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# Role of Comorbidities in a Cohort of COPD Patients Undergoing Pulmonary Rehabilitation

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**ABSTRACT (word count = 292)**

**Background.** COPD is often associated with other chronic diseases. These patients are often admitted to hospital-based rehabilitation programs.
**Objectives.** To determine the prevalence of chronic comorbidities in COPD patients undergoing pulmonary rehabilitation (PR) and to assess their influence on the outcomes.
**Design.** Observational retrospective cohort study.
**Setting.** A single rehabilitation centre.
**Patients.** 2,962 inpatients and outpatients with COPD (73% male, age 71 [SD 8] yr, $FEV_1$ 49.3 [SD14.8] % of predicted), graded 0, 1 or ≥2 according to the Comorbidity categories and included in a PR program.
**Measurements.** We analyzed the number of self-reported comorbidities and recorded the Charlson index. We then calculated the percentage of patients with a predefined positive response to pulmonary rehabilitation (=minimally clinical important difference-MCID) as measured by improvement in exercise tolerance (6MWD), dyspnea (MRC), and/or health-related quality of life (SGRQ).
**Results.** 51% of the patients reported at least one chronic comorbidity added to COPD. Metabolic (systemic hypertension, diabetes, and/or dyslipidemia) and heart diseases (chronic heart failure and/or coronary heart disease) were the most frequently reported comorbid combinations (61 and 24%, respectively) among the overall diseases associated with COPD. The prevalence of patients with MCID was different across the Comorbidity categories and outcomes. In a multiple categorical logistic regression model, the Charlson index (OR 0.72, 96%CI 0.54 to 0.98 and 0.51, 96%CI 0.38 to 0.68, versus 6MWD and SGRQ respectively), metabolic diseases (OR 0.57, 96%CI 0.49-0.67 versus 6MWD) and heart diseases (OR 0.67, 96%CI 0.55 to 0.83 versus SGRQ) reduced the probability to improve outcomes of rehabilitation.
**Conclusions.** Most patients with COPD undergoing PR have one or more comorbidities. Despite the presence of comorbidities does not preclude the access to rehabilitation, the improvement in exercise tolerance and quality of life after rehabilitation may be reduced depending on comorbidity.

**Keywords**: rehabilitation, comorbidities, outcomes

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality (1, 2). Although alarming, this prospective probably underestimates the true burden of this disease on health status, health care costs and overall actual and projected prognoses (3). COPD is also an important risk factor for other chronic diseases that contribute to morbidity and mortality (4).

Comorbidities are defined as other chronic medical conditions that accompany a disease process (5), and they are particularly prevalent in the elderly (6–8). The most common chronic conditions associated with COPD are hypertension, diabetes, coronary artery disease, heart failure, pulmonary infections, cancer, and pulmonary vascular disease (9–14). Comorbidities are an important determinant of health-related quality of life in COPD patients (13, 15, 16).

Pulmonary rehabilitation is a non-pharmacological comprehensive intervention effective in the long-term management of symptomatic COPD of all grades of severity (17), even in the elderly (18). Pulmonary rehabilitation improves symptoms, quality of life and exercise performance (19) and is effective in decreasing consumption of health care resources (20).

The aim of this study was to determine the frequency and the prevalence of chronic comorbidities in patients with COPD and to assess their influence on the effects of pulmonary rehabilitation.

## METHODS

### Patients

Our study was approved by the our institutional review board.

Of all the patients who were admitted to the hospital for rehabilitation purposes from January 2003 to December 2005 (n=4,055), we selected 2,962 COPD for retrospective analysis. Patients were selected according to the following criteria: primary diagnosis of (i) COPD (491 codes) as defined and classified according to the GOLD guidelines (19) and/or (ii) pulmonary emphysema (492 code) and (iii) respiratory failure (518.8x codes). Spirometric severity of COPD was established according to the GOLD guidelines (21). Therefore, patients with asthma or any other pulmonary diseases (either obstructive and restrictive) were excluded from this study. Discharge diagnosis was made by a physician specializing in pulmonary medicine. The diagnosis of each patient was recorded in an electronic database according to the codes of the International Classification of Diseases, version 9-CM (22).

