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Differential response to pulmonary rehabilitation in COPD: multidimensional profiling

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ABSTRACT The aim of the present study was to profile a multidimensional response to pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (COPD).

Dyspnoea, exercise performance, health status, mood status and problematic activities of daily life were assessed before and after a 40-session pulmonary rehabilitation programme in 2068 patients with COPD (mean forced expiratory volume in 1 s of 49% predicted). Patients were ordered by their overall similarity concerning their multidimensional response profile, which comprises the overall response on MRC dyspnoea grade, 6MWD, cycle endurance time, Canadian Occupational Performance Measure performance and satisfaction scores, Hospital Anxiety and Depression Scale anxiety and depression, and St George's Respiratory Questionnaire total score, using a novel non-parametric regression technique.

Patients were clustered into four groups with distinct multidimensional response profiles: n=378 (18.3%; "very good responder"), n=742 (35.9%; "good responder"), n=731 (35.4%; "moderate responder"), and n=217 (10.5%; "poor responder"). Patients in the "very good responder" cluster had higher symptoms of dyspnoea, number of hospitalisations <12 months, worse exercise performance, worse performance and satisfaction scores for problematic activities of daily life, more symptoms of anxiety and depression, worse health status, and a higher proportion of patients following an inpatient PR programme compared to the other three clusters.

A multidimensional response outcome needs to be considered to study the efficacy of pulmonary rehabilitation services in patients with COPD, as responses to regular outcomes are differential within patients with COPD.

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Introduction

Pulmonary rehabilitation (PR) is a comprehensive intervention designed to improve the physical and psychological condition of people with chronic respiratory disease [1]. Daily symptoms, exercise performance and health status generally improve following PR [2]. Therefore, PR is recognised as a fundamental part of the integrated care of people with chronic obstructive pulmonary disease (COPD) [3].

Since financial resources for PR are often limited or even non-existing [4], identification of (clusters of) patients that do (or do not) respond to PR will become necessary in the near future to improve its cost-effectiveness. This requires consensus about the key performance measures of PR services. To date, changes in exercise performance and health status are often used to qualify individuals with COPD as responders or non-responders to PR [5–10]. Nevertheless, changes in the abovementioned outcomes following PR are mostly differential. Indeed, patients may improve health status without an improvement in exercise capacity or *vice versa*; and patients may improve walk distance without an improvement in cycle endurance or *vice versa* [8, 11–13]. So, the choice for exercise performance and/or health status as key performance measures seems too simple, and the use of non-linear statistics seems inevitable. Moreover, multiple other outcomes (*i.e.*, symptoms of dyspnoea, cycle endurance time, performance of problematic activities of daily life, and symptoms of anxiety and depression [2, 12, 14, 15]) have been identified by healthcare professionals as essential to evaluate the efficacy of PR services [4]. So, a comprehensive evaluation of the efficacy of PR in individuals with COPD is complex, and requires a thorough initial and outcome assessment [1, 16]. Therefore, we sought to profile a multidimensional response to PR in patients with COPD, including symptoms of dyspnoea, exercise performance, health status, mood status, and problematic activities of daily life, using a non-parametric regression technique.

Methods

Patients

We extracted data from the Integrated Knowledge System based on BioXM™ (Biomax Informatics AG, Munich, Germany) of 3349 patients with the diagnosis of COPD who were evaluated during the initial assessment of a comprehensive PR programme at CIRO, centre of expertise for chronic organ failure in Horn (The Netherlands) between January 2006 to December 2012 [16]. Of these records, 706 patients dropped out during the PR, while 575 patients had 5 or more missing values for the response indicators (please see below for more details) at baseline and/or outcome assessment. Finally, 2068 patients (42.9% women) met the following inclusion criteria: a primary diagnosis of COPD, a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio of $\leqslant$0.70, and completion of PR. This analysis also included patients with exacerbations prior to and/or during the study. Ethical approval was not indicated because all of the tests were done as part of the routine initial assessment [16], and analysed retrospectively. The Board of Directors of CIRO approved the use of de-identified patients' records.

Testing

As part of routine 3-day initial assessment [16], patients underwent, amongst other tests and questionnaires, a maximal incremental cycle test during which peak work rate was determined. Subsequently, on a different day, patients performed a constant work rate test at 75% of the determined peak work rate [17]. Patients also performed two 6-min walk tests [18] and the test with the longest 6-min walk distance (6MWD) was used for further analysis [19, 20]. Spirometry, physical examination, medical history and Medical Research Council (MRC) dyspnoea scale data were obtained. Patients underwent an intake by an occupational therapist, including the Canadian Occupational Performance Measure (COPM) to identify and discuss specific problematic activities of daily life [21]. In addition, patients identified their perception of how well they were performing the problematic activities of daily life (performance score; COPM-P) and how satisfied they were with this level of performance (satisfaction score; COPM-S). These scores were ascertained by using the cue cards to identify a score between 1 ("not able to do it" or "not at all satisfied", respectively) to 10 points ("able to do it extremely well" or "extremely satisfied"). The COPM is reliable in COPD [22] and responsive to PR [15]. Mood status has been assessed using the Hospital Anxiety and Depression Scale (HADS) [23]. HADS is divided in an anxiety subscale (HADS-A) and a depression subscale (HADS-D). Total scores for each subscale can range from 0 (optimal) to 21 (worst) points. A score from 8 to 10 indicates a mild mood disturbance, a score from 11 to 14 a moderate mood disturbance and a score from 12 to 21 a severe mood disturbance [23]. For assessment of disease-specific health status, the St. George Respiratory Questionnaire (SGRQ) has been used. The SGRQ consists of 50 items, divided in three domains (symptoms, activities and impact), providing three domain scores. A total score is also provided (SGRQ-T). Scores can range from 0 (optimal) to 100 points (worst) [24].

