Original Article

Efficacy of standard Rehabilitation in COPD Outpatients with Co-morbidities.

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All authors declare to have no conflict of interest of any nature with this paper.

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ABSTRACT 198

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ABSTRACT (word count = 198)

A prospective study was performed to 1) confirm the prevalence pattern of the most frequent co-morbidities and 2) evaluate whether characteristics of patients, specific co-morbidities, and increasing number of co-morbidities are independently associated with poorer outcomes in a population of complex COPD submitted to rehabilitation (PR).

Three-hundred and sixteen outpatients (age 68±7 yrs) were studied. Co-morbidities and proportion of patients with a pre-defined minimally significant change in exercise tolerance (6MWD, +54 mt), breathlessness (MRC score, -1 point) and quality-of-life (SGRQ, -4 points) as outcomes were recorded.

Sixty-two % of patients reported co-morbidities; systemic hypertension (35%), dyslipidemia (13%), diabetes (12%), and coronary disease (11%) were the most frequent. Above 45% of them improved over MCID in all the outcomes. In a logistic regression model, baseline 6MWD (OR 0.99 95%CI 0.98-0.99, p=0.001), MRC (OR 12.88 95%CI 6.89-24.00, p=0.001), and PaCO₂ (OR 1.08 95%CI 1.00-1.15, p=0.034) related 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 co-morbidities in COPD outpatients referred to rehabilitation was confirmed. The individual’s disability and the presence of osteoporosis only were independently associated with poorer rehabilitation outcomes. (registered at ClinicalTrials.gov: NCT00992498.)

Keywords: Rehabilitation, Co-morbidities, Outcomes, MCID.
INTRODUCTION

Co-morbidities are usually defined as chronic clinical conditions associated with a disease process, particularly relevant in elderly patients (1-4). So far, it has been pointed out that Chronic Obstructive Pulmonary Disease (COPD), a common disease in the older population, is often associated with co-morbidities (5-8), sharing systemic pathological features with some of them (6,9). In this complex condition, co-morbidities per se represent an important determinant of health-related quality of life (10, 11) and its 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 co-morbidities 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, respectively.

The present study has been, therefore, prospectively designed to confirm 1) the prevalence pattern of the most frequent co-morbidities and to evaluate; 2) whether baseline characteristics of patients, specific co-morbidities, and increasing number of co-morbidities are independently associated with poorer outcomes in a population of COPD referred to a standard outpatients PR program.
METHODS

This observational trial was prospectively conducted at four outpatient clinics in Italy, skilled in the rehabilitation of respiratory patients. Three out of the four facilities were located in university teaching hospital (Pavullo-MO, Pisa, and Parma), whereas one (Napoli) was located in a private hospital. The centre of Pavullo-MO acted as study coordinator.

The institutional review board and ethical committee of each hospital has approved the study. Trial has been registered at ClinicalTrials.gov website with code-number NCT00992498.

Patients

All the symptomatic patients with a confirmed diagnosis of COPD were consecutively recruited over a 1 year period (January 2008 to January 2009) at the 4 centres. The primary diagnosis of COPD was made according to the GOLD definition and classification (16); an expert physician, graduated in respiratory medicine coordinated the study at each centre and was in charge of the confirming diagnosis and verifying criteria of exclusion.

On admission, patients were excluded from this study if they had diagnosis of asthma or any other pulmonary disease (either obstructive or restrictive). Furthermore, COPD patients were also excluded if recovering from a recent exacerbation (in the preceding 4 weeks) or if unstable due to other unstable conditions. Finally, patients with highly disabling neuro-muscular conditions or cognitive impairments which might have interfered with the adherence to the physical rehabilitation program, were also excluded.

Figure 1 shows the patients’ flow diagram: pre-to-post comparison were made in those patients completing PR.

Co-morbidities
Co-morbid conditions were diagnosed according to the International Classification of Health Problems in Primary Care (17). The Charlson index (18), which assigns to each disease a score that is proportional to the disease-related risk of death on the individuals’ self-reported co-morbidities, 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 charts review, biochemical data and specific procedures which were certified during the observation period.

Population in study was grouped into 3 categories as follows: 0 (score=0, i.e. absence of associated disease), 1 (score=1, i.e. presence of one associated disease), and \( \geq 2 \) (score\( \geq 2 \), i.e. presence of at least two associated diseases).