### Comorbidities

Comorbid conditions were diagnosed according to the International Classification of Health Problems in Primary Care (23) and retrieved from the medical files. All patients were grouped according to the following Comorbidity categories: 0 (absence of associated chronic conditions), 1, and ≥2 (depending on the relative number of associated chronic conditions).

The frequency (as % of total) of each chronic disaese and combined diseases — Heart Disease (chronic heart failure, coronary heart disease), Metabolic Disease (systemic hypertension, diabetes, dyslipidemia-namely Metabolic syndrome), Skeletal Disease (osteoporosis, arthrosis),and Other Disease (1-3)— among the total amount of comorbidities was established. The prevalence of the same single or combined comorbidities has been also calculated taking the whole cohort of COPD into account.

Individuals' self-reported comorbidities as assessed by the Charlson index (24), which assigns to each disease a score that is proportional to the disease-related risk of death, was also retrieved by these files. Charlson index has been computed during the hospital access by the physician in charge of each admitted patient. The computed Charlson index was not adjusted for age and did not include COPD in the individual's score, as previously suggested (25).

### Pulmonary Rehabilitation

Patients were selected for pulmonary rehabilitation according to the BTS statement (17) and were treated as inpatients or outpatients, depending on relative indications, preference, and the individual's loss of functional limitations other than those related to the lung. Most patients were directly transferred from acute care hospitals. Daily sessions -up to a minimum of 15— including peripheral and/or respiratory muscle training were were conducted as previously reported (26, 27).

### Pulmonary Rehabilitation Outcomes

The prevalence of patients with a positive response to pulmonary rehabilitation corresponding to the minimally clinical important difference (MCID) of each outcome was calculated in terms of three major measures (28-30) : exercise tolerance (+54 m in the 6-min walked distance test [6MWD]) (31), breathlessness (–1 point on the 1 to 5-point modified Medical Research Council [MRC] scale) (32), and quality of life (–4 points on the

St. George's Respiratory Questionnaire [SGRQ]) (33). The percentage of patients who withdrew from pulmonary rehabilitation was also recorded in the study cohort.

**Statistics**

Analyses were carried out using SPSS software (SPSS 8.0 for Windows; SPSS, Chicago, IL). Qualitative variables are expressed as percentages; quantitative variables are expressed as means with standard deviation (SD). Comparison of categorical variables among comorbidity categories was made using the $\chi^2$ test.

Correlations between rehabilitation outcomes (MRC, 6MWD, SGRQ) and categorical variables in study were first analysed with the univariate method (*for details see the online supplement material*). The multivariate logistic regression model was then applied to define the predictive role of comorbidities and other potential confounders when related to the outcomes of the rehabilitation program (*for details see the online supplement material*).

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

## RESULTS

The COPD patients treated in the study period and included in this analysis (n=2,962) were 73% of all those respiratory patients who attended the pulmonary rehabilitation program in our center between January 2003 and December 2005. Main anthropometric and clinical characteristics of the patients are reported in Table 1. Most patients were male (73%) with moderate-to-severe COPD and a disability grade (mean 6MWD, MRC and SGRQ values) that led to elective indication for rehabilitation. Patients with very severe COPD who were on long-term oxygen therapy represented about 9% of the total cohort.

Fifty-one percent (1,519 patients) of the cohort reported at least one comorbidity (38, 11, and 2% in Comorbidity categories 1, 2, and >2, respectively). Distribution of staging and functional status was no different across the categories.

Figure 1A shows the frequency distribution (% of total) of the main chronic diseases in those COPD patients who had at least one comorbidity: The six most frequent disaeses represented >85% of the total number of comorbidities. Other, less frequently reported comorbidities were atherosclerosis (2%), cancer (1%), dementia (1%), and liver (2%), renal (3%), stomach (1%), and intestinal (1%) diseases. The frequency distribution (% of total) of the comorbidity combinations is shown in Figure 1B; Heart Disease (24%), Metabolic Disease (62%) and Skeletal Disease (7%) were the most frequently reported.

