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## **Clustering of COPD patients and their response to pulmonary rehabilitation**

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## **SUMMARY AT A GLANCE**

Pulmonary rehabilitation (PR) is fundamental in the management of chronic obstructive pulmonary disease (COPD). This population is heterogeneous with different responsiveness rates. We identified four clusters of COPD patients and their response to PR in the aim to better understand PR outcome and adapting it to patients' profiles and needs.

## **ABSTRACT**

**Background and objective:** Pulmonary rehabilitation (PR) is fundamental in the management of chronic obstructive pulmonary disease (COPD). COPD patients show a large clinical heterogeneity that may influence their response to PR. Identification of homogeneous clusters of patients who may or may not respond to PR is important to personalize patient care. This study aimed at identifying distinct clinical phenotypes of COPD patients and assessing their respective 6-min walking distance (6MWD) response to in-patient PR.

**Methods:** This is a cohort-based analysis of COPD patients admitted to a PR center between January 2012 and December 2017. Pre-PR patients' characteristics, lung function and 6-min walking test parameters were introduced in a hierarchical ascending clustering approach to identify distinct clusters.

**Results:** Out of 835 patients, 4 distinctive clusters were identified. The most likely to show clinically significant 6MWD improvement post-PR (responders) were cluster 1 (younger men, GOLD I-II, average walkers, obese; non-response rate: 16%), cluster 2 (older women, GOLD II-III, slow walkers; 18%), and cluster 3 (older men, GOLD II-III, dyspneic, slow walkers; 11%). The most likely to be non-responders were cluster 4 (older men, GOLD III-IV, dyspneic, very slow walkers, oxygen-dependent; 26%).

**Conclusion:** Our data identified homogeneous patient clusters representing clinically relevant subgroups of COPD patients regarding their 6MWD response to PR. Clusters having the largest probability of being non-responders were older, more severe, with severe oxygen desaturation and dyspnea, limited 6MWD and requiring long-term oxygen therapy. These results may improve patient phenotyping in clinical practice and allow individualization of therapy.

## **INTRODUCTION**

While patients with chronic obstructive pulmonary disease (COPD) may be considered as a homogeneous population with a similar diagnosis, there is a significant heterogeneity among these patients on many clinical characteristics (for example lung function impairment, symptoms, functional capacities) as well as regarding treatment responses. Pulmonary rehabilitation (PR) is a fundamental intervention implemented to improve the physical and psychological conditions of patients with COPD.<sup>1,2</sup> Some studies showed however that a significant proportion of COPD patients may not show significant functional benefits following PR,<sup>3,4</sup> therefore rising important concerns regarding the clinical management of these patients and the cost-effectiveness of PR.

Cluster analysis<sup>5</sup> is an analytic method which aims to identify homogeneous subgroups, also known as clusters, among a large heterogeneous group. Clustering has been previously used in pulmonary studies: for instance, Augustin et al.<sup>6</sup> identified 7 clusters of COPD patients based on lung function measurements, and Geidl et al.<sup>7</sup> identified 4 clusters of COPD patients based on their physical activity. These studies, among others, used patients' characteristics and lung function to determine different profiles of COPD patients and some studies have evaluated the response to PR in these clusters.<sup>8-9</sup> This statistical method helps to better identify subgroups of patients and may contribute to adapt treatment to specific clusters' needs.<sup>10-12</sup>

A recent retrospective analysis used the hierarchical ward cluster algorithm technique to identify clusters of response to PR based on a multidimensional evaluation.<sup>9</sup> They evaluated the response based on the 6-min walking distance (6MWD) and the Saint George Respiratory Questionnaire.

This phenotyping helped better understand PR responses in different sub-groups of COPD patients. To date, no study has clustered COPD patients based solely on their clinical characteristics and 6-min walking test (6MWT) performance, to subsequently evaluate their functional response to PR using the 6MWD improvement and the corresponding minimal clinically significant difference to define non-responders<sup>13</sup>. This might evaluate the importance of the 6MWT for COPD patient phenotyping and help better understand PR outcome based on initial clinical characteristics and 6MWT performance.

Therefore, we aimed i) to cluster patients with COPD admitted to PR, based on patients' clinical characteristics and 6MWT results (6MWD, pulse oxygen saturation (SpO<sub>2</sub>), heart rate (HR) and dyspnea) and ii) to evaluate the response to PR in each of these clusters based on the improvement in 6MWD, one of the most widely used outcome of PR associated with physical activity, lung function and quality of life.<sup>13-15</sup> We hypothesized that distinct clusters will be identified based on specific clinical characteristics and 6MWT results, and that these clusters will show a heterogeneity in the response to PR. This should provide novel identification and interpretation of clusters who are likely to respond or not to PR, which may contribute to optimize the implementation of PR in COPD patients.

