmonary disease (COPD), a common disease in the older population, is often associated with comorbidities [5–8], sharing systemic pathological features with some of them [6, 9]. In this complex condition, comorbidities *per se* represent an important determinant of health-related quality of life [10, 11] and clinical outcomes [12].

Pulmonary rehabilitation (PR) is the only non-pharmacological and comprehensive intervention showing a marked efficacy on the individual's functions in symptomatic COPD patients of all grades of severity [13, 14].

In a retrospective study on a wide cohort of unselected complex COPD inpatients admitted to a single centre for a standard PR course, we were able to show the pattern of prevalence of comorbidities and their impact on rehabilitation outcomes [15]. In particular, half of these patients reported at least one associated chronic disease, and the presence of combined metabolic and/or heart diseases reduced the PR success rate in terms of exercise tolerance and quality of life.

Therefore, our study has been designed prospectively to confirm the prevalence pattern of the most frequent comorbidities and to evaluate whether baseline characteristics of patients, specific comorbidities or increasing number of comorbidities are independently associated with poorer outcomes in a population of COPD patients referred to a standard outpatient PR programme.

METHODS

This observational trial was conducted prospectively at four outpatient clinics in Italy specialising

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in the rehabilitation of respiratory patients. Three out of the four facilities were located in university teaching hospitals (Pavullo, Pisa and Parma), whereas one (Naples) was located in a private hospital. E. Clini, at the Pavullo centre, acted as study coordinator. The institutional review board and ethical committee of each hospital approved the study.

Patients

All the symptomatic patients with a confirmed diagnosis of COPD were recruited consecutively over a 1-yr period (January 2008–January 2009) at the four centres. The primary diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition and classification [16]; an expert physician, qualified in respiratory medicine, coordinated the study at each centre and was in charge of confirming diagnoses and verifying exclusion criteria.

On admission, patients were excluded from this study if they had a diagnosis of asthma or any other pulmonary disease (either obstructive or restrictive). Furthermore, COPD patients were excluded if recovering from a recent exacerbation (in the preceding 4 weeks) or if unstable due to other conditions. Finally, patients with highly disabling neuromuscular conditions or cognitive impairments which might have interfered with the adherence to the physical rehabilitation programme, were also excluded. Figure 1 shows the study design as a flow diagram: pre-to-post comparisons were made in those patients completing PR.

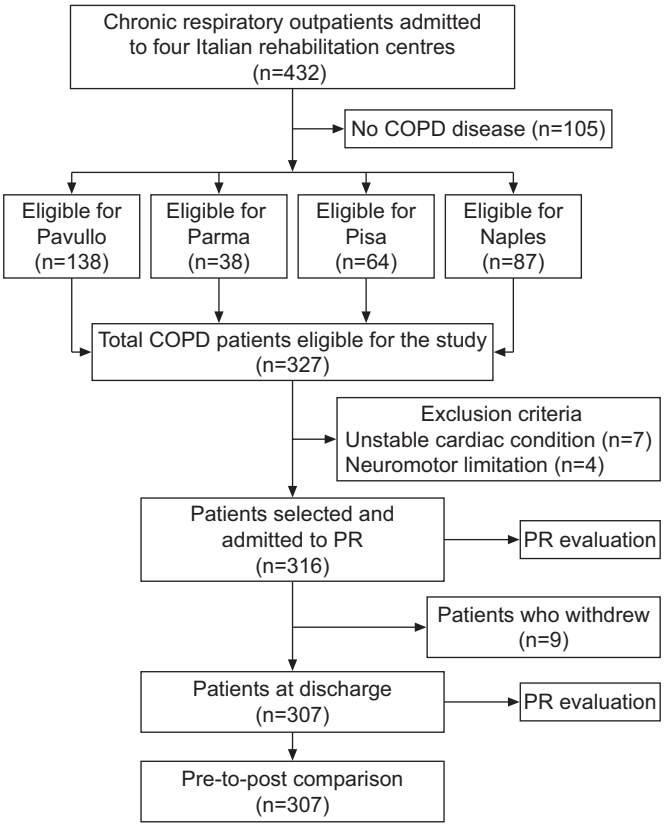

FIGURE 1. Study flow diagram. COPD: chronic obstructive pulmonary disease; PR: pulmonary rehabilitation.