Taking the whole cohort of COPD into account, systemic arterial hypertension was the most prevalent comorbidity (27.4%), followed by chronic heart failure (10.5%) and diabetes (10.3%), whereas the prevalence of combined Heart disease, Metabolic Disease and Skeletal Disease was 16, 38 and 5% respectively (figure not displayed).

The mean value changes after pulmonary rehabilitation were 67 [SD 47] m in 6MWD, –1.1 [SD 0.7] MRC score, and –6.4 [SD 4.5] SGRQ score. However, the number and percent of patients with MCID in the MRC score and SGRQ score (but not in 6MWD) were different ($p<0.05$) across the Comorbidity categories (Table 2). Withdrawal rate from pulmonary rehabilitation (3%) was no different across the same categories (Table 2).

The univariate analysis for binary variables has shown that age (with SGRQ, p=0.001), Charlson index (with 6MWD and SGRQ, p=0.001), $FEV_1$ (with MRC, p=0.032), Heart Disease (with 6MWD and SGRQ, p=0.001), Metabolic Disease (with 6MWD, p=0.001; MRC, p=0.004; SGRQ, p=0.043), and Skeletal Disease (with MRC, p=0.049)

significantly related with outcomes and then entered the multivariate analysis. For detailed statistics see also the table as in the online supplement material section.

Table 3 displays the results of the multiple logistic regression analysis. Age, $FEV_1$, Charlson index, and Heart Disease and Metabolic Disease combinations entered the prediction equation as independent variables. In particular, airway obstruction significantly predicted the improvement in MRC score; Charlson index and Metabolic Disease were inversely related to improvement in 6MWD; and Heart Disease directly and indirectly predicted the improvement in 6MWD and SGRQ, respectively.

Overall results did not change when taking the subgroups of COPD undergoing inpatient and outpatient (13% of total) rehabilitation.

## DISCUSSION

Our study shows that most patients with COPD undergoing pulmonary rehabilitation have one or more chronic comorbidities and that the severity of comorbidities, particularly the simultaneous presence of metabolic and/or heart diseases, significantly reduces the beneficial effects of pulmonary rehabilitation on exercise tolerance and perceived quality of life.

Complex chronic comorbidities may significantly affect the clinical severity of COPD (7, 11, 18, 32), being present in up to 56% of COPD patients as compared to non-COPD subjects of the same age (32). The prevalence of chronic comorbidities varies among the studies (9, 25). Although the methodology was similar, the prevalence of at least 1 comorbidity in our cohort was lower (about 65%) than the prevalence reported in other studies (>70%) (34, 35). Indeed, the population we examined was selected because it included only patients referred for pulmonary rehabilitation. The prevalence of comorbidities in COPD patients referred for pulmonary rehabilitation has not been firmly examined before (36, 37), probably because of the relatively low number of patients and inclusion/exclusion criteria of pulmonary rehabilitation. Most (>90%) of the patients included in our study had moderate-to-severe COPD (stages 2 and 3 according to the GOLD guidelines), suggesting that patients with very severe (stage 4) COPD, possibly with more and more severe chronic comorbidities (6, 38), are less frequently referred for rehabilitation. Interestingly, the reported comorbidity Charlson score (24, 39) in our patients was similar (1.26 to 2.85) to that reported in other studies (36, 40, 41).

Systemic hypertension, chronic heart failure, diabetes, coronary heart disease, dyslipidemia and osteoporosis-arthrosis ranked as the six most frequent among all the reported comorbidities; these six represented >85% altogether (Figure 1A), and their proportions were similar to those reported in previous studies (37). The same features were also observed with regard to the prevalence of these diseases within the cohort of studied COPD (see also Results).