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Intervention

All patients underwent PR, as described previously [25]. In brief, CIRO+ provides a state-of-the-art interdisciplinary PR programme for patients with COPD consisting of 40 sessions, in line with the 2013 American Thoracic Society/European Respiratory Society Statement on PR [1]. PR can be inpatient (8 weeks, 5 days·week^{-1}) or outpatient (8 weeks, 3 half days·week^{-1}, followed by 8 weeks 2 half days·week^{-1}). The outpatient PR programmes took place in the CIRO+ rehabilitation network. During baseline assessment, a careful characterisation of the extra-pulmonary features of patients with COPD was performed, which determined the application of various treatments: physical exercise training, occupational therapy, nutritional counselling, psychosocial counselling, education and exacerbation management. Physical exercise training was the cornerstone of the programme, consisting of strengthening exercises, treadmill walking and stationary cycling. All exercises were performed at moderate-to-high intensity to obtain an overload stimulus. Moreover, the training intensity increased during the rehabilitation period, based on dyspnoea and fatigue symptom scores. All patients underwent flexibility exercises, general physical exercise for lower and upper extremities, and daily supervised 30-min outdoor walks. Patients, who were too dyspnoeic to perform endurance/interval/resistance training, received lower-limb high-frequency neuromuscular electrical stimulation [26].

Statistics

Data are presented as mean±SD or as frequency, as appropriate. Moreover, the patient data were ordered based on the overall similarity concerning selected attributes. The attributes that drove the ordering process of the patients in the map are the overall response and the differences in the response indicators. The overall response is based on the weighted standardised differences between initial and outcome assessment of all eight response indicators: MRC, 6MWD, cycle endurance time, COPM-P, COPM-S, HADS-A, HADS-D, and SGRQ-T. Thus, patients with a similar response profile are placed closed to each other in the map. Based on the ordering of the patients in the map, the hierarchical ward cluster algorithm has been applied, to cluster the patients into four response clusters. The values of all attributes included in the analyses could then be recalled cluster by cluster to be exported for the statistical tables. For the clustering of patients, the Viscovery Data Mining Suite, version 6.1 by Viscovery Software GmbH (Vienna, Austria; www.viscovery.net) was used, which is based on the technology of self-organising maps (SOMs, also referred to as Kohonen maps). SOMs represent an ordered representation of multi-dimensional data which simplifies complexity and reveals meaningful relationships, and have been used before in COPD [27].

Four clusters of patients with substantially different response profiles have been generated. The efficacy of the pulmonary rehabilitation programme has been evaluated based on the minimal clinically important difference (MCID). The following MCIDs were used: −1 grade on MRC dyspnoea scale [8]; +30 m on 6MWD [19, 20]; +100 s on cycle endurance time [13]; +2 points on COPM-P [15]; +2 points on COPM-S [15]; −1.5 points on HADS-A [28]; −1.5 points on HADS-D [28]; and −4 points on SGRQ-T [29].

Please see online supplement for all details on the statistics.

Results

Baseline characteristics

On average, patients had moderate-to-very severe COPD, an impaired exercise capacity, a poor health status, and experienced problems during the performance of activities of daily life. Moreover, patients were on multiple pulmonary and non-pulmonary drug treatments (table E1 in the supplementary material). Patients with long-term oxygen therapy generally had more symptoms of dyspnoea, and worse exercise performance, mood status and health status compared with patients without long-term oxygen therapy (table 1).

Response to pulmonary rehabilitation: whole group

Significant improvements were found for symptoms of dyspnoea (MRC: −0.4±1.1), 6MWD (27±57 m), cycle endurance time (208±328 s), performance of problematic activities of daily life (COPM-P: 2.0±1.7 points), the satisfaction with the performance of the problematic activities of daily life (COPM-S: 2.6±2.1 points), symptoms of anxiety (HADS-A: −1.4±3.5 points), symptoms of depression (HADS-D: −1.4±3.5 points), and health status (SGRQ total score: −5.3±12.6 points) (all $p<0.01$).