Aggregated diseases - *Heart Disease* (chronic heart failure [CHF], coronary heart disease), *Metabolic Disease* (systemic hypertension, diabetes, dyslipidemia - namely Metabolic syndrome), *Skeletal Disease* (osteoporosis, arthrosis), and *Other Diseases* (chronic disease interesting kidney, liver, digestive system, cerebral or peripheral vascular diseases) - among the total amount of co-morbidities were finally established.

**PR Program**

Outpatients were referred to PR according to the ATS-ERS statement and recommendations (13); they reached their rehabilitation clinic and performed activities on a half-day session basis. The rehabilitation program included standard activities (peripheral limb training, educational sessions, and chest physiotherapy, psychological, and nutritional counselling when indicated) and was similarly conducted at the four facilities. Physiotherapists involved in this program were previously instructed to homogenise the type and duration of all activities. Program consisted of three hour/sessions and three
session/week up to a minimum of 21 (which was the required number for program completion); each session was conducted as previously reported (20).

**Rehabilitation Outcomes**

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

The pre-defined study outcomes were: six-minute walked distance (6MWD) which was performed according to the standard and recommended method (21), perceived breathlessness recalled in chronic situation as assessed by the 1 to 5-point modified Medical Research Council (MRC) scale (22), and perceived health-related quality of life by means of the Italian validated version of St. George’s Respiratory Questionnaire (SGRQ) (23). The minimally clinical important difference (MCID) was considered to assess PR efficacy 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.

**Other measures**

Lung function was measured at baseline by means of standard spirometry and arterial blood sample for gas analysis. Anthropometry was assessed by means of the body mass index (BMI).

**Statistics**

Analysis were carried out using a statistical package (SPSS 8.0 for Windows; Chicago, IL) and applied according to the current methodology (27).

Qualitative and quantitative variables were expressed as frequency/percentages (%) and means with standard deviation (SD), respectively.
Presence/absence of co-morbidities - evaluated for each single or aggregated disease - together with other demographic and baseline functional variables were first compared with pre-defined improvement (Yes or No) of both 6MWD, MRC and SGRQ post PR by a univariate analysis; comparisons were made by the usual methods, with chi-square test ($\chi^2$) used for non-categorical variables. The significant variables 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 Exp-$\beta$/Odds Ratio-OR with 95% confidential interval-CI throughout) has been adjusted for age, sex, and Charlson index as the potential confounders. Additional tests to exclude collinearity among the independent variables (Variance Inflaction Factor < 5; Tolerance index close to 1; Condition index <15) have been performed.

All results were considered to be statistically significant at a level of $p < .05$.

RESULTS

Figure 1 shows the patients’ contribution to the study in each centre. Eleven out of the 327 eligible patients were excluded from the study due to the exclusion criteria, at similar rate in the 4 centres. Ninety-seven % of the recruited patients completed the program and were included in the analysis. Completers performed 24±2 sessions over 9 (range 7 to 9) consecutive weeks.

Main descriptive anthropometric and functional characteristics of patients are reported in Table 1; no difference among centers were reported. In addition, COPD patients excluded from the study presented characteristics similar to those of included ones (data not showed). Most patients were male (74%) with moderate-to-severe grade of airways obstruction (86%) according to the GOLD stage and definition (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 to a PR outpatients program; no differences were seen among comorbid categories for these values.

The frequency distribution (% of total) of the single or aggregated co-morbidities associated to COPD are illustrated in Figure 2A and 2B, respectively. Sixty-two % of patients had at least one coexisting co-morbidity. Systemic hypertension, dyslipidemia, diabetes, coronary disease, CHF and osteoporosis ranked as the six most prevalent co-morbidities (89% of total) in this COPD population. The other reported co-morbidities were chronic hepatitis (4%), gastritis (3%), peripheral (2%) and cerebro-vascular disease (1%) and renal failure (1%).

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

Forty-seven, 71, and 71% of the study population improved beyond the MCID value for 6MWD, MRC and SGRQ, respectively. Withdrawal rate from PR (approximately 3% in all sample) was no different across the co-morbidities categories (data non reported).

Results by univariate analysis of the individual’s 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 ($\beta$ -1.25, OR 0.28, 95%CI 0.11 to 0.70, p<0.01). The baseline level of both 6MWD ($\beta$ -0.01, OR 0.99 95%CI 0.98-0.99, p=0.001) and MRC ($\beta$ 2.56, OR 12.90 95%CI 6.89-24.00, p=0.001) significantly related with the proportion of patients who improved 6MWD and MRC after PR, respectively. Arterial carbon dioxide pressure (PaCO$_2$) level at baseline was positively correlated ($\beta$ 0.070, OR
1.07 95%CI 1.00 to 1.15 p<0.01) to the MCID improvement of MRC. None of the variables significant at the univariate analysis significantly related to the MCID improvement of SGRQ.