Metabolic Disease and Heart Disease were the two most frequent disease combinations among all the reported comorbidities (Figure 1B). It is to note that the used term of Metabolic Disease only approximates the internationally shared definition of "*metabolic syndrome*" (42). Notwithstanding, metabolic alterations together with chronic heart diseases are well known to independently worsen the prognosis of adults (1–3). In elderly patients with complex comorbidities, obesity and low physical activity are factors that increase the risk of death by 15 and 3%, respectively (3). Both these factors are important determinants of survival in COPD patients (36, 43, 44) and are likely to be improved with comprehensive rehabilitation (17). Therefore, it is not surprising to find this

frequent pattern of comorbidities in COPD patients enrolled in pulmonary rehabilitation programs.

Exercise performance, dyspnea and quality of life (as assessed by the SGRQ) are widely recognized as important patient-centered outcomes of COPD, whose favorable change indicates the clinical effect of treatment (21), particularly pulmonary rehabilitation (45). The MCID method here adopted to define the *a priori* criteria for outcome improvement seems appropriate and of reference in this field (29). The proportion of patients with significant changes in MRC (higher percentage in category ≥2) and SGRQ (higher percentage in category 0) was different across the Comorbidity categories (Table 2). However, the magnitude of their change after rehabilitation was similar in these groups, confirming the ability of pulmonary rehabilitation to individually target (whenever possible) the reasonably reachable goals for reducing disability.

The proportion of patients who reported a positive change in all three pulmonary rehabilitation outcomes in our study was >50%. Overall, this percentage was higher than that in a previous study (29) in COPD outpatients. These differences might be partially explained by the different site (inpatient facility for most of our COPD patients) and the different grade of physical disability (mean 285 versus 335 m in the 6MWD in ref. 29 and in our study, respectively) recorded at baseline.

To our knowledge, our study is the first to investigate the predictive role of comorbidities on the effect of pulmonary rehabilitation. So far, this information is still lacking in the field of rehabilitation with regard to COPD patients. Only one study (38) has considered the independent role of comorbidities on functional outcomes (balance and gait) after physical intervention in over 700 elderly patients who were recovering from stroke or who had Parkinson's disease or osteoarthritis. The investigators observed that the determinants of poor recovery were characterized by the combination of "*more disabling diseases*" (COPD, heart failure, peripheral artery disease, diabetes and cancer) rather than the effect of each chronic disease independently, by age, cognitive status, and functional status at admission.

Our findings are consistent with those of ref. 38: indeed, we have shown that the combinations of chronic comorbidities (metabolic and/or heart diseases), but not each chronic disease per se associated with COPD, independently predict improvement after pulmonary rehabilitation (Table 3). Additionally, the overall impact of comorbidities (here quantified by means of the Charlson index) inversely predicts the improvement of both exercise tolerance and quality of life after rehabilitation. This suggests that the more complex cases are those less likely to benefit from pulmonary rehabilitation.

The presence of associated metabolic disorders is inversely related to improvement in 6MWD. Indeed, it is likely that the systemic complications associated with hypertension, diabetes, dyslipidemia and overweight limit the ability to improve physical performance in terms of exercise tolerance, as known in humans (46).

Interestingly, the presence of combined heart diseases acts as both positive and negative predictor depending on the outcome investigated. In particular, it directly relates to the improvement in 6MWD but inversely relates to the change in quality of life (SGRQ).

Despite the heavy contribution that cardiac dysfunction may give per se to health status and prognosis in adults (47), training during rehabilitation in these chronic diseases appears to be recommended (48). These diseases, even if associated with COPD, are not likely to alter the individual's ability to improve his or her physical performance. On the other hand, the combination with chronic heart diseases (but not of the metabolic disorders) inversely predicts the effect of pulmonary rehabilitation on the quality of life of COPD patients. We can only speculate that this particular interaction and disease

complexity may negatively impact the potential benefit of rehabilitation on the individual's perceived health status, as reported previously (49).

Thus, from one hand the presence of more complex comorbidities among COPD patients undergoing pulmonary rehabilitation does not necessary mean that this process is likely to less benefit those patients. From the other hand, however, it probably implies that outcomes should be better targeted and intervention should be better tailored to take account of this factor. Interestingly enough, despite rehabilitation in our cohort of COPD has been delivered in two different setting (13% as outpatient), the overall results were similar in these subgroups of patients, thus confirming a quite homogeneous cohort and making the clinical message even stronger.