Multidimensional response profiling: whole sample

The 2068 patients with COPD were clustered into four groups with distinct multidimensional response profiles: n=378 (18.3%) in the cluster "very good responder", n=742 (35.9%) in the cluster "good responder", n=731 (35.4%) in the cluster "moderate responder", and n=217 (10.5%) in the cluster "poor responder" (table 2). The response to PR was best in the very good responder cluster on all outcome

TABLE 1 Baseline characteristics

Baseline	All patients	Men without LTOT	Women without LTOT	Men with LTOT	Women with LTOT
Patients n (%)	2068 (100)	1012 (48.9)	740 (35.8)	168 (8.1)	148 (7.2)
Age years	64±9	66±9	61±9[#]	66±8[¶]	65±7[¶]
FEV_1 L	1.3±0.6	1.5±0.6	1.2±0.5[#]	1.0±0.4[#¶]	0.7±0.3[#,¶,+]
FEV_1 % predicted	49±19	50±18	53±18[#]	33±9[#,¶]	35±14[#,¶]
FEV_1/FVC %	40±12	41±12	43±12[#]	32±9[#,¶]	34±9[#,¶]
K_{CO} % predicted	66±23	71±24	63±21[#]	61±23[#]	53±17[#,¶,+]
P_{aO_2} kPa	9.6±1.4	9.6±1.3	9.7±1.4	9.7±1.7	9.4±1.6
P_{aCO_2} kPa	5.3±0.8	5.2±0.6	5.2±0.6	6.0±1.2[#,¶]	6.3±1.1[#,¶,+]
S_{aO_2} %	95.0±2.3	95.0±2.1	95.1±2.4	94.8±2.4	94.4±2.8[#,¶]
MRC dyspnoea grade	3.3±1.1	3.1±1.1	3.2±1.1	4.2±1.0[#,¶]	4.2±1.1[#,¶]
Exacerbation <12 m n	2.1±2.4	1.9±2.4	2.1±2.2	3.1±2.7[#,¶]	3.0±2.8[#,¶]
Admission <12 m n	0.7±1.4	0.5±1.1	0.6±1.2	2.1±2.2[#,¶]	1.6±1.5[#,¶]
CC index, points	1.4±1.2	1.5±1.2	1.2±0.9[#]	1.6±1.4[¶]	1.3±1.0
BMI kg·m^{-2}	25.6±5.3	25.8±4.95	25.0±5.5[#]	26.2±5.4	26.0±6.0
FFMI kg·m^{-2}	16.7±2.4	17.7±2.2	15.3±1.9[#]	17.7±2.4[¶]	15.7±2.4[#,+]
6MWD m	447±115	474±111	452±102[#]	357±107[#,¶]	340±105[#,¶]
6MWD % predicted	70.3±16.4	70.8±15.4	74.5±15.3[#]	54.9±15.9[#,¶]	61.5±16.7[#,¶,+]
PWR watts	72±31	83±34	65±23[#]	57±18[#,¶]	46±15[#,¶,+]
PWR % predicted	56.9±25.4	51.8±21.3	68.4±28.0[#]	36.9±14.1[#,¶]	55.6±21.8[¶,+]
V_{O_2} % predicted	68.6±31.1	55.0±15.8	88.0±36.5[#]	NA	NA
Ventilation %MVV	84.3±21.4	84.3±20.8	84.4±21.5	NA	NA
CWRT s	315±234	354±256	298±221[#]	239±165[#,¶]	211±109[#,¶]
COPM-P, points	4.3±1.3	4.5±1.3	4.2±1.3[#]	3.7±1.4[#,¶]	3.7±1.4[#,¶]
COPM-S, points	3.7±1.7	4.0±1.7	3.5±1.7[#]	3.4±1.6[#]	3.2±1.5[#]
HADS-A, points	7.2±4.3	6.3±4.0	8.0±4.3[#]	7.7±4.8[#]	8.9±4.7[#]
⩾8 points %	44.0	34.0	52.0[#]	54.0[#]	63.0[#,+]
HADS-D, points	6.8±4.1	6.3±3.8	6.9±4.2[#]	7.9±4.3[#,¶]	7.9±4.5[#]
⩾8 points %	41.0	36.0	42.0[#]	54.0[#,¶]	54.0[#]
SGRQ-T, points	53.5±17.0	51.8±16.9	52.0±16.9	63.7±15.0[#,¶]	62.4±13.8[#,¶]
BODE index, points	3.5±1.2	3.1±1.9	3.1±2.0	5.5±1.9[#,¶]	5.5±2.1[#,¶]
ADO index, points	4.4±1.7	4.3±1.6	3.9±1.7[#]	6.0±1.3[#,¶]	5.7±1.4[#,¶]