## **METHODS**

### **Study design and population**

We conducted a single center cohort-based analysis of data from patients diagnosed with COPD and admitted to a cardiopulmonary rehabilitation center (Dieulefit Santé, Drome, France) over a 6-year period (from 2012 to 2017). The study was approved by an independent French ethics

committee (ID-RCB number: 2019-A02104-53). Data were collected from the center's electronic medical record database (Calystène, Eybens France) and from the 6MWT data recording system (Sleepinnov, Moirans, France). The following factors of exclusion were applied: having data from only one 6MWT (e.g. pre-PR only), having a rehabilitation duration shorter than 3 weeks<sup>16</sup> or longer than 5 weeks, having two 6MWTs with different amounts of oxygen supplementation.

### **Pulmonary rehabilitation**

The PR program used in the center was the same over the 6-year period and was conducted according to current recommendations.<sup>2</sup> It consisted in a 3-to-4-weeks in-patient program, with activities 5 days per week. Each day the patient attended the following exercise sessions: 25-min aerobic training on a cycling ergometer or a treadmill (5-min warm-up, 15-min training, 5-min cool-down), 30-min low-intensity group gym session (upper and lower limbs exercises, respiratory exercises), 30-min group walk outdoors, and 30-min muscle strength training. In addition to exercise sessions, the patients had sessions of therapeutic education about COPD, oxygen supply, stress management and physical activity. When necessary, they also had respiratory exercises using draining techniques, nutritional interventions and psychosocial counselling.

### **Pre- and post-PR evaluations**

The 6MWT was performed once pre- and once post-PR in a 40-meter-long corridor according to current recommendations.<sup>17</sup> SpO<sub>2</sub> and HR were measured using a portable pulse oximeter (NONIN wristOx2 3150, Plymouth, USA). The data was sent to a Bluetooth-connected electronic tablet (Sleepinnov BlueNight, Moirans, France) where the following measurements

were recorded: 6MWD (expressed in absolute values, i.e. in meters, and in relative values, i.e. in percentage of theoretical walking distance according to Troosters et al.<sup>18</sup>), SpO<sub>2</sub> (in percentage, resting and lowest values), HR (in bpm, resting and highest values), and perceived dyspnea (measured on a 10-cm visual analogic scale, at rest and end exercise). The 6MWT was conducted at the beginning and at the end of the PR program, 1-2 days after admission, 1-2 days before discharge. Patients were then classified as “responders” if they gained  $\geq 30$ m in 6MWD (the minimal clinically significant difference, MCID<sup>13</sup>) and “non-responders” if they did not. Oxygen was used during the test if the patient was already admitted to the center under long-term oxygen therapy (LTOT) prescribed by their pneumologist. Patients under LTOT used oxygen during the PR program as well.

Lung function (total lung capacity (TLC) and forced expiratory volume in the first second (FEV1)) was measured at the beginning of the PR program by pulmonary plethysmography (Jaeger MasterScreen Body, Hoechberg, Germany), based on medical prescription only.

### **Statistical Analysis**

Descriptive statistics are presented as medians (with interquartile range) or mean and standard deviation according to the normality of the values for the quantitative variables and frequencies (%) for the qualitative variables.

To define cluster of patients, an unsupervised clustering method was used: hierarchical ascending clustering with the Euclidian distance and Ward linkage. The following variables were considered: age, BMI, pre-PR values of the 6MWT (i.e. 6WMD, minimal SpO<sub>2</sub>, maximal HR, end-of-test dyspnea) and oxygen supply. The number of clusters was defined on the basis of the inertia plot, the Dunn indice and the clinical interpretation to avoid too small sample sizes per



groups. According to these criteria, four clusters were retained. To compare patients according to the four identified clusters, a Chi<sup>2</sup> test was used for qualitative variables and a non-parametric Mann-Whitney test or an ANOVA was used for quantitative variables. A Bonferonni correction for multiple tests was applied and a corrected p-value threshold was considered for significance. A threshold of 0.05 was considered significant. Statistical analyses were performed by using SAS9.4 (SAS Institute Inc., Cary, NC, USA) and R v4.0.4 (The R Foundation for Statistical Computing).

## RESULTS

### Characteristics of the population

835 patients were included for analysis. Characteristics of the patient population are shown in Table 1. The population consisted of seniors, equally men and women, mostly GOLD II and III (65% of the patients) with limited walking capacity (84% had 6MWD <80% predicted).

### Clustering of patients

Four homogeneous clusters were identified in the heterogeneous sample of COPD patients and are summarized in Table 2, Figure 1, and Figure 2. Their main characteristics, by comparing each cluster to the others, were as follow:

**Cluster 1**, referred to as: **Younger men, GOLD I-II, average walkers, obese, responders (n=16%)**: mostly younger men, mostly GOLD I and II, with very high BMI, average 6MWD (430±116m, 70±17% predicted), and large exercise HR response. This Cluster had a significant improvement in 6MWD of +76±53m. Sixteen percent of the Cluster were non-responders to PR.