Despite the new and original contribution given by our findings, our study presents limitations which need to be addressed. First, this is a retrospective cohort analysis which only enables us to design a further prospective trial to confirm the results. Second, the pattern of comorbidities in our single-center COPD cohort, although consistent, should be confirmed in a multicenter study where a objective confirmation on the single diagnosis is also considered. Third, diagnosis of the comorbidities is based on a self-reported method; therefore, the predictive role of the metabolic and heart diseases on the effects of pulmonary rehabilitation cannot be corroborated by more precise biological or pathogenetic indicators. Four, other potential individual factors like socio-economic status, smoking habit and pack years were not retrospectively available nor they were taken into account as potential confounders in the predictive analysis.

Notwithstanding these important factors which limit the generalizability of this study by using a single site, our findings underline the necessity to globally assess COPD patients for their functions and comorbidities in order to determine the most appropriate approach for treating them (50).

To conclude, this study shows that chronic comorbidities are very frequent, in COPD patients undergoing rehabilitation but a positive effect is reached in >50% of them. Comorbidity risk score and the combinations of both heart and metabolic diseases, in particular, independently predict the effect of pulmonary rehabilitation on exercise capacity and quality of life.

In the context of the current evidence and taking the discussed limitations into account, our findings enable physicians to carefully investigate the impact of comorbidities as potential predictors and confounders in the population of COPD patients enrolled in rehabilitation programs.

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**TABLE 1.** Anthropometric, demographic and functional characteristics of the study cohort.

*Data are presented as mean with SD*

| | | All Patients | Comorbidity categories | | | *p* |
|---|---|---|---|---|---|---|
| | | | 0 | 1 | ≥2 | |
| Patients, no. | | 2,962 | 1,443 | 1,138 | 381 | |
| Age, yr. | | 71.1 (8.0) | 70.9 (8.3) | 71.3 (7.6) | 71.3 (7.7) | 0.429 |
| Sex, M/F no. (%) | | 2,150/812 (72/28) | 1,060/383 (73/27) | 816/322 (71/29) | 274/107 (72/28) | 0.188 |
| Charlson index | | 1.52 (0.72) | 1.25 (0.56) | 1.79 (0.78) | 2.76 (0.68) | 0.001 |
| $FEV_1$, % pred. | | 49.3 (14.8) | 48.8 (14.9) | 50.0 (14.5) | 49.5 (15.4) | 0.128 |
| ATS-ERS staging, no. (%) | | | | | | 0.100 |
| Mild | | 2 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | |
| Moderate | | 1,400 (47.2) | 648 (44.9) | 571 (50.1) | 181 (47.5) | |
| Severe | | 1,251 (42.2) | 640 (44.3) | 451 (39.6) | 160 (41.9) | |
| Very severe | | 309 (10.4) | 155 (10.7) | 114 (10.0) | 40 (10.4) | |
| | | | | | | |
| 6MWD (baseline), m | | 335.2 (95.6) | 333.5 (96.2) | 344.2 (93.1) | 313.8 (98.4) | 0.001 |
| MRC grade (baseline) | | 3.7 (0.92) | 3.7 (0.91) | 3.6 (0.91) | 3.9 (0.96) | 0.030 |
| SGRQ total score (baseline) | | 39.5 (16.4) | 40.5 (16.8) | 39.8 (17.0) | 36.3 (12.9) | 0.414 |

*Definition of abbreviations*: $FEV_1$ = 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.** Patients with a pre-defined positive response (MCID) to pulmonary rehabilitation in terms of improvement in exercise tolerance, dyspnea and quality of life.

*Data are presented as mean with SD*

| | All patients (n=2,962) | Comorbidity categories | | | $\chi^2$ |
|---|---|---|---|---|---|
| | | 0 (n=1,443) | 1 (n=1,136) | ≥ 2 (n=383) | |
| 6MWD +54 m, no. (%) | 1,822 (61.5) | 904 (62.6) | 680 (59.8) | 238 (62.4) | 0.298 |
| MRC grade –1 no. (%) | 2,416 (81.5) | 1,170 (81.0) | 914 (80.3) | 332 (87.1) | 0.010 |
| SGRQ total –4 no. (%) | 1,845 (62.2) | 962 (66.6) | 658 (57.9) | 225 (59.0) | 0.001 |
| | | | | | |
| Withdrawal rate (%) | 2.82 | 1.89 | 3.44 | 1.26 | 0.561 |

See Table 1 for definition of abbreviations.