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; K_{CO}: transfer factor of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; MRC: Medical Research Council; CC index: Charlson Comorbidity index; BMI: body mass index; FFMI: fat-free mass index; 6MWD: 6-min walk distance; PWR: peak work rate; V'_{O_2}: oxygen uptake; MVV: maximal voluntary ventilation; CWRT: constant work-rate test; COPM-P: Canadian Occupational Performance Measure, performance score; COPM-S: Canadian Occupational Performance Measure, satisfaction score; HADS-A: Hospital Anxiety and Depression Scale, anxiety scores; HADS-D Hospital Anxiety and Depression Scale, depression scores; SGRQ-T: St. George's Respiratory Questionnaire, total score; BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; ADO: age, dyspnoea, airflow obstruction; NA: Not assessed. Missing data in men without long-term oxygen therapy were MRC, n=33; 6MWD, n=43; V'_{O_2}, n=47; ventilation, n=47; CWRT, n=110; COPM-P, n=106; COPM-S, n=106; HADS-A, n=34; HADS-D, n=34; SGRQ-T, n=71. Missing data in women without long-term oxygen therapy: MRC, n=15; 6MWD, n=33; VO2, n=49; ventilation, n=49; CWRT, n=75; COPM-P, n=58; COPM-S, n=58; HADS-A, n=31; HADS-D, n=31; SGRQ-T, n=53. Missing data in men with long-term oxygen therapy: MRC, n=2; 6MWD, n=7; CWRT, n=19; COPM-P, n=12; COPM-S, n=12; HADS-A, n=11; HADS-D, n=11; SGRQ-T, n=21. Missing data in women with long-term oxygen therapy: MRC, n=1; 6MWD, n=7; CWRT, n=34; COPM-P, n=8; COPM-S, n=8; HADS-A, n=12; HADS-D, n=12; SGRQ-T, n=24. [#]: p<0.01 *versus* men without long-term oxygen therapy; [¶]: p<0.01 *versus* women without long-term oxygen therapy; [+]: p<0.01 *versus* men with long-term oxygen therapy.

measures compared with the other clusters (table 2, figure 1). Indeed, a clinically relevant improvement was achieved in 85% of the outcomes of the patients in cluster "very good responder", while this was only achieved in 11% of the outcome of the patients in poor responder cluster (table 2, figure 2).

Cluster characteristics: whole sample

Table 3 summarises the baseline characteristics of the patients after stratification for the multidimensional response clusters. Age, the proportion of women, the degree of airflow limitation and the transfer factor for carbon monoxide were comparable between clusters. Patients in the very good responder cluster had significantly higher symptoms of dyspnoea, number of hospital admissions in the last 12 months, a worse exercise performance, worse performance and satisfaction scores for problematic activities of daily life, more symptoms of anxiety and depression, a worse health status, and a higher proportion of patients following an inpatient PR programme compared with the other three clusters. Moreover, patients from the very good responder cluster had a higher proportion of long-term oxygen therapy users, a higher body

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TABLE 2 Outcomes of pulmonary rehabilitation

Outcome	All patients	Very good responder	Good responder	Moderate responder	Poor responder
Patients n (%)	2068 (100)	378 (18.3)	742 (35.9)	731 (35.4)	217 (10.5)
ΔMRC dyspnoea grade	−0.4±1.1	−1.3±1.2	−0.5±1.0[#]	−0.2±1.0[#,¶]	0.2±1.0[#,¶,+]
−1 grade % pts	40.9	73.4	46.1[#]	27.9[#,¶]	17.8[#,¶]
−2 grades % pts	16.0	39.7	13.7[#]	11.3[#]	2.5[#,¶,+]
Δ6MWD m	27±57	96±52	36.1±34.1[#]	3±36[#,¶]	−48±45[#,¶,+]
⩾30 m % pts	45.4	95.5	55.5[#]	22.3[#,¶]	1.4[#,¶,+]
⩾60 m % pts	23.2	74.7	23.0[#]	3.5 [#,¶]	0.0[#,¶,+]
ΔCWRT, s	208±328	525±326	290±313[#]	39±193[#,¶]	−17±222[#,¶,+]
⩾100 s % pts	51.9	87.7	68.5[#]	27.9[#,¶]	17.9 [#,¶,+]
⩾200 s % pts	37.1	79.1	48.9[#]	12.9[#,¶]	10.5[#,¶]
ΔCOPM-P, points	2.0±1.7	3.3±1.5	2.3±1.4[#]	1.3±1.4[#,¶]	0.4±1.2[#,¶,+]
⩾2 points % pts	49.8	81.8	61.3[#]	32.7[#,¶]	10.5[#,¶,+]
⩾4 points % pts	12.8	36.2	13.7[#]	3.3[#,¶]	0.5[#,¶]
ΔCOPM-S, points	2.6±2.1	4.1±1.9	3.1±1.8[#]	1.8±1.7[#,¶]	0.5±1.6[#,¶,+]
⩾2 points % pts	61.6	88.8	74.2[#]	47.7[#,¶]	16.8[#,¶,+]
⩾4 points % pts	26.2	53.4	33.0[#]	11.8[#,¶]	2.1[#,¶,+]
ΔHADS-A, points	−1.4±3.5	−3.2±3.6	−1.9±3.4[#]	−0.7±3.1[#,¶]	1.3±2.8[#,¶,+]
⩾−1.5 points % pts	43.5	65.0	48.8[#]	35.6[#,¶]	13.4[#,¶,+]
⩾−3.0 points % pts	31.8	53.0	35.5[#]	24.1[#,¶]	7.0[#,¶,+]
ΔHADS-D, points	−1.4±3.5	−3.4±3.5	−2.1±3.4[#]	−0.5±2.9[#,¶]	1.6±2.8[#,¶,+]
⩾−1.5 points % pts	44.8	69.9	52.1[#]	34.6 [#,¶]	9.1[#,¶,+]
⩾−3.0 points % pts	33.3	58.2	39.8[#]	21.3 [#,¶]	6.4 [#,¶,+]
ΔSGRQ-T, points	−5.3±12.6	−16.0±12.7	−7.9±10.2[#]	−0.4±10.7 [#,¶]	5.3±9.0[#,¶,+]
⩾−4 points % pts	53.6	84.1	66.5[#]	36.1[#,¶]	14.9[#,¶,+]
⩾−8 points % pts	39.7	74.1	49.5 [#]	22.3[#,¶]	4.8[#,¶,+]