**Cluster 2**, referred to as: **Older women, GOLD II-III, slow walkers, responders (n=37%)**: mostly older women, mostly GOLD II and III, with reduced 6MWD (362±118m, 58±18% predicted). This Cluster had a significant improvement in 6MWD of +97±67m. Eighteen percent of the Cluster were non-responders to PR.

**Cluster 3**, referred to as: **Older men, GOLD II-III, dyspneic, slow walkers, responders (n=32%)**: mostly older men, mostly GOLD II and III, dyspneic, with reduced 6MWD (388±114m, 65±17% predicted). This Cluster had a significant improvement in 6MWD of +79±62m. Eleven percent of the Cluster were non-responders to PR.

**Cluster 4**, referred to as: **Older men, GOLD III-IV, very slow walkers, oxygen-dependent, very dyspneic, non-responders (n=15%)**: mostly older men, mostly GOLD III and IV, with severely reduced 6MWD (290±103m, 47±17% predicted), with severe exercise desaturation and dyspnea, and almost all of them had LTOT. This Cluster had a significant improvement in 6MWD of +66±60m. Twenty-eight percent of them were non-responders to PR.

### **Comparison of Clusters**

Comparisons between clusters are presented in table 2. Cluster 1 is significantly younger compared to Clusters 2, 3 and 4 ( $p<0.01$ ). BMI is significantly higher in Cluster 1 and lower in Cluster 2 compared to Clusters 3 and 4 ( $p<0.01$ ). Cluster 4 had the lowest value of FEV1 compared to Clusters 1, 2 and 3 ( $p<0.01$ ). Pre-PR, Cluster 4 had the lowest 6MWD and the lowest SpO<sub>2</sub> compared to Clusters 1, 2 and 3. Exercise-induced HR increase was significantly higher in Cluster 1 compared to Clusters 2 and 4. Finally, Clusters 3 and 4 had significantly higher end-of-test dyspnea compared to Cluster 1. Similar differences in 6MWT variables were observed in post-PR (Table 2). The analysis of each Cluster's response to PR showed that

Cluster 4 had the highest probability (28%) of being a non-responder, significantly higher than Cluster 2.

## **DISCUSSION**

Out of a cohort of 835 heterogeneous COPD patients, four distinctive homogeneous Clusters were identified using the pre-PR patients' clinical characteristics and 6MWT responses. These Clusters showed distinct responses to PR regarding the improvement in 6MWD. These results may help to understand the factors underlying the response to PR and help to anticipate whether a patient might benefit from PR in terms of physical exercise capacity.

The highly heterogeneous nature of the enrolled patient population reflects clinical practice. The decision to take a non-supervised hierarchical ascending clustering approach to this study's data set was made because it was thought that this would better stratify patients and allow more robust determination of PR outcomes in subgroups. The four homogenous patient clusters identified represent clinically relevant subgroups of patients with COPD admitted to PR who each behave similarly in clinical settings. For example, Cluster 1 included patients with the best lung function values (GOLD I-II) compared to Clusters 2 and 3 (GOLD II-III) and Cluster 4 (GOLD III-IV). This can be due, at least in part, to disease severity aggravation with age since Clusters 2, 3 and 4 were older than Cluster 1. Regarding the different walking distance profiles, Cluster 1 demonstrated the best performance and the worst was for Cluster 4, which may also be due to age and disease severity. Cluster 4 had the most severe oxygen desaturation and dyspnea during exercise, probably due to severe ventilatory limitation and impaired gas exchange during exercise. Cluster 4 also had the highest proportion of LTOT emphasizing the severity of the

disease in these patients. Of note, these patients showed the most impaired 6MWT responses despite the use of oxygen supplementation during walking. Cluster 1 showed a significantly higher BMI compared to the other clusters, but interestingly this was not associated with more severe functional impairments during the 6MWT. These patients may illustrate the complex interaction between obesity and COPD as previously emphasized,<sup>19</sup> overweight and obesity being, to a certain extent, associated with some protective mechanisms for COPD patients.<sup>20</sup>