**TABLE 3.** Factors predicting the pulmonary rehabilitation outcomes in the cohort of COPD studied.

| Dependent Variable | Variable | B | S.E. | Exp (β) Odds Ratio | 96% CI | *p* |
|---|---|---|---|---|---|---|
| | | | | | | |
| 6MWD improvement | Charlson index | –0.31 | 0.14 | 0.72 | 0.54 to 0.98 | 0.024 |
| | Heart Disease | 0.86 | 0.11 | 2.36 | 1.85 to 3.01 | 0.001 |
| | Metabolic Disease | –0.55 | 0.07 | 0.57 | 0.49 to 0.67 | 0.001 |
| | | | | | | |
| MRC improvement | $FEV_1$ | 0.53 | 0.13 | 1.71 | 1.34 to 2.40 | 0.001 |
| | Metabolic Disease | 0.16 | 0.09 | 1.17 | 0.93 to 1.77 | 0.104 |
| | Skeletal Disease | –0.36 | 0.20 | 0.69 | 0.66 to 1.48 | 0.074 |
| | | | | | | |
| SGRQ Improvement | Age | 0.30 | 0.07 | 1.35 | 1.15 to 1.59 | 0.001 |
| | Charlson index | –0.66 | 0.14 | 0.51 | 0.38 to 0.68 | 0.001 |
| | Heart Disease | –0.38 | 0.10 | 0.67 | 0.55 to 0.83 | 0.001 |
| | Metabolic Disease | –0.09 | 0.07 | 0.91 | 0.77 to 1.07 | 0.249 |

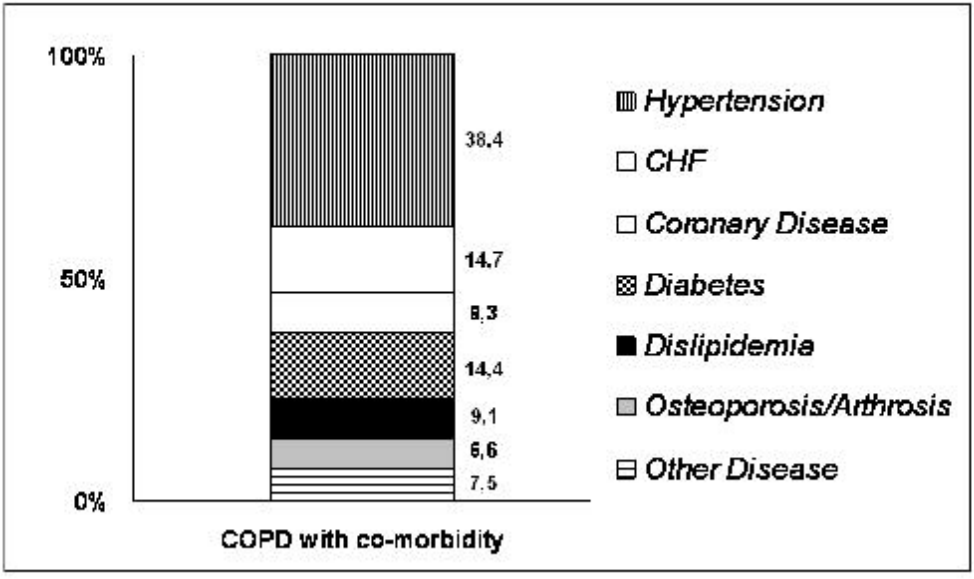
See Table 1 for definition of abbreviations.

For details of the included variables, see the Results section.