Data are presented as mean±SD, unless otherwise stated. Δ: change; MRC: Medical Research Council; 6MWD: 6-min walk distance; CWRT: constant work-rate test; COPM-P: Canadian Occupational Performance Measure, performance score; COPM-S: Canadian Occupational Performance Measure, satisfaction score; HADS-A: Hospital Anxiety and Depression Scale, anxiety scores; HADS-D- Hospital Anxiety and Depression Scale, depression scores; SGRQ-T: St. George's Respiratory Questionnaire, total score. Missing data: MRC, n=988; 6MWD, n=107; CWRT, n=279; COPM-P, n=228; COPM-S, n=228; HADS-A, n=240; HADS-D, n=240; SGRQ-T, n=449. [#]: p<0.01 *versus* cluster very good responder cluster; [¶]: p<0.01 *versus* good responder cluster; [+]: p<0.01 *versus* moderate responder cluster.

mass index and a higher fat-free mass index at baseline compared with the patients of the moderate responder and poor responder clusters.

Multidimensional response profiling, after stratification for sex and use of long-term oxygen therapy

The current sample consisted of 1012 male and 740 female COPD patients without long-term oxygen therapy, and 168 male and 148 female COPD patients with long-term oxygen therapy. These four subgroups were also divided up into four clusters with distinct multidimensional response profiles (see tables E2 to E5 and figures E1 to E4 in the online supplementary material for all details). The response to PR was best in the very good responder cluster on all outcome measures compared with the other clusters, irrespective of sex and the use of long-term oxygen therapy.

Cluster characteristics after stratification for sex and use of long-term oxygen therapy

Tables E6 to E9 in the online supplementary material summarise the baseline characteristics of the four clusters of each subgroup. In brief, in the male patients without long-term oxygen therapy (table E6), baseline scores for problematic activities of daily life, symptoms of anxiety and depression, and health status were significantly worse in the very good responder cluster compared to the other clusters. The degree of dyspnoea and the 6MWD was significantly worse in the patients of the very good responder cluster compared with the good responder or moderate responder clusters, but were comparable to values of the patients of the poor responder cluster.

In the female patients without long-term oxygen therapy (table E7), the patients in the very good response cluster had a significantly higher baseline degree of dyspnoea, and worse health status compared with the other three clusters. Moreover, baseline 6MWD was lower compared with moderate response and poor response clusters.