The four identified Clusters showed significantly different improvement in 6MWD following a standardized PR program, leading to significantly different rates of non-responders to PR based on the MCID of 30m<sup>13</sup>. Patients from Cluster 4 with the lowest FEV1 and the most impaired exercise tolerance showed the highest 6MWD non-response rate to PR (28%), which is clearly above the rate of non-responders in the other Clusters from the present study. This non-response rate to PR based on a 6MWD improvement  $\geq 30\text{m}$  is however relatively low compared to previous studies evaluating the response to PR with a similar approach,<sup>4,21</sup> indicating that the intensive PR program conducted within the present center leads to a large functional improvement in this population of COPD patients. The impaired exercise tolerance demonstrated by the 6MWT results in Cluster 4 could be the reason for a smaller functional benefit from PR in this Cluster, since these patients may be limited during exercise training sessions, performing lesser exercise workload or duration, finally leading to less muscular and cardiorespiratory improvement. The potential mechanisms responsible for smaller 6MWD improvement, e.g. greater fatigability<sup>22</sup>, in this Cluster remain however to clarify. This particular group of patients (Cluster 4) may require specific attention and optimization of PR program to allow them improving their physical capacities post-PR.<sup>23</sup> Conversely, the present study indicates that older

age and high BMI as in Clusters 3 and 1, respectively, were associated with 6MWD improvement post-PR similar to younger patients without obesity (e.g. Cluster 2), suggesting that most older or overweight/obese patients can still show clinically significant improvement in 6MWD post-PR.<sup>24,25</sup>

The patient clusters identified in this study could be used as the basis for clinical phenotyping in routine practice. For example, patients who are identified in Cluster 4 may require specific PR modalities in order to optimize their functional benefits. For these patients with severe airflow obstruction, severe oxygen desaturation and dyspnea, and LTOT, a special care plan can be suggested including respiratory muscle training to improve respiratory muscle strength and endurance, and to relieve dyspnea.<sup>26</sup> Other modalities can be suggested, such as interval exercise training<sup>27</sup> or noninvasive ventilation during exercise.<sup>28</sup> The infographic provided in Figure 2 is meant to help practitioners identify patients with the highest probability of becoming non-responders and to put more attention in their care plan with adapted techniques to their specific needs. Further studies identifying clusters of homogeneous subgroups of COPD patients and describing their specific, multidimensional, responses to treatments (including PR) as recently proposed by Marques et al.<sup>29</sup>, are required in order to help practitioners to identify treatable traits and the corresponding adequate treatments.

### **Limitations**

The novelty of this study is the use of a cluster analysis to identify homogeneous groups of patients at admission to PR who present similar characteristics and to determine for each Cluster a PR responder status. The 6MWT was however the only test available pre- and post-PR, making

this an important limitation of the study because only one aspect of the effect of PR was evaluated, leaving aside other physical and psychosocial benefits of PR.

The present approach consisting in clustering patients based on their pre-PR characteristics could be complemented by a similar clustering approach focusing on PR-induced changes in clinical characteristics. The study by Spruit et al.<sup>9</sup> using this approach identified for instance distinct COPD patient clusters based on their multidimensional response to PR, i.e. further emphasizing the clinical complexity of individual responses to PR.

## **Conclusion**

The present study identified four clusters of COPD patients admitted to PR based on their clinical characteristics and 6MWT responses, i.e. data available in almost all clinical settings. Among these Clusters, there were different rates of response to PR. The cluster showing the highest probability of having a post-PR 6MWD improvement <30m included older patients, GOLD III-IV, with walking limitation, severe desaturation, severe dyspnea and under LTOT. Further studies are needed to cluster COPD non-response to PR while considering more variables such as psychological evaluation, muscle strength, among others, to provide a multidimensional evaluation of PR response and to design specific PR programs for the clusters with high probability of being non-responders. Identification of patients likely to show smaller responses to PR may help to target patients benefiting the most<sup>30</sup> and to adapt PR settings for non-responders to standard PR.<sup>11</sup>

**Summary conflict of interest statements:** all authors have no conflict of interest to declare

**Author contributions:** YAC, SB, IA, DV, FH, and SV contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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## **ABBREVIATIONS**

PR: pulmonary rehabilitation

COPD: chronic obstructive pulmonary disease

LTOT: long term oxygen therapy

6MWD: six-minute walking distance

6MWT: six-minute walking test

BMI: body mass index

SpO<sub>2</sub>: oxygen saturation

HR: heart rate

TLC: total lung capacity

FEV1: forced expiratory volume in the first second

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## TABLES

**Table 1.** Characteristics of the population before pulmonary rehabilitation (n = 835)

		n (%) median [Q1;Q3]
Sex	Male	438 (52)
	Female	397 (48)
Age (years)		66 [59;74]
LTOT (n, %)		150 (18)
BMI (kg/m <sup>2</sup> )		25 [21;30]
BMI classification	underweight (<18.5)	94 (11)
	normal (18.5-25)	324 (39)
	overweight (25-30)	207 (25)
	obese (30-35)	109 (13)
	very obese (≥35)	101 (12)
TLC (% predicted)		106 [89;122]
FEV1 (% predicted)		53 [36;71]
GOLD classifications	mild (≥80)	97 (19)
	moderate (50-80)	189 (36)
	severe (30-50)	152 (29)
	very severe (<30)	82 (16)
6MWD (m)		375 [282;460]
6MWD (% predicted)		61 [48;73]

Data are presented as median [Q1 ; Q3] or n. LTOT, long term oxygen therapy; BMI, body mass index; TLC, total lung capacity; FEV1, forced expiration volume in 1 s; GOLD, global initiative for chronic obstructive lung disease; 6MWD, 6-minute walking distance.