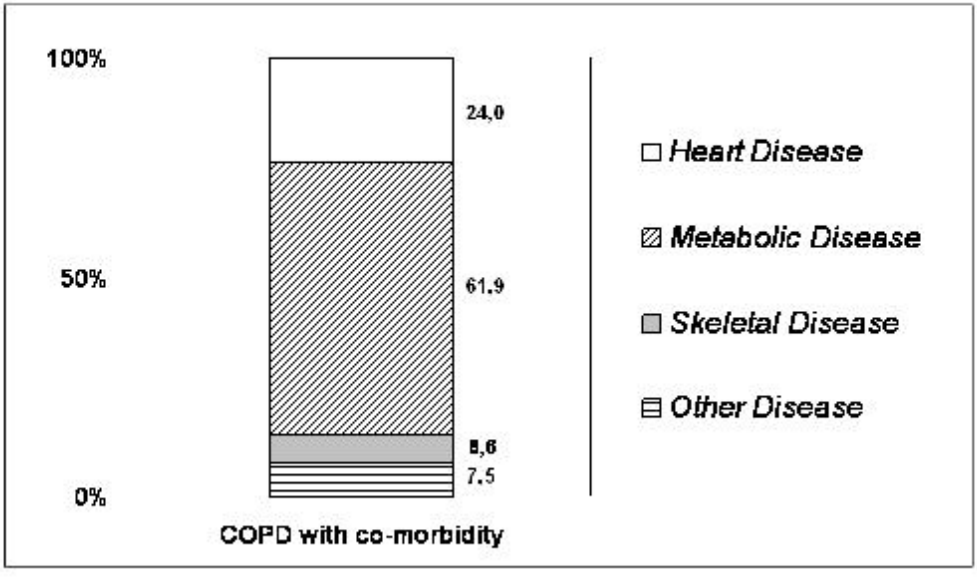
***Legend to Figure 1.*** Frequency distribution (% of total) of individual chronic comorbidities (*A*) and combinations of comorbidities (*B*) added to COPD in the population in study.

CHF= chronic heart failure.

Panel A


100%
50%
0%
38.4
14.7
8.3
14.4
9.1
6.6
7.5
Hypertension
CHF
Coronary Disease
Diabetes
Dislipidemia
Osteoporosis/Arthrosis
Other Disease
COPD with co-morbidity

Panel B


100%
50%
0%
24.0
61.9
8.6
7.5
COPD with co-morbidity
Heart Disease
Metabolic Disease
Skeletal Disease
Other Disease

**ONLINE SUPPLEMENT MATERIAL**

*Methods and statistics*

Statistical analysis have been applied according to the current methodology [1].

The correlates of improvement of the rehabilitation outcomes (MRC, 6MWD and SGRQ) were initially analyzed by the univariate analysis taking categorical variables into account. The variables used for analysis were categorised as follows; age above or below 70 years, Charlson index above or below 2 points, either Metabolic, Heart, Skeletal and Other Disease combinations according to their presence or absence, forced expiratory volume in 1 sec [$FEV_1$] above or below 50% of predicted value. These categories were then selected based on a arbitrary cut-off, nor any different modality was taken into account. Results of this univariate analysis are shown in the Table (Table 1 [suppl]) of this online supplemental material.

We have then applied the logistic regression analysis for defining their predictive role of comorbidities and other potential confounders when related to the outcomes of the rehabilitation program. For each outcome taken as a dependent variable, those correlates which were significant then entered into a multiple logistic regression analysis for defining their predictive role. The model was adjusted for sex as the only potential confounders of outcome changes. In the multiple logistic regression analysis, the independent variable was considered to predict the outcome if its Exp (β) differed from 1 and if the 96% confidence limits did not include 1.

***Reference***

(1) Altman, D. G., D. Machin, T. N Bryant, and M. J Gardner. Statistics with Confidence. London, UK: British Medical Journal; 2000.