Comorbidities

Comorbid conditions were diagnosed according to the International Classification of Health Problems in Primary Care [17]. The Charlson index [18], which assigns a score to each disease that is proportional to the disease-related risk of death from the individuals' self-reported comorbidities, computed on admission of each patient. The calculated Charlson index was not ''adjusted for age'' and did not compute COPD in the individual's score, as previously suggested [19]. Diagnostic confirmation was indirectly assessed by means of chart review, biochemical data and specific procedures which were certified during the observation period.

Population in study was grouped into three categories as follows: 0 (absence of associated disease), 1 (presence of one associated disease), and $\geqslant 2$ (presence of at least two associated diseases).

Finally, certain comorbidities were aggregated into groups, these were: heart disease (chronic heart failure (CHF) and coronary heart disease), metabolic disease (systemic hypertension, diabetes and dyslipidaemia, *i.e.* metabolic syndrome), skeletal disease (osteoporosis and arthrosis) and other diseases (chronic disease involving kidney, liver, digestive system and cerebral or peripheral vascular diseases).

PR programme

Outpatients were referred to PR according to the American Thoracic Society/European Respiratory Society statement and recommendations [13]. Outpatients reached their rehabilitation clinic and performed activities during a half-day session. The rehabilitation programme included standard activities (peripheral limb training, educational sessions, chest physiotherapy, and psychological and nutritional counselling when indicated) and was similarly conducted at the four facilities. Physiotherapists involved in this programme were previously instructed to homogenise the type and duration of all activities. The programme consisted of 3-h sessions three times a week. A minimum of 21 sessions was the required number for programme completion; each session was conducted as previously reported [20].

Rehabilitation outcomes

Pre-to-post comparisons were made in all patients who completed the programme. The assessment at the end of the programme was performed after the 21st session was completed. Physiotherapists, unaware of the study purposes, were responsible for measurements.

The pre-defined study outcomes were: 6-min walk distance (6MWD), which was performed according to the standard and recommended method [21]; perceived breathlessness recalled in a chronic situation as assessed by the 1–5-point modified Medical Research Council (MRC) scale [22]; and perceived health-related quality of life assessed by means of the validated Italian version of the St George's Respiratory Questionnaire (SGRQ) [23]. The minimum clinically important difference (MCID) to assess PR efficacy was considered in these three outcomes; in particular, MCID was +54 m for 6MWD [24], -1 point for MRC [25] and -4 points for SGRQ [26]. The percentage of patients who withdrew from PR was also recorded.

TABLE 1 Anthropometric, demographic and functional baseline characteristics of the study cohort at admission for pulmonary rehabilitation

	All patients	Comorbidity categories			p-value
		0	1	⩾2	
Patients n	316	120	109	87	
Age yrs	68.3±7.6	67.5±7.0	68.5±7.1	69.1±8.8	0.357
Males/females n	235/81	87/33	77/32	71/16	0.107
Charlson score	2.66±1.22	2.20±0.76	2.63±1.07	3.30±1.56	**0.001**
BMI kg·m^{-2}	27.2±5.2	26.3±3.8	28.0±4.8	27.3±7.1	0.093
P_{a,CO_2} mmHg	41.4±5.1	40.8±5.4	42.1±5.4	41.5±5.4	0.232
P_{a,O_2} mmHg	71.9±9.7	72.8±10.2	71.5±9.8	71.1±9.1	0.450
FEV1 % pred	49.6±14.0	50.2±15.2	50.5±14.1	47.5±11.9	0.268
COPD stage#					0.421
Mild	14 (4.4)	7 (5.8)	4 (3.6)	3 (3.4)	
Moderate	147 (46.5)	48 (40.0)	57 (52.2)	42 (48.2)	
Severe	127 (40.1)	52 (43.3)	41 (37.6)	34 (39.0)	
Very severe	28 (8.8)	13 (10.8)	7 (6.4)	8 (9.1)	
6MWD m	396.9±82.5	409.7±82.3	390.9±71.1	386.6±94.0	0.096
MRC score	3.21±0.85	3.14±0.86	3.34±0.79	3.14±0.88	0.136
SGRQ score	42.7±15.8	42.7±16.0	43.1±16.3	42.2±15.2	0.948

Data are presented as mean±SD or n (%), unless otherwise stated. BMI: body mass index; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension; FEV1: forced expiratory volume in 1 s; % pred: % predicted; COPD: chronic obstructive pulmonary disease; 6MWD: 6-min walk distance; MRC: Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire. #: mild COPD is defined as FEV1/forced vital capacity (FVC) ratio ⩽0.7 and FEV1 ⩾80% pred, moderate COPD as FEV1/FVC ratio ⩽0.7 and FEV1 50–80% pred, severe COPD as FEV1/FVC ratio ⩽0.7 and FEV1 30–50% pred, and very severe COPD FEV1/FVC ratio ⩽0.7 and FEV1 <30% pred. Bold indicates statistically significant p-value.