**Table 2.** Characteristics of the 4 identified Clusters

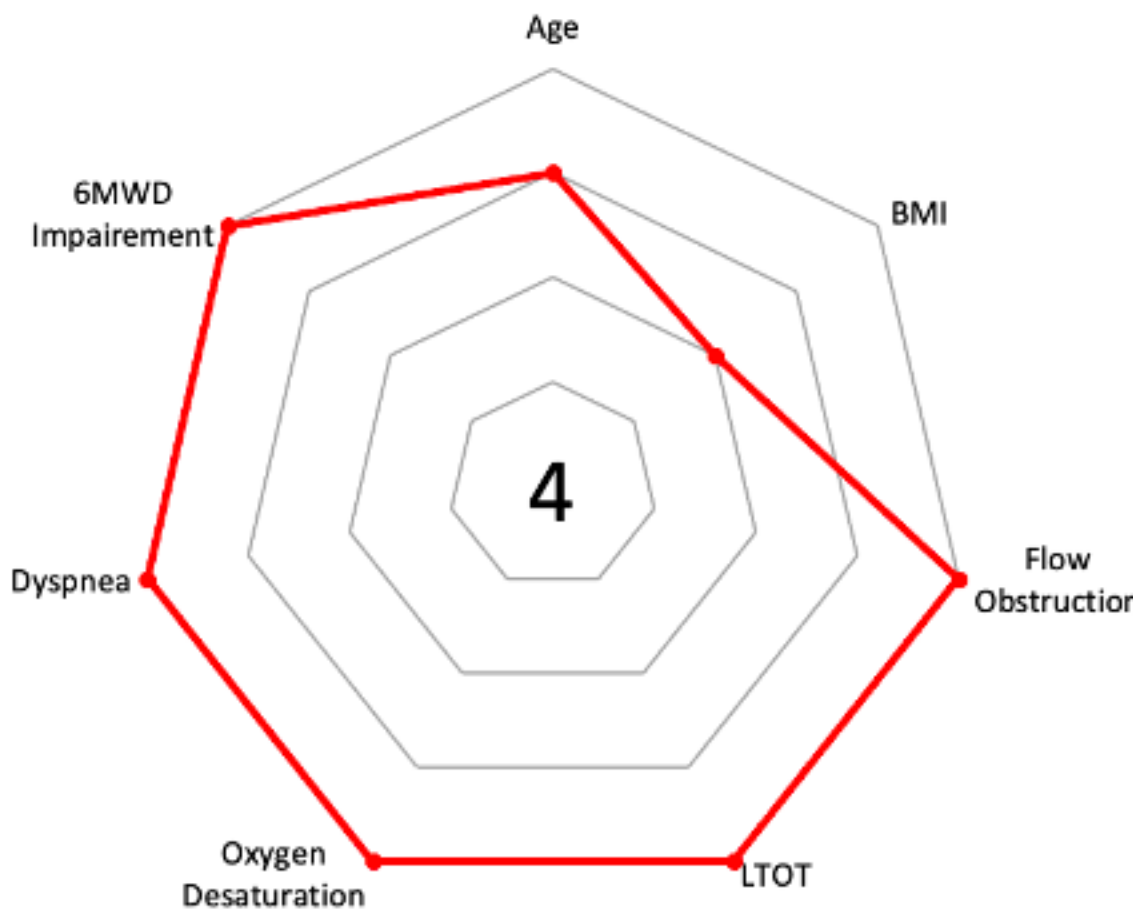
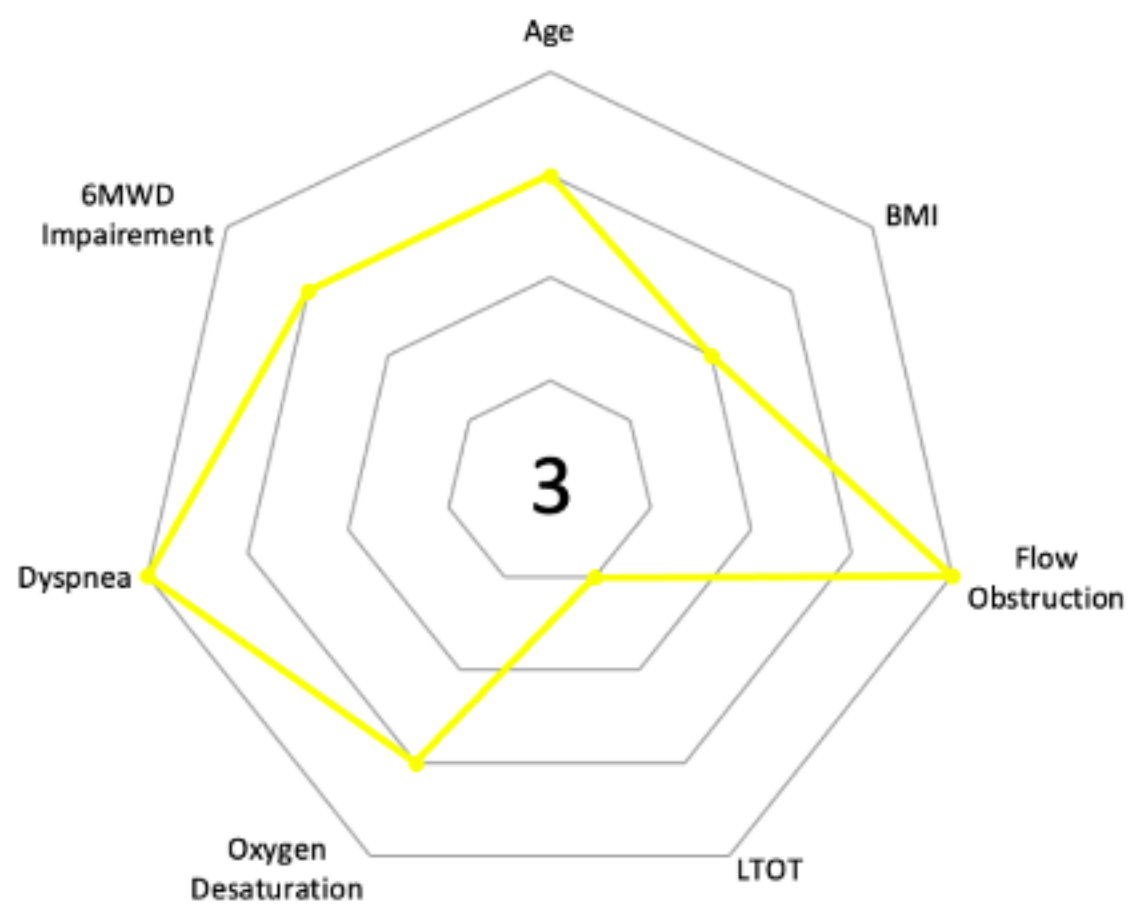
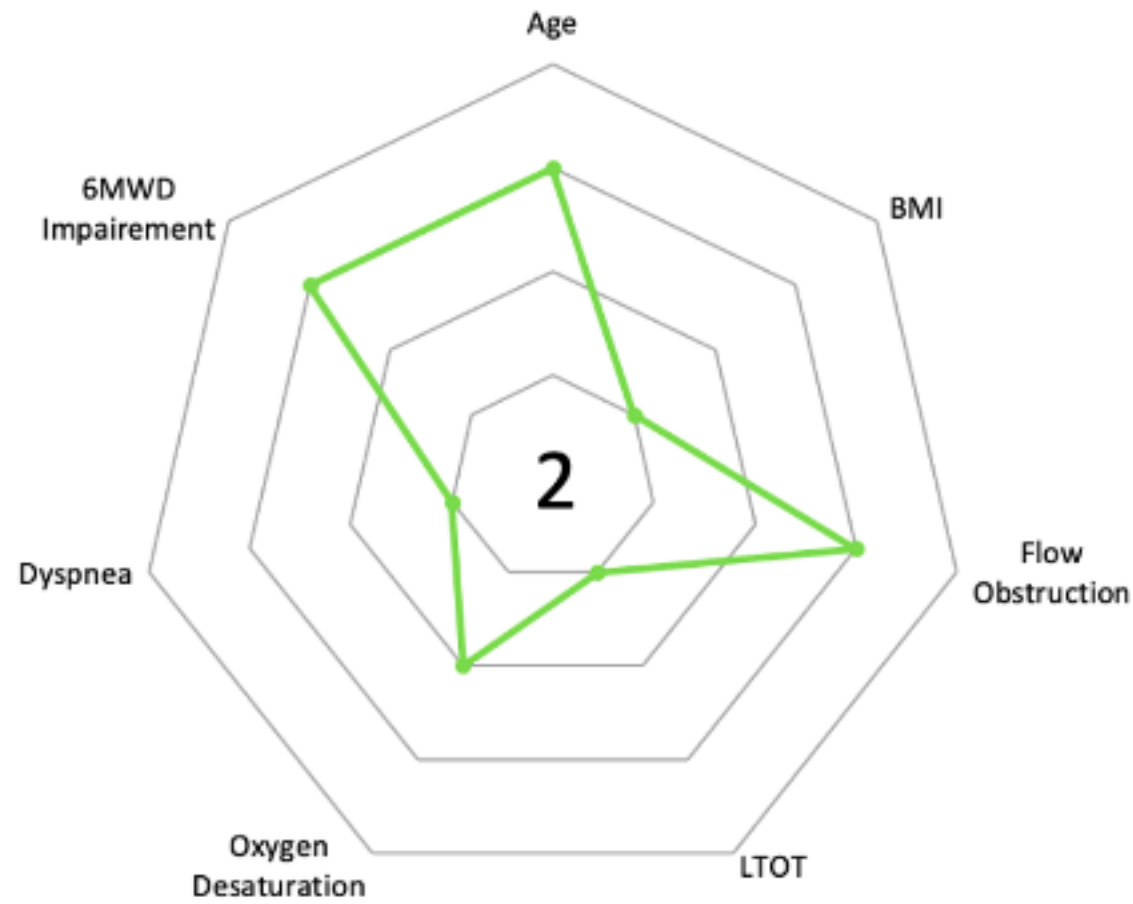
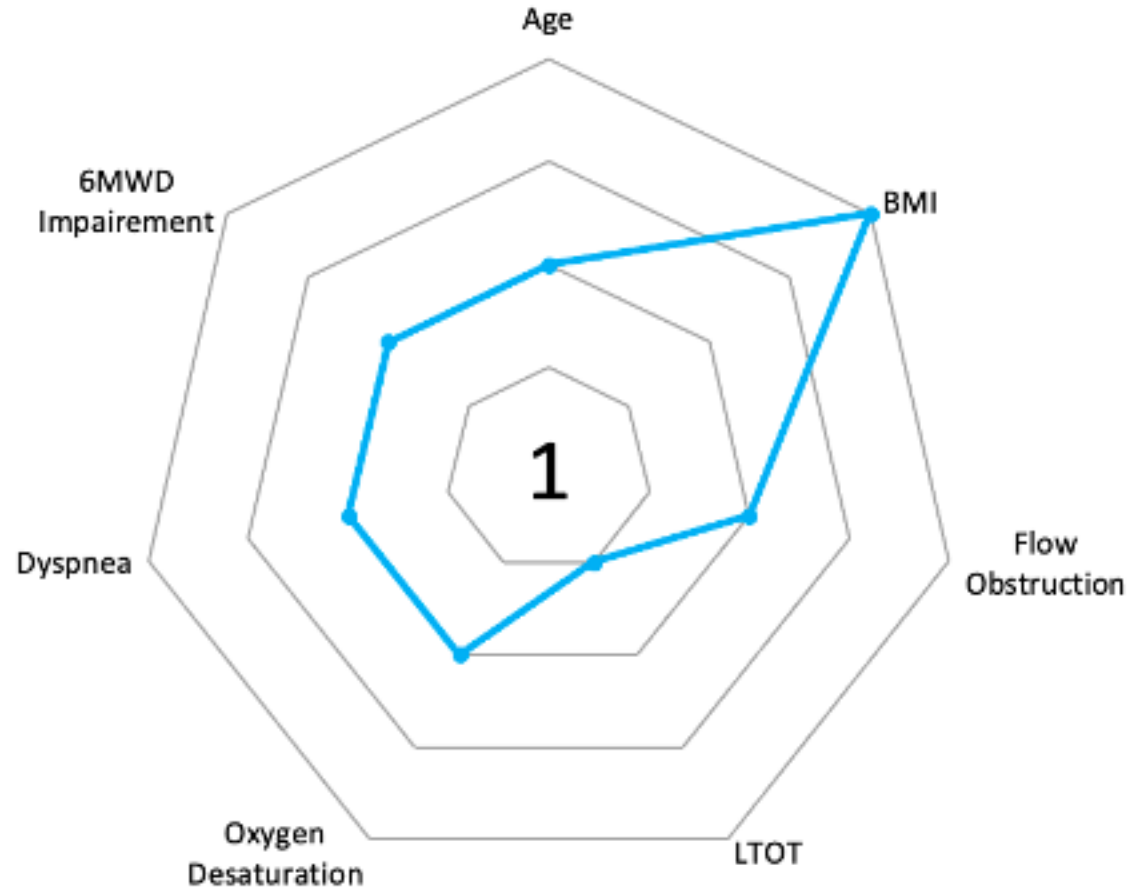
Variables	Cluster 1 n=137 (16)	Cluster 2 n=305 (37)	Cluster 3 n=264 (32)	Cluster 4 n=129 (15)
Sex (F)	56 (41)	172 (56)*	121 (46)	48 (37) <sup>+</sup>
(M)	81 (59)	133 (44)*	143 (54)	81 (63) <sup>+</sup>
Age (years)	59 [10]	65 [12]*	70 [10]*	67 [11]* <sup>+</sup>
BMI (kg/m <sup>2</sup> )	36 [6]	22 [4]*	26 [5]*	25 [6]* <sup>+</sup>