***Table 1 [suppl]-*** *Correlates of improvement in the univariate analysis*

| | ***6MWD*** | | | | ***MRC*** | | | | ***SGRQ*** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Variables* | OR | 96% CI | P | | OR | 96% CI | P | | OR | 96% CI | P |
| **Age** | 1.04 | 0.89 to 1.20 | 0.609 | | 0.83 | 0.69 to 1.00 | 0.059 | | 0.74 | 0.64 to 0.86 | **0.001** |
| **Age (<70 yr)** | 1.02 | 0.94 to 1.11 | | | 0.90 | 0.82 to 1.00 | | | 0.85 | 0.78 to 0.92 | |
| **Age (>70 yr)** | 0.98 | 0.92 to 1.05 | | | 1.08 | 0.99 to 1.18 | | | 1.14 | 1.06 to 1.22 | |
| **Sex** | 0.96 | 0.82 to 1.14 | 0.704 | | 1.14 | 0.92 to 1.41 | 0.215 | | 0.93 | 0.79 to 1.10 | 0.455 |
| **Sex (m)** | 1.02 | 0.90 to 1.20 | | | 1.18 | 0.96 to 1.36 | | | 0.84 | 0.62 to 1.04 | |
| **Sex (f)** | 0.97 | 0.85 to 1.16 | | | 1.09 | 0.87 to 1.25 | | | 0.78 | 0.59 to 1.01 | |
| **Charlson index** | 1.77 | 1.36 to 2.32 | **0.001** | | 1.12 | 0.80 to 1.57 | 0.476 | | 1.84 | 1.41 to 2.41 | **0.001** |
| **Charlson index (<2)** | 1.04 | 1.02 to 1.07 | | | 1.01 | 0.98 to 1.03 | | | 1.05 | 1.02 to 1.07 | |
| **Charlson index (>2)** | 0.58 | 0.46 to 0.75 | | | 0.89 | 0.65 to 1.21 | | | 0.57 | 0.44 to 0.72 | |
| **$FEV_1$** | 1.04 | 0.86 to 1.25 | 0.665 | | 1.17 | 1.01 to 1.36 | **0.032** | | 1.00 | 0.86 to 1.16 | 0.982 |
| **$FEV_1$ (< 50% pred.)** | 1.02 | 0.74 to 1.20 | | | 1.08 | 1.00 to 1.16 | | | 1.00 | 0.93 to 1.07 | |
| **$FEV_1$ (< 50% pred.)** | 0.92 | 0.85 to 0.99 | | | 0.91 | 0.85 to 0.99 | | | 0.99 | 0.92 to 1.08 | |
| | | | | | | | | | | | |
| **Heart disease** | 2.46 | 1.96 to 3.10 | **0.001** | | 1.03 | 0.80 to 1.32 | 0.812 | | 0.71 | 0.58 to 0.87 | **0.001** |
| **Heart disease (present)** | 2.16 | 1.77 to 2.64 | | | 1.02 | 0.82 to 1.26 | | | 0.75 | 0.64 to 0.89 | |
| **Heart disease (absent)** | 0.87 | 0.85 to 0.90 | | | 0.99 | 0.95 to 1.03 | | | 1.05 | 1.02 to 1.09 | |
| **Metabolic disease** | 0.55 | 0.47 to 0.64 | **0.001** | | 2.07 | 1.24 to 3.45 | **0.004** | | 0.87 | 0.74 to 1.01 | **0.043** |
| **Metabolic disease (present)** | 0.69 | 0.63 to 0.76 | | | 1.86 | 1.12 to 3.16 | | | 0.91 | 0.83 to 1.00 | |
| **Metabolic disease (absent)** | 1.26 | 1.18 to 1.34 | | | 1.72 | 1.03 to 2.92 | | | 1.05 | 0.99 to 1.12 | |
| **Skeletal disease** | 1.26 | 0.88 to 1.81 | 0.203 | | 0.70 | 0.47 to 1.05 | **0.049** | | 0.80 | 0.56 to 1.13 | 0.211 |
| **Skeletal disease (present)** | 1.25 | 0.88 to 1.76 | | | 0.71 | 0.49 to 1.05 | | | 0.81 | 0.58 to 1.12 | |
| **Skeletal disease (absent)** | 0.98 | 0.97 to 1.00 | | | 1.01 | 0.99 to 1.04 | | | 1.01 | 0.99 to 1.02 | |