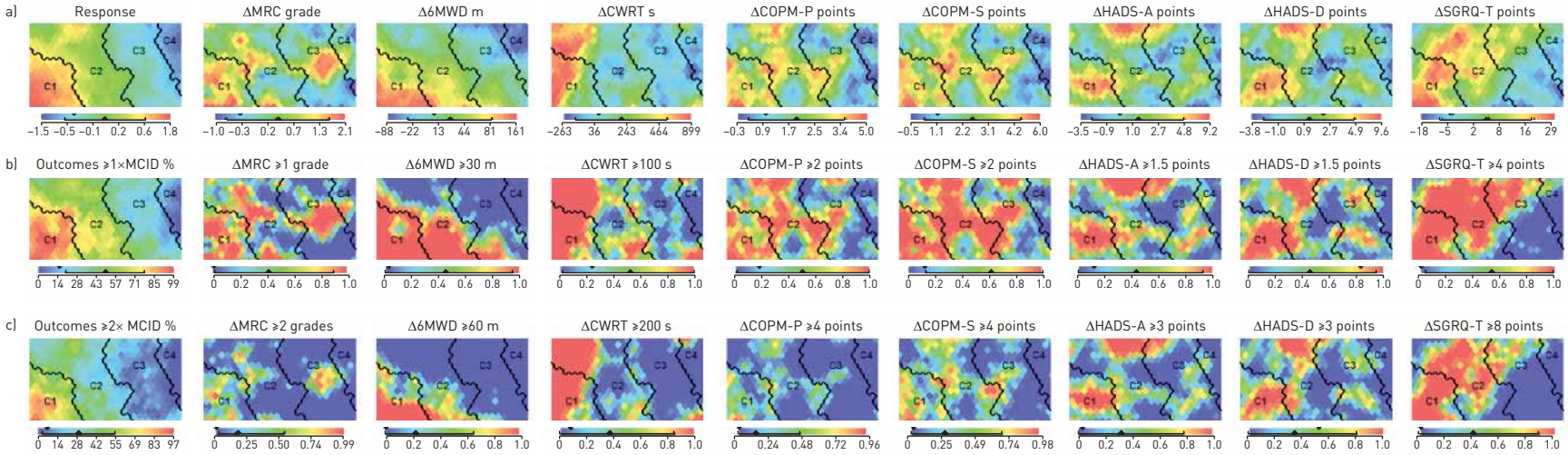

FIGURE 1 Panels generated using Viscovery (Viscovery Software GmbH; Vienna, Austria). The Viscovery program placed all patients on a specific position on all maps based on their multidimensional response profile. The more subjects resemble in terms of their response to pulmonary rehabilitation the closer they are on the map. Contrarily, the more they differ the further they are away from each other. When looking at an outcome measure of pulmonary rehabilitation, patients "raise a red flag" if they had a very good response, "a green flag" when the response was good to moderate, and "a blue flag" when the response was poor. In this way the maps can be interpreted. Using the topology of the self-organising map, the Viscovery program could identify four different clusters of patients with chronic obstructive pulmonary disease (COPD) with a significantly different multidimensional response profile. C1: cluster 1 "very good responder" (n=378); C2: cluster 2 "good responder" (n=742); C3: cluster 3 "moderate responder" (n=731); C4: cluster 4 "poor responder" (n=217). a) Left panel shows the multidimensional response outcome. All other attribute pictures in a) are the absolute change in Medical Research Council (MRC)dyspnoea grade, 6-min walk distance (6MWD), cycle endurance time (constant work-rate test; CWRT), Canadian Occupational Performance Measure, Performance (COPM-P), Canadian Occupational Performance Measure, Satisfaction (COPM-S), Hospital Anxiety and Depression Scale, anxiety (HADS-A), Hospital Anxiety and Depression Scale, depression (HADS-D), and St. George's Respiratory Questionnaire total score (SGRQ-T). b) Left panel shows the proportion of clinically relevant outcomes (exceeding at least 1× minimally clinical important difference (MCID)). All other panels are the proportion of patients per outcome showing a clinically relevant improvement (exceeding at least 1× MCID). c) First panel shows the proportion of clinically relevant outcomes (exceeding at least 2× MCID). All other panels are the proportion of patients per outcome showing a clinically relevant improvement (exceeding at least 2× MCID).

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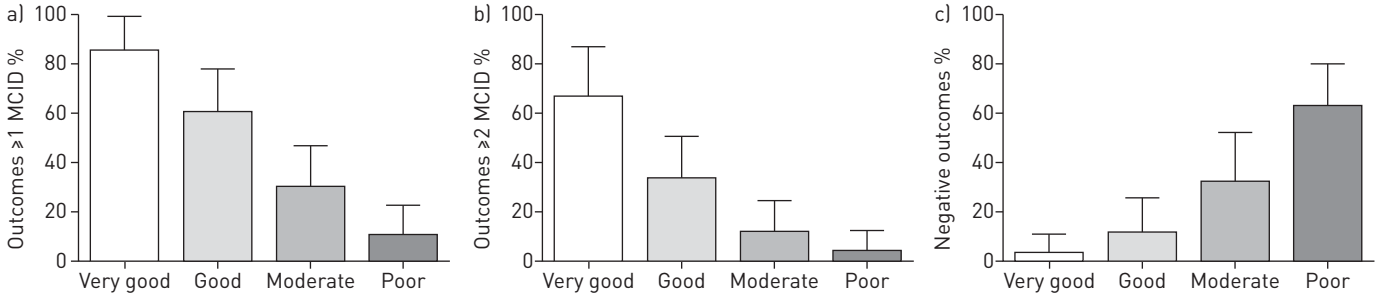

FIGURE 2 Proportion of outcomes which exceed the pre-defined minimal clinically important difference (MCID) at least a) once or b) twice, or c) have negative outcomes, in the very good responder (white bar), good responder (light grey bar), moderate responder (dark grey bar) and poor responder (black bar) clusters.

In the male patients with long-term oxygen therapy (table E8), the patients in the poor response cluster had a significantly lower body mass index and fat-free mass index compared with the other three clusters. Moreover, the patient in the very good response cluster had a significantly worse health status compared to the patients of the moderate response and poor response clusters.

In the female COPD patients with long-term oxygen therapy (table E9), baseline 6-min walk distance was significantly lower in the patients of the very good response cluster compared with the other three clusters. Moreover, the patients in the poor response cluster had a significantly better satisfaction scores for the problematic activities of daily life compared to the other three clusters.

Discussion

The current findings corroborate that responses to regular PR outcomes are differential in a large sample of patients with COPD. Moreover, this is the first study to show that patients with COPD can be clustered based on their multidimensional response to a comprehensive PR programme, identifying groups of patients with a very good, good, moderate or poor response.

Differential response to PR

Generally, PR is beneficial for adults with chronic respiratory disease, including COPD [1]. Nevertheless, the response to PR may vary considerably between patients with COPD [5, 8, 9, 14, 30, 31]. Moreover, individual patients respond differential on various types of outcome measures [8, 11]. The current results in a convenience sample of 2068 well-characterised patients with COPD corroborate these findings (figure 1). These findings emphasise that key performance measures to evaluate the efficacy of PR in patients with COPD have to be chosen very carefully and should focus on multiple domains. The choice for exercise performance and/or health status as key performance measure is too simple. Indeed, to better understand the response to PR in patients with COPD, non-linear statistics were needed. The unbiased approach to cluster patients based on their multidimensional response in a large sample of well-characterised patients with COPD is a major strength of the current analyses. Indeed, the use of Viscovery SOMs allows detailed insight in the differential responses to PR (figure 1). This is a true novelty of the current analyses.