A linear regression model with Δ-outcome values as the dependent variables confirmed these findings (data not reported).

**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 co-morbidities in this population of patients and to evaluate whether baseline characteristics of patients, specific co-morbidities, and increasing number of co-morbidities may independently predict a poorer response to a current clinical model of outpatient rehabilitation.

As the first result, most (62% of cases) of COPD referred to rehabilitation have at least one associated chronic co-morbidity. Eighty-six % of them were in 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 co-morbidities 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 US (28). Some difference as recorded among the neuro-muscular diseases, may arise from the *a priori* selection of candidates to PR. Indeed, patients with advanced and severely disabling
musculo-skeletal diseases and/or cognitive impairment, which may preclude adhesion to the program, are more likely to be excluded.

The only robust data in the same area on a wide population (about 3,000 patients) recently indicated the presence of at least one self-reported co-morbidity in 51% of patients admitted (15), thus probably under-estimating the current report of 62% due to the retrospective nature of that study.

The six more frequent coexisting diseases were systemic hypertension, dyslipidemia, diabetes, coronary disease, CHF and osteoporosis which altogether represented 89% of the cohort (Figure 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 (Figure 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 relative contribution of these or other single or aggregated co-morbidities 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 above 40% of the total population. This is quite in accordance with previously reported papers in similar settings (13).

The main finding from this study highlights the impact of chronic co-morbidities and other individual’s characteristics at baseline on response to PR.

Overall, it is noteworthy that individual co-morbidities (either alone or in combination) did not preclude indication and/or effectiveness of a rehabilitation course. Indeed, patients reported only less than 3% withdrawal rate during PR with no difference across co morbid
categories, thus confirming the high feasibility of our program, which reproduces the internationally shared standards, as for management and costs (13,20,31,32).

In contrast with our retrospective analysis (15), the coexistence of osteoporosis negatively predicts the 6MWD improvement (see Figure 3). It cannot be excluded that populations are not comparable between the two studies. Nonetheless, coexisting osteoporosis is highly prevalent (about 25%, 39% in women) in a representative population of outpatients COPD (28), who are likely to be similar to those of our present study. Despite the fact that the prevalence of osteoporosis in our study is substantially lower (below 10%), mainly due to the a priori exclusion from PR of the most disabled and not compliant 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 predict 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) under rehabilitation course. This is fairly confirmed in fragile elderly patients treated by physical rehabilitation after stroke (36), where disabling co-morbidities, including osteoporosis and arthrosis, are the main determinants of low physical recovery.

Among all the other valuable factors which may predict response to PR in our study, baseline level of 6MWD, MRC and PaCO₂ significantly enter the multivariate regression equation (Figure 3). In all cases, the worst was the baseline condition (lower 6MWD or higher MRC and PaCO₂) the higher proportion of patients gained the MCID outcome after PR. Despite the lesser degree of improvement to 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 less physical performance and lower gas exchange capacity (likewise in emphysema type COPD) corresponds to a more elevated probability of improving their functional status (37) independent on the presence of co-morbid “complex” phenotype.

Similar results have been already demonstrated in a smaller group of patients taken from the “real life” and submitted to out-patient rehabilitation (38). Thus, these patients should not be definitively excluded from standard PR in the usual clinical setting.

Finally, present PR outcomes were chosen as the strongest, easiest and validated measures to represent the effectiveness of rehabilitation course in relation to patients with co-morbidities. Overall, we cannot exclude that co-morbidities would have been also associated to different outcomes (i.e. mood, workload exercise, functional status, health care utilization). However, since this is a study purely generating hypothesis, it is likely that a different impact of co-morbidities (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 co-morbidities) directly relate to a poorer outcome change after PR in these patients.