Other measurements

Lung function was measured at baseline by means of standard spirometry and arterial blood samples were taken for gas analysis. Anthropometry was assessed by means of the body mass index.

Statistics

Analysis were carried out using a statistical package (SPSS 8.0 for Windows; SPSS Inc., Chicago, IL, USA) and applied according to the current methodology [27]. Qualitative and quantitative variables are presented as n (%) and mean±SD, respectively.

Presence or absence of comorbidities, evaluated for each single or aggregated disease, together with other demographic and baseline functional variables were first compared with predefined improvement (yes or no) of both 6MWD, MRC and SGRQ post-PR by a univariate analysis; comparisons were made by the usual methods, using the Chi-squared test for noncategorical variables. The significant variables were then entered in a multivariate logistic regression model (taking MCID improvement of 6MWD, MRC and SGRQ as the dependent variables) to define their predictive role. This multivariate model (data presented as exponential β, OR and 95% CI) has been adjusted for age, sex and Charlson index as potential confounders. Additional tests to exclude collinearity among the independent variables (variance inflaction factor <5; tolerance index close to 1; condition index <15) were performed. All results were considered to be statistically significant at a level of $p<0.05$.

RESULTS

Figure 1 shows the patients' contribution to the study in each centre. 11 out of the 327 eligible patients were excluded from the study due to the exclusion criteria, at a similar rate in the four centres. 97% of the recruited patients completed the programme and were included in the analysis. Completers performed 24±2 sessions over nine (range 7–9) consecutive weeks.

Main descriptive anthropometric and functional characteristics of patients are reported in table 1; no differences among centres were reported. In addition, COPD patients excluded from the study presented characteristics similar to those of included patients (data not shown). Most patients were male (74%) with moderate-to-severe airways obstruction (86%) according to the GOLD stages and definitions [16]. The baseline level of physical disability and perceived function, as assessed by the outcome measures (6MWD, MRC and SGRQ), identify a typical COPD candidate for a PR outpatients programme; no differences were seen among comorbid categories for these values.

The n (%) of the single or aggregated comorbidities associated with COPD are illustrated in figure 2a and b, respectively. 62% of patients had at least one coexisting comorbidity. Systemic hypertension, dyslipidaemia, diabetes, coronary disease, CHF and osteoporosis ranked as the six most prevalent comorbidities (89% of total) in this COPD population. The other reported comorbidities were chronic hepatitis (4%), gastritis (3%), peripheral (2%) and cerebrovascular disease (1%), and renal failure (1%).

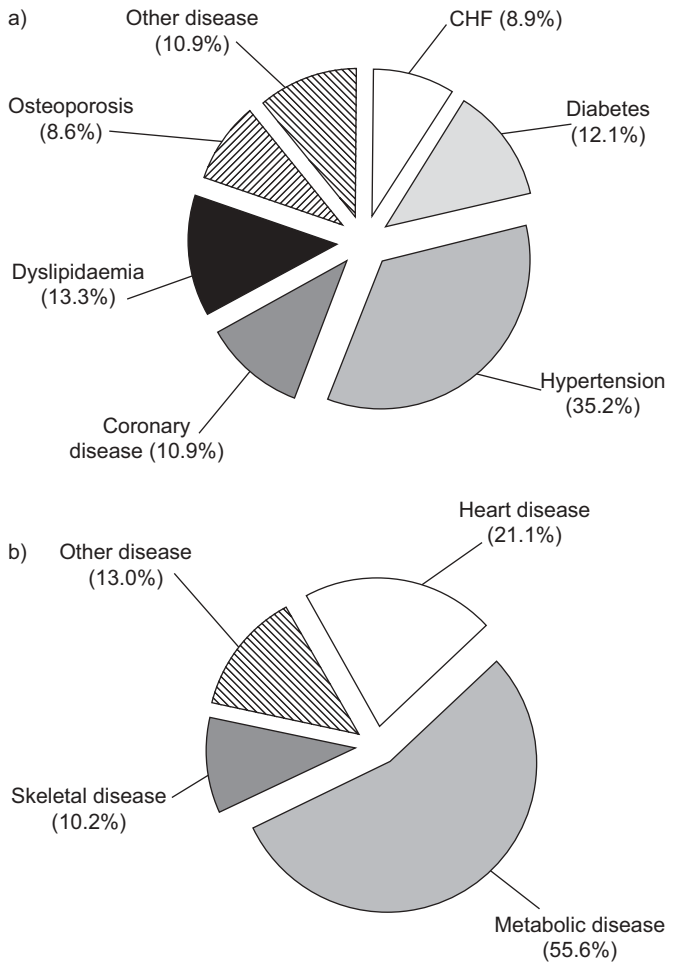

FIGURE 2. Frequency distribution (% of total) of a) single and b) aggregated chronic comorbidities in the cohort. CHF: chronic heart failure. For a list of other diseases, refer to the Methods section.