Clinically relevant improvements

In the very good responder cluster, the minimal clinically relevant improvement was achieved in 85% of the outcomes at least once and, in 67% of the outcomes, at least twice (table 2; figure 1). These findings suggest that the patients with COPD in the very good responder cluster are truly benefiting from PR, on (almost) all domains. Moreover, patients in the other clusters also still achieved a clinically relevant improvement in 60% (good responder cluster), 30% (moderate responder cluster) and 11% of the outcomes (poor responder cluster) (table 2). These findings prove again the clinical value of PR in patients with COPD who are still symptomatic even though they did receive the optimal medical care before enrolment. The fact that patients in the poor response cluster still have some clinically relevant improvements in individual outcomes also confirms, that we have to be very careful in defining key outcome measures of PR.

Poor response to pulmonary rehabilitation

The poor response in a subgroup of patients with COPD (figure 2) may be surprising at first sight, as PR provides a comprehensive approach. Then again, the heterogeneity in pulmonary and extra-pulmonary features [32–34] is a clinical challenge to personalise PR programmes for patients with COPD. Consequently, not all patients with COPD are expected to benefit from PR [5, 8, 9, 14, 30, 31]. These are

TABLE 3 Baseline characteristics after stratification for multidimensional response clusters

Baseline	Very good responder	Good responder	Moderate responder	Poor responder
Patients n (%)	378 (18.3)	742 (35.9)	731 (35.4)	217 (10.5)
Age years	62.9±8.8	63.7±9.0	64.2±8.7	64.4±9.1
Sex % women	41.8	43.9	42.7	42.4
FEV_1 L	1.31±0.64	1.31±0.54	1.31±0.57	1.27±0.56
FEV_1 % predicted	47.4±20.2	48.9±17.8	48.8±18.3	47.9±18.8
K_{CO} % predicted	67.7±22.7	67.0±23.8	64.9±21.9	64.1±22.2
LTOT use % pts	21.7	15.9	12.2#	12.4#
P_{aO_2} kPa	9.6±1.4	9.7±1.4	9.6±1.3	9.7±1.3
P_{aCO_2} kPa	5.2±0.7	5.2±0.6	5.2±0.6	5.3±0.8
S_{aO_2} %	94.9±2.6	95.0±2.4	95.1±2.1	95.0±2.1
MRC grade	3.7±1.1	3.3±1.1#	3.2±1.1#	3.2±1.1#
Exacerbation <12 m n	2.5±2.6	2.1±2.5	2.0±2.4#	2.0±1.9
Admission <12 m n	1.1±1.8	0.7±1.2#	0.6±1.3#	0.7±1.3#
CC index points	1.4±1.2	1.4±1.2	1.4±1.1	1.4±1.1
BMI kg·m^{-2}	26.3±5.6	25.9±5.5	25.1±5.0#,¶	24.8±4.6#,¶
FFMI kg·m^{-2}	17.1±2.7	16.8±2.4	16.6±2.3#	16.5±2.2#
6MWD m	405±123	452±113#	461±112#	457±104#
6MWD % predicted	63.3±17.4	71.4±15.6#	72.3±16.0#	71.7±15.7#
PWR watts	68.2±32.3	73.5±31.4	72.9±30.5	70.4±28.3
PWR % predicted	50.5±22.7	59.1±27.0#	57.7±24.3#	57.3±26.3#
V'_{O_2} % predicted	64.2±24.6	70.5±32.7	68.3±31.1	69.8±34.1
Ventilation %MVV	84.3±22.3	84.0±21.2	83.9±20.8	87.2±22.6
CWRT s	295±173	320±225	326±265	296±238
COPM-P points	3.8±1.3	4.2±1.3#	4.5±1.3#,¶	4.5±1.4#,¶
COPM-S points	3.2±1.6	3.6±1.7#	4.0±1.7#,¶	4.1±1.8#,¶
HADS-A points	8.4±4.3	7.2±4.2#	6.8±4.3#	6.3±4.3#,¶
⩾8 points % pts	57.0	45.0#	38.0#,¶	36.0#
HADS-D points	8.0±4.1	6.7±4.0#	6.4±4.0#	5.9±3.9#,¶
⩾8 points % pts	55.0	40.0#	36.0#	32.0#
SGRQ points	61.5±15.2	53.6±16.5#	50.2±17.1#,¶	50.4±17.0#
BODE index points	4.0±2.3	3.4±2.1#	3.3±2.1#	3.4±2.0#
ADO index points	4.7±1.8	4.3±1.8#	4.3±1.6#	4.4±1.7
Inpatient/outpatient %	64/36	41/59#	31/69#,¶	25/75#,¶