As a practical message, the presence of co-morbidities should not preclude per se access to and effectiveness of rehabilitation process in complex COPD.
Acknowledgment

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REFERENCES


**TABLE 1.** Anthropometric, demographic and functional baseline characteristics of the study cohort at admission to PR. *Data are presented as mean with standard deviation (SD) or percentage (%).*

<table>
<thead>
<tr>
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<th>All Patients</th>
<th>Co-morbidity categories</th>
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<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
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<tr>
<td>Patients, no.</td>
<td>316</td>
<td>120</td>
<td>109</td>
</tr>
<tr>
<td>Age, yr.</td>
<td>68.3 (7.6)</td>
<td>67.5 (7.0)</td>
<td>68.5 (7.1)</td>
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<tr>
<td>Sex, M:F</td>
<td>235:81</td>
<td>87:33</td>
<td>77:32</td>
</tr>
<tr>
<td>Charlson index, score</td>
<td>2.66 (1.22)</td>
<td>2.20 (0.76)</td>
<td>2.63 (1.07)</td>
</tr>
<tr>
<td>BMI, kg·m⁻¹</td>
<td>27.2 (5.2)</td>
<td>26.3 (3.8)</td>
<td>28.0 (4.8)</td>
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<tr>
<td>PaCO₂, mmHg</td>
<td>41.4 (5.1)</td>
<td>40.8 (5.4)</td>
<td>42.1 (5.4)</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>71.9 (9.7)</td>
<td>72.8 (10.2)</td>
<td>71.5 (9.8)</td>
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<tr>
<td>FEV₁, % pred.</td>
<td>49.6 (14.0)</td>
<td>50.2 (15.2)</td>
<td>50.5 (14.1)</td>
</tr>
<tr>
<td>COPD staging*, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>14 (4.4)</td>
<td>7 (5.8)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>147 (46.5)</td>
<td>48 (40.0)</td>
<td>57 (52.2)</td>
</tr>
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<td>Severe</td>
<td>127 (40.1)</td>
<td>52 (43.3)</td>
<td>41 (37.6)</td>
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<tr>
<td>Very severe</td>
<td>28 (8.8)</td>
<td>13 (10.8)</td>
<td>7 (6.4)</td>
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<td>6MWD, meters</td>
<td>396.9 (82.5)</td>
<td>409.7 (82.3)</td>
<td>390.9 (71.1)</td>
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<td>MRC, grade</td>
<td>3.21 (0.85)</td>
<td>3.14 (0.86)</td>
<td>3.34 (0.79)</td>
</tr>
<tr>
<td>SGRQ, total score</td>
<td>42.7 (15.8)</td>
<td>42.7 (16.0)</td>
<td>43.1 (16.3)</td>
</tr>
</tbody>
</table>

*Mild COPD is defined as FEV₁/FVC ratio ≤ 0.7 and FEV₁ ≥ 80% prd; moderate COPD as FEV₁/FVC ratio ≤ 0.7 and FEV₁ 50-80 % prd; severe COPD as FEV₁/FVC ratio ≤ 0.7 and FEV₁ 30-50 % prd; and very severe COPD FEV₁/FVC ratio ≤ 0.7 and FEV₁ < 30 % prd.*
Definition of abbreviations: PR, Pulmonary Rehabilitation; BMI, Body Mass Index; PaO₂ and PaCO₂ arterial pressure of oxygen and carbon dioxide respectively; FEV₁ = forced expiratory volume in 1 sec; 6MWD = 6-min walked distance test; MRC = Medical Research Council dyspnea score; SGRQ = St. George’s Respiratory Questionnaire total score.
TABLE 2. Univariate analysis of individual’s variables at baseline comparing mean values and/or proportion of patients according to whether or not (Yes or No) an improvement larger than MCID was seen in each PR outcome.
See Table 1 for definition of abbreviations.
Figure 1. Study flow diagram

Chronic Respiratory Outpatients admitted in 4 Italian rehabilitation centres
(n = 432)

Eligible for Pavullo MO
(n = 138)

Eligible for Parma
(n = 38)

Eligible for Pisa
(n = 64)

Eligible for Naples
(n = 87)

Total COPD eligible for the study
(n = 327)

Exclusion criteria
- Cardiac unstable condition (n = 7)
- Neuro-motorial limitation (n = 4)

Patients selected and admitted to PR
(n = 316)

PR Evaluation

Patients who withdrew
(n = 9)

Patients at discharge
(n = 307)

PR Evaluation

Pre-to-Post Comparison
(n = 307)
Figure 2. Frequency distribution (% of total) of single (A) and aggregated (B) chronic co-morbidities in the cohort of COPD in study.

Definition of abbreviations: CHF = chronic heart failure.
For Other disease see Methods.
Figure 3. Individual's factors entering the multivariate prediction analysis of improvement after PR in the cohort of COPD patients. Data are presented as Exp (β) Odds Ratio (OR) con 95% IC.

* p< 0.01; ** p=0.001
See Table 1 for definition of abbreviations.