Metabolic disease (55%) was the most frequent aggregated disease reported in our cohort; obesity was the most frequent phenotype (73%) in this condition.

47%, 71% and 71% of the study population improved beyond the MCID value for 6MWD, MRC and SGRQ, respectively. Withdrawal rate from PR (~3% in all samples) was no different across the comorbidity categories (data not shown).

Results of the univariate analysis of the individuals' variables at baseline comparing proportion of patients reaching MCID (yes or no) in each outcome after PR are shown in table 2.

Figure 3 shows results from the multiple logistic regression model for variables which were significant at the univariate analysis. Only the presence of osteoporosis was inversely related to MCID improvement in 6MWD (β -1.25; OR 0.28, 95% CI 0.11–0.70; $p<0.01$). The baseline level of both 6MWD (β -0.01; OR 0.99, 95% CI 0.98–0.99; $p=0.001$) and MRC (β 2.56; OR 12.90, 95% CI 6.89–24.00; $p=0.001$) correlated significantly with the proportion of patients who improved 6MWD and MRC after PR, respectively. Arterial carbon dioxide tension (P_{a,CO_2}) level at baseline was positively correlated (β 0.070; OR 1.07, 95% CI 1.00–1.15; $p<0.01$) to the MCID improvement of MRC score. None of the significant variables in the univariate analysis significantly related to the MCID improvement of SGRQ in the multivariate analysis.

A linear regression model with Δoutcome values as the dependent variables confirmed these findings (data not shown).

DISCUSSION

It is known that chronic diseases frequently associated with elderly COPD patients influence the individual's clinical outcomes [4–8, 12]; rehabilitation, more than pharmacotherapy, represents a valid, comprehensive therapeutic approach for these patients [13, 14]. This prospective trial was designed to observe the prevalence of comorbidities in this population of patients and to evaluate whether baseline characteristics of patients, specific comorbidities and increasing number of comorbidities may independently predict a poorer response to the current clinical model of outpatient rehabilitation.

As the first result, most (62% of cases) of the COPD patients referred for PR have at least one associated chronic comorbidity. 86% of them had a moderate-to-severe degree of airway obstruction (GOLD stage II and III), which is the population more likely to be treated at the outpatient level [13].

Although the prevalence of chronic comorbidities among COPD patients may vary according to the population and the method used to confirm diagnosis [6, 10], our findings are in line with those reported in a large population of outpatients in the USA [28]. Some differences recorded among the neuromuscular diseases may arise from the *a priori* selection of candidates to PR. Indeed, patients with advanced and severely disabling musculoskeletal diseases and/or cognitive impairment, which may preclude adhesion to the programme, are more likely to be excluded.

The only robust data in the same area on a wide population (~3,000 patients) recently indicated the presence of at least one self-reported comorbidity in 51% of the patients admitted [15], probably underestimating the current report of 62% due to the retrospective nature of that study.

The six most frequent coexisting diseases were systemic hypertension, dyslipidaemia, diabetes, coronary disease, CHF and osteoporosis, which together represented 89% of the cohort (fig. 2a) and have same similar features as observed in our retrospective study [15]. Association within both metabolic or cardiac diseases were confirmed as the most prevalent pathologies aggregated to COPD (76% of total), over other reported combinations (fig. 2b). It is well known that metabolic and cardiac alterations are clinical conditions that, *per se*, worsen the prognosis in adult subjects [29, 30]. The assessment of the relative contribution of these or other single or aggregated comorbidities to the long-term prognosis of these COPD patients was beyond the scope of our study.

Above all, we found that the proportion of patients who reported a significant change, according to MCID, was always >40% of the total population. This is in accordance with previously reported papers in similar settings [13].