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; K_{CO}: transfer factor of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; MRC: Medical Research Council; CC index: Charlson Comorbidity index; BMI: body mass index; FFMI: fat-free mass index; 6MWD: 6-min walk distance; PWR: peak work rate; V'_{O_2}: oxygen uptake; MVV: maximal voluntary ventilation; CWRT: constant work-rate test; COPM-P: Canadian Occupational Performance Measure, performance score; COPM-S: Canadian Occupational Performance Measure, satisfaction score; HADS-A: Hospital Anxiety and Depression Scale, anxiety scores; HADS-D Hospital Anxiety and Depression Scale, depression scores; SGRQ-T: St. George's Respiratory Questionnaire, total score; BODE: body mass index, airflow obstruction, dyspnoea, exercise capacity; ADO: age, dyspnoea, airflow obstruction. #: p<0.01 *versus* very good responder cluster; ¶: p<0.01 *versus* good responder cluster. No statistically significant differences in baseline characteristics between moderate responder and poor responder clusters.

clinically relevant observations, as patients, members from their social circle, healthcare professionals, policy makers and payers have a clear interest in the cost-effectiveness of interventions related to the integrated care of patients with COPD. So, to provide true transparency to its main stakeholders, PR services need to give detailed insights in the efficacy of pulmonary rehabilitation on the individual outcome measures, as well as in a multidimensional outcome measure.

The poor response to rehabilitation in a subgroup of patients does not seem to be COPD-specific and/or rehabilitation-specific. Indeed, also subgroups of patients with chronic neurological diseases [35], chronic cardiac diseases [36], or chronic musculoskeletal diseases [37] respond poorly to specialised rehabilitative interventions. Moreover, response to pharmacological therapy [38, 39], ambulatory oxygen therapy [40], bronchoscopic interventions [41] and lung volume reduction surgery [42] is also poor in subgroups of patients with COPD. These findings emphasise the need for a personalised approach of patients with chronic conditions, and the awareness that a "one size fits all" approach will not result in optimal chronic disease management [43].

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Response prediction

It was beyond the aim of the current study to predict response based on the baseline characteristics. Nevertheless, it seems difficult to predict at the start of the programme who will end up in which cluster, as only 22.2%, 6.5% or 2.8% of the baseline values differed significantly ($p<0.01$) between the poor responder cluster and the very good responder, good responder and moderate responder clusters, respectively (tables E6 to E9). The analyses do emphasise that sex, age and the degree of airflow limitation cannot be used to identify possible responders (or non-responders) to PR as these were comparable between response clusters. Moreover, the baseline mean Charlson comorbidity score was comparable between the response clusters (table 3). These findings suggest that self-reported comorbidities generally do not influence the multidimensional response to PR. Recently, Mesquita *et al.* [44] also showed that changes in exercise performance and health status were not affected by comorbidities that were based on objective measurements.

Methodological considerations

The PR programme at CIRO+ is executed according to the 2013 ATS/ERS Statement on Pulmonary Rehabilitation [1], and provided by a skilled and dedicated team. Nevertheless, individual programmes most probably varied between patients based on the results of the initial assessment [16]. Indeed, the key to success may, at least in part, be hidden in the actual content of the PR programme. Detailed information on the exact content of the individual programme is lacking in the current study. Therefore, the present results are hypothesis-generating rather than definitive. Interestingly, the proportion of outpatients increased while the multidimensional response to PR worsened, in particular in the patients without long-term oxygen therapy (tables E6 and E7). Whether and to what extent these differences are due to the PR setting (inpatient *versus* outpatient) and/or the frequency of the programme (5 days per week for 8 weeks *versus* 3 days per week for 8 weeks followed by 2 days per week for 8 weeks) remains to be determined in a randomised controlled trial.

The current multidimensional response profiling was based on eight outcome measures, including two types of functional exercise performance, health status, mood status, a situational measure of dyspnoea, and problematic activities of daily life, which were identified by healthcare professionals as essential [4]. Obviously, other PR outcome measures, such as physical activity, self-efficacy and disease-specific knowledge, may also be of interest for patients with COPD [1]. The current statistical approach allows the addition of other outcome measures to the multidimensional response profiling. Future, prospective studies need to apply their own multidimensional response profiling and, in turn, should try to corroborate the current cluster findings. Obviously, to enable concise statistical analyses at any point in time, the entire PR process (*e.g.*, referral, baseline assessment, the rehabilitative interventions, short-term outcome assessment and follow up) must be managed and monitored by appropriate information and computer technology infrastructure. Indeed, it may even be a critical success factor for chronic disease management in general, and PR in particular.

To conclude, the current study is the first to profile the multidimensional response to PR using a non-parametric regression technique. The current approach allows us to cluster patients with COPD into groups, and, in turn, identify who benefits most or least from PR after completion of the programme. For the poor responders, we may need to redesign ongoing PR programmes. The current results are the next step in providing detailed insights in the performance metrics of PR in patients with COPD and the future optimisation of the impact of PR. Healthcare professionals and payers need to start realising that patients with COPD will respond differentially on the PR outcome measures that are regularly used [1]. Choosing only one or two outcomes as key performance indicators (*e.g.*, exercise performance and health status) seems to ignore the clinical complexity of rehabilitating patients with COPD. The time has come to start using multidimensional outcome profiling to identify the right COPD patients for the right PR programme.

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