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Trajectories of COPD patients' response to repeated pulmonary rehabilitation programs

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SUMMARY AT A GLANCE (50 words)

We evaluated the trajectories of response to repeated pulmonary rehabilitation (PR) in COPD patients, using the six-minute walking distance (6MWD) to determine the functional response to PR. We demonstrate that a response to repeated PR is not systematically **identical**, especially for non-responders to initial PR.

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ABBREVIATIONS

PR: pulmonary rehabilitation

COPD: chronic obstructive pulmonary disease

6MWD: six-minute walking distance

6MWT: six-minute walking test

BMI: body mass index

SpO₂: oxygen saturation

HR: heart rate

TLC: total lung capacity

FEV₁: forced expiratory volume in the first second

GOLD: global initiative of obstructive lung disease

MCID: minimal clinically important difference

ABSTRACT

Background and objective: Pulmonary rehabilitation (PR) is **essential** in the management of chronic obstructive pulmonary disease (COPD), but the long-term effects and the outcomes of repeated programs especially in non-responders remain to be clarified. The aim of this study is to evaluate the long-term effect of PR 12 months after and the effect of repeated PR depending on the patient's response to the first PR.

Methods: This is a single center retrospective analysis of COPD patients admitted to two or three PR programs between January 2012 and December 2017, using the six-minute walking distance (6MWD) to determine the functional response to PR.

Results: One hundred ninety patients completed PR twice and 62 completed PR three times with 10-14 months delay between programs. The effect of the first PR program (PR1) on 6MWD was mostly lost after one year. The 6MWD change after the second PR program (PR2) was smaller than after PR1 ($+65 \pm 30$ m post-PR1, $+44 \pm 20$ m post-PR2; $p = 0.001$). Out of the 149 responders post-PR1, 44 (30%) became non-responders post-PR2. Out of the 41 non-responders post-PR1, 23 (56%) became responders post-PR2. Patients with long term oxygen therapy and severe exercise dyspnea were most likely to remain non-responders to repeated PR.

Conclusion: This study showed that most of the 6MWD improvement following PR disappears over 12 months and emphasized the clinical relevance of repeating PR including for non-responders to initial PR. However, some patients did not respond systematically to PR and may require specific PR modalities to improve their functional status.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has become the third leading cause of death in the world¹ requiring a comprehensive intervention plan designed to improve physical and psychological condition of these patients. Pulmonary rehabilitation (PR) was designed for people with chronic respiratory disease and is recommended as a fundamental part of the COPD management plan.^{2,3} Daily symptoms, exercise performance and health status generally improve following PR.⁴⁻⁶

However, the benefits in exercise capacity, as well as other outcomes resulting from PR, tend to decline over the months following the completion of the intervention.⁷ There are several likely reasons for this decline in outcomes including physical deconditioning, progression of the respiratory disease and its comorbidities and intervening exacerbations.⁸⁻¹⁰

To mitigate this long-term decline in clinical outcomes, some clinicians prescribe repeated PR programs. A few studies have been conducted to show clinical advantages of repeated PR in patients with COPD, including a decreased rate of exacerbations, fewer hospitalizations, and improved quality of life.^{7,8,11} Other studies have evaluated the effect of repeated PR on the 6-minute walking distance (6MWD), with small samples of patients, showing significant improvement in 6MWD following repeated PR with 12-24 months between programs¹¹⁻¹³, but to date, no studies have described the change in responsiveness to repeated PR (between responders and non-responders).

Larger studies are needed to study the response to repeated PR depending on the response profile to the first PR (i.e. in patients identified as non-responders to the first program), because program repetition has significant implications for health-care resources. There is no evidence

to provide guidance as to whether repeating the program to patients previously identified as non-responders can be systematically recommended.

The objectives of the study were 1) to assess the long-term effect of PR in COPD patients, 2) to evaluate the effect of repeated PR, and 3) to determine trajectories of response following repeated PR. We hypothesize that a non-responder to a first PR may become responder to subsequent PR.

METHODS

Study design and population

We conducted a single center retrospective analysis of data from patients diagnosed with COPD admitted to a cardiopulmonary rehabilitation center (Dieulefit Santé, Drome, South Eastern France) for two programs over a 6-year period (from 2012 to 2017). The study was approved by a French independent 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 six-minute walking test (6MWT) data recording system (BluenightAcor+, Sleepinnov, Moirans, France). Cross-analysis of the two data sources yielded 1910 COPD patients. The following factors of exclusion were applied: admitted after an acute exacerbation or hospitalization, having only one PR, having a readmission earlier than 10 months or later than 14 months post-PR1, having data from less than four 6MWT (i.e. pre-PR1, post-PR1, pre-PR2, post-PR2), having a rehabilitation duration shorter than 3 weeks¹⁴ or longer than 5 weeks, differing amounts of oxygen supplementation during the 6MWTs. 1720 patients were excluded and 190 patients were included for analysis with at least one readmission 10-14 months post-PR1 following medical prescription (Figure 1).

Pulmonary rehabilitation

The PR program used in the center was the same over the 6-year period and was conducted according to current recommendations³. It consisted in a 3-to-4-weeks in-patient program, with activities 5 days per week. Each day the patient attended the following 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 outside, and a 30-min muscle strength training session. In addition, the patients had sessions of therapeutic education concerning COPD, oxygen supply, stress management and physical activity. When judged clinically necessary, they also had psychosocial counselling.

Evaluations

The 6MWT was performed in a 40-m hallway according to current recommendations¹⁵ with the exception that the test was performed once only. Oxygen saturation (SpO₂) and heart rate (HR) were measured using a portable pulse oximeter (NONIN wrist Ox2 model 3150, Plymouth, USA, data collected every 4 seconds, the SpO₂ accuracy was $\pm 2\%$ and HR accuracy was ± 3 bpm). The data was sent to a Bluetooth-connected electronic tablet (Sleepinnov BlueNight Acor+ application, Moirans, France) where the following measurements were recorded: 6MWD (in meters and in percentage of theoretical walking distance), SpO₂ (in %, 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 (pre-PR) and at the end of the PR (post-PR) of every program for each patient. Patients were then classified as “responders” if they gained ≥ 30 m in 6MWD (the minimal clinically significant difference, MCID⁶) and “non-responders” if they did not. Oxygen was used during the test (pre- and post-PR) if the patient was already admitted under long term

oxygen therapy prescribed by their pulmonologist. These patients also used oxygen during the PR program.

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

Other variables were reported: comorbidities, reasons for admission, physical activity questionnaire (Ricci and Gagnon)¹⁶, and the number of exercise sessions during PR.

Statistical Analysis

Descriptive statistics are presented as medians (with interquartile range) or mean (\pm standard deviation, SD) for the quantitative variables and frequencies (%) for the qualitative variables.

A simple imputation method was carried out in cases where the missing data were few (< 5%).

Otherwise, a multiple imputation method that was defined according to the observed missing data pattern was implemented. To compare patients according to their PR response status

(responders vs. non-responders; non-responders to PR1 and PR2 vs. non-responders to PR1 and responders to PR2 vs. responders to PR1 and non-responders to PR2 vs. responders to PR1 and responders to PR2), a Chi² test was used for qualitative variables and a non-parametric Mann-

Whitney test was used for quantitative variables. In case where more than 2 comparisons were performed, a correction for multiple tests was applied using Bonferroni approach. To identify

factors associated with a probability of responding to repeated PR, a univariable analysis was performed using a logistic regression model. Variables with a p-value less than 0.10 in the

univariable analysis were then included in a multivariable logistic regression model. Finally, a linear model was applied to evaluate the relation between the gain in 6MWD and the predictors.

The forward method was used in continuous 6MWD gain analysis for the selection of predictors and the Bayesian information criteria (BIC) was used to choose the best model. A threshold of

0.05 was considered significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of the whole population

Characteristics of the 190 patients' population before starting the first PR program (pre-PR1) are given in Table 1. A flow chart of patients' inclusion is presented in Figure 1. Eighty-seven percent were readmitted to PR following the prescription by their pulmonologist of a yearly follow-up program. There was no significant difference in gender distribution. Most patients were overweight or obese and were GOLD II or III. The average walked distance pre-PR showed important functional limitation with 80% of the patients having a 6MWD < 80% predicted distance. Most patients desaturated during exercise and were severely dyspneic.

Response to PR1 and PR2

The PR program lasted for 25 ± 4 days (mean \pm SD). The delay between PR1 and PR2 was 354 ± 50 days. Data collected during the 6MWT are provided in Table 2 and Figure 2. Based on the physical activity questionnaire, only 25% of the patients stayed active during the 10-14 months period between the PR programs, compared to 17% pre-PR1. The patients showed a mean significant improvement in 6MWD both post-PR1 ($+65 \pm 30$ m) and post-PR2 ($+44 \pm 20$ m) but the 6MWD change post-PR2 was smaller than post-PR1 ($p = 0.001$). 6MWD pre-PR2 was not significantly different compared to pre-PR1. SpO₂, HR and dyspnea did not differ between all pre- and post-PR 6MWT. At pre-PR2, FEV1 showed a non-significant ($p = 0.17$) reduction compared to pre-PR1 (pre-PR1 $46 \pm 21\%$ versus pre-PR2 $42 \pm 16\%$ predicted). The BMI did not change over time (results not shown).

Comparison of responders and non-responders to PR1 and PR2

Post-PR1, 78% of the patients were classified as responders and 22% non-responders. Post-PR2, the percentage of non-responders was significantly higher since 33% of the patients did not achieve the 6MWD MCID of 30 m. The multivariable analysis (Table 3) indicated that being a responder to PR2 was significantly associated to being a responder to PR1. Also, the use of oxygen decreased the probability of being responders at PR2 by 40%.

Out of the 149 responders to PR1, 44 (30%) became non-responders to PR2. Out of the 41 non-responders to PR1, 23 (56%) became responders. Hence, we described 4 classes of change in 6MWD response (Figure 3, Table 4): 55% were responders to PR1+PR2, 10% were non-responders to neither; 23% were responders to PR1 but not to PR2; 10% were non-responders to PR1 but became responders to PR2. Two variables pre-PR1 showed significant differences between the 4 identified classes: LTOT and end-of-test dyspnea. Non-responders to PR1 who stayed non-responders to PR2 (NR1-NR2) were those under LTOT ($p = 0.03$) and had the highest end-of-test dyspnea ($p = 0.04$). On the contrary, responders to PR1 who stayed responders to PR2 (R1-R2) were those with the least LTOT ($p = 0.03$).

Subgroup