TABLE 2 Univariate analysis of individuals' variables at baseline comparing mean values and/or proportion of patients according to whether or not (yes or no, respectively) an improvement larger than the mimimum clinically important difference (MCID) was seen in each pulmonary rehabilitation outcome

	Variable (MCID)								
	6MWD (+54 m)			MRC score (-1 point)			SGRQ score (-4 points)		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Age yrs	67.2±7.6	68.2±7.4	0.072	68.2±7.8	68.0±7.2	0.808	68.1±7.6	68.8±6.9	0.524
Males/females n	107/35	123/42	0.871	158/60	69/:20	0.162	149/57	65/36	0.753
BMI kg·m^{-2}	27.5±4.7	26.8±5.6	0.283	27.6±5.6	26.6±4.0	0.158	26.7±3.7	26.2±4.3	0.400
FEV$_1$ % pred	49.3±13.0	49.8±14.9	0.755	49.0±14.5	51.0±13.0	0.294	49.4±14.1	48.7±17.1	0.730
Charlson score	2.58±1.3	2.73±1.1	0.340	2.66±1.2	2.65±1.1	0.979	2.56±1.0	2.75±1.4	0.375
P_{a,O_2} mmHg	71.4±9.6	72.3±9.9	0.459	72.0±10.1	71.0±8.9	0.456	71.3±9.8	74.9±10.1	**0.012**
P_{a,CO_2} mmHg	41.8±5.6	41.0±5.2	0.213	42.0±5.7	40.3±4.4	**0.025**	42.0±5.3	40.6±5.3	0.061
Baseline 6MWD	372.3±85.9	418.0±73.4	**0.001**	389.5±77.9	421.8±75.8	**0.001**	406.4±73.6	396.7±81.2	0.356
Baseline MRC	3.22±0.8	3.20±0.8	0.827	3.55±0.6	2.36±0.6	**0.001**	3.21±0.8	3.33±0.9	0.311
Baseline SGRQ	42.8±16.4	42.6±15.4	0.935	42.8±15.6	41.0±16.2	0.408	44.5±15.5	38.3±15.9	**0.005**
Comorbidities									
Single									
Chronic Heart Failure	12 (40)	18 (60)	0.470	11 (34)	19 (62)	0.336	21 (70)	9 (30)	0.177
Diabetes	21 (51)	20 (49)	0.493	14 (34)	27 (66)	0.490	26 (63)	15 (37)	0.711
Hypertension	57 (48)	62 (52)	0.646	32 (27)	87 (73)	0.265	75 (63)	44 (37)	0.497
Coronary disease	14 (38)	23 (62)	0.274	26 (70)	11 (30)	0.542	19 (51)	18 (49)	0.709
Dyslipidaemia	23 (51)	22 (49)	0.479	27 (60)	18 (40)	0.570	28 (62)	17 (38)	0.537
Osteoporosis	7 (24)	22 (76)	**0.012**	16 (55)	13 (45)	0.964	18 (62)	11 (38)	0.256
Other diseases	15 (41)	22 (59)	0.733	24 (65)	13 (35)	0.450	27 (73)	10 (27)	**0.046**
Aggregated									
Heart disease	24 (40)	36 (60)	0.279	37 (62)	23 (38)	0.425	39 (65)	21 (35)	0.677
Metabolic disease	73 (46)	85 (54)	0.985	118 (75)	40 (25)	0.069	103 (65)	55 (35)	0.606
Skeletal disease	7 (24)	22 (76)	**0.012**	16 (55)	13 (45)	0.964	18 (62)	11 (38)	0.256
Comorbid categories									
0	57 (49)	60 (51)	0.497	71 (61)	46 (39)	**0.016**	88 (75)	29 (25)	0.365
1	48 (45)	58 (55)	0.804	89 (84)	17 (16)	**0.000**	70 (66)	47 (44)	0.073
⩾2	37 (44)	47 (56)	0.634	59 (70)	25 (30)	0.205	60 (71)	24 (29)	0.239

Data are presented as mean±SD or n (%), unless otherwise stated. 6MWD: 6-min walk distance; MRC: Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension. Bold indicates statistically significant p-values.

The main finding of this study highlights the impact of chronic comorbidities and other individuals' characteristics at baseline in response to PR.

Overall, it is noteworthy that individual comorbidities (either alone or in combination) did not preclude indication and/or effectiveness of a PR course. Indeed, patients reported <3% withdrawal from PR, with no difference across comorbid categories. This confirms the feasibility of our programme, which reproduces the internationally shared standards for management and costs [13, 20, 31, 32].

In contrast to our retrospective analysis [15], the coexistence of osteoporosis negatively predicts 6MWD improvement (fig. 3). It cannot be excluded that the populations are not comparable between the two studies. Nonetheless, coexisting osteoporosis is highly prevalent (~25% in the COPD population, 39% in females) in a representative population of outpatients COPD [28], who are likely to be similar to those in the present study. Despite the fact that the prevalence of osteoporosis in our study is substantially lower (<10%), mainly due to the *a priori* exclusion from PR of the most disabled and noncompliant individuals, the clinical impact of this disease is known to reduce *per se* the quality of life and the physical function in the large population [33].

Therefore, it is likely that both direct bone frailty and/or associated muscle weakness, which typically occur in COPD patients referred to PR, might have enhanced the contribution of this phenotype to predicting response. Nonetheless, long-term abuse of corticosteroids and a specific drug-related myopathy [34] might also have determined significant bone damage, which is not only related to increased risk of fracture [35] but may even explain reduction in performance (walking capacity) during a course of PR. This has been confirmed in fragile elderly patients treated using physical rehabilitation

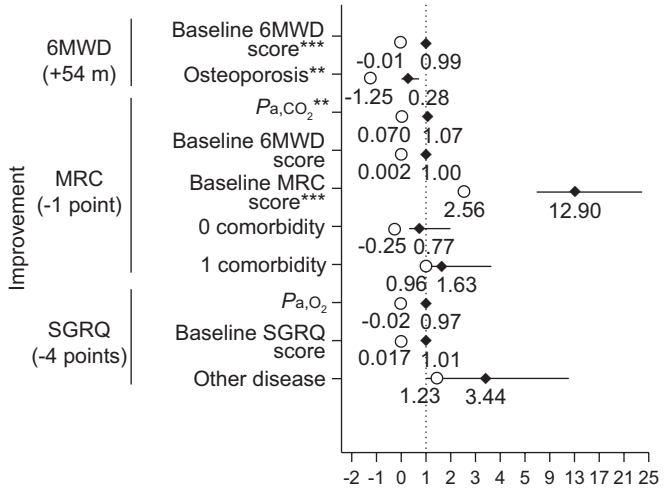

FIGURE 3. Individuals' factors entering the multivariate prediction analysis of improvement after pulmonary rehabiliation in the cohort of chronic obstructive pulmonary disease patients. Data are presented as β (○) and exponential β-OR (◆) and 95% CI (—). 6MWD: 6-min walk distance; MRC: Medical Research Council dyspnoea scale; SGRQ: St George's Respiratory Questionnaire; P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension. **: $p<0.01$; ***: $p<0.001$.

after stroke [36], where disabling comorbidities, including osteoporosis and arthrosis, are the main determinants of poor physical recovery.

Among all the other valuable factors that may predict response to PR in our study, baseline level of 6MWD, MRC and P_{a,CO_2} significantly affect the multivariate regression equation (fig. 3). In all cases, the worse the baseline condition (lower 6MWD or higher MRC and P_{a,CO_2}) the higher the proportion of patients gained the MCID outcome after PR. While a degree of improvement less than the MCID in those patients with a better baseline condition could be due to a possible ceiling effect, these findings inform us that inclusion of patients with poorer physical performance and lower gas exchange capacity (similarly to emphysema-type COPD) corresponds to a more elevated probability of improving their functional status independent on the presence of a ''complex'' comorbid phenotype [37].

Similar results have been already demonstrated in a smaller group of patients taken from a real-life setting and submitted for outpatient rehabilitation [38]. Thus, these patients should not be definitively excluded from standard PR in the usual clinical setting.

Finally, PR outcomes in the present study were chosen as the strongest, easiest and best validated measures to represent the effectiveness of rehabilitation course in relation to patients with comorbidities. Overall, we cannot exclude that comorbidities would also have been associated with different outcomes (*i.e.* mood, workload exercise, functional status and healthcare utilisation). However, since this is a purely hypothesis-generating study, it is likely that a different impact of comorbidities (number and/or type) on different outcomes could not be expected *a priori*.

In conclusion, this prospective study confirms the high prevalence of associated chronic diseases in COPD outpatients referred to standard rehabilitation; the degree of functional disability as measured at baseline and the presence of coexisting osteoporosis (but not the increasing number of comorbidities) relate directly to a poorer outcome after PR in these patients.

As a practical message, the presence of comorbidities should not preclude *per se* access to and effectiveness of rehabilitation process in complex COPD.

CLINICAL TRIAL

This study is registered at ClinicalTrials.gov with clinical trial identifier number NCT00992498.

STATEMENT OF INTEREST

None declared.

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