TLC (% predicted)	104 [26]	109 [35]	109 [26]	103 [34]
FEV1 (% predicted)	62 [22]	56 [25]	59 [23]	39 [20]* <sup>+\$</sup>
LTOT	5 (4)	29 (10)	10 (4)	126 (98)* <sup>+\$</sup>
<b><u>Pre-PR 6MWT</u></b>				
6MWD (m)	430 [116]	362 [118]*	388 [114]*	290 [103]* <sup>+\$</sup>
6MWD (% predicted)	70 [17]	58 [18]*	65 [17]*	47 [17]* <sup>+\$</sup>
Minimal SpO <sub>2</sub> (%)	89 [5]	89 [5]	88 [5]	86 [6]* <sup>+\$</sup>
Δ SpO <sub>2</sub> (%)	-3 [4]	-4 [5]	-4 [5]	-7 [6]* <sup>+\$</sup>
Δ HR (bpm)	23 [14]	14 [15]*	20 [15]	15 [13]* <sup>\$</sup>
End-of-test dyspnea	5 [2]	4 [2]*	6 [2]*	6 [2]* <sup>+</sup>
<b><u>Post-PR 6MWT</u></b>				
6MWD (m)	507 [111]	459 [118]*	467 [114]*	356 [113]* <sup>+\$</sup>
6MWD (% predicted)	82 [15]	73 [18]*	78 [17]	57 [18] <sup>*\$</sup>
Minimal SpO <sub>2</sub> (%)	89 [6]	88 [6]	88 [5]	85 [6] <sup>*\$</sup>
Δ SpO <sub>2</sub> (%)	-3 [4]	-4 [5]	-4 [5]	-8 [6] <sup>*\$</sup>
Δ HR (bpm)	28 [17]	19 [16]*	22 [16]*	19 [16]*
End-of-test dyspnea	4 [2]	4 [2]	5 [2]*	6 [2]* <sup>+</sup>
<b><u>Response to PR (Δ 6MWD)</u></b>				
Non-Responders (< 30m)	22 (16)	33 (11)	47 (18)	36 (28) <sup>+</sup>
Responders (≥ 30m)	115 (84)	272 (89)	217 (82)	93 (72) <sup>+</sup>

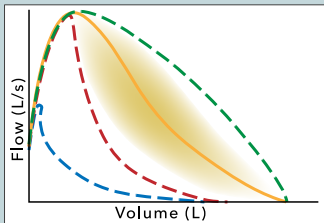
Data are presented as mean [SD] or n (%). BMI, body mass index; TLC, total lung capacity; FEV1, forced expiration volume in 1 s; LTOT, long term oxygen therapy; 6MWT, 6-minute walking test; 6MWD, 6-minute walking distance; SpO<sub>2</sub>, pulse oxygen saturation; Δ SpO<sub>2</sub>, drop in pulse oxygen saturation, Δ HR, rise in heart rate. Significant difference after Bonferroni correction if p < 0.05 \* compared to Cluster 1, <sup>+</sup> compared to Cluster 2, and <sup>\$</sup> compared to Cluster 3.

## **FIGURE LEGENDS**

**Figure 1.** Radar presentation of the 4 identified clusters. The classification is on a scale of 1 to 4. The closest to the center, the less severe the variables are. The further from the center, the more severe they are. BMI, body mass index; LTOT, long-term oxygen therapy; 6MWD, 6-minute walking distance

**Figure 2.** Infographic illustrating the four identified clusters of COPD patients and their respective 6-min walking distance response to pulmonary rehabilitation.





### Cluster 1

Younger men  
GOLD I-II  
Average walkers  
Obese  
Responders



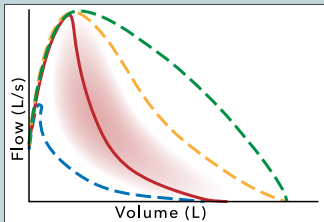
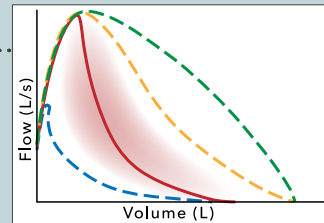
430m +77m  
16% non-responders

### Cluster 2

Older women  
GOLD II-III  
Slow walkers  
Responders



362m +97m  
18% non-responders



### Cluster 3

Older men  
GOLD II-III  
Slow walkers  
Dyspneic  
Responders



388m +79m  
11% non-responders

### Cluster 4

Older men  
GOLD III-IV  
Very slow walkers  
Dyspneic  
Oxygen therapy  
Non-responders



290m +66m  
28% non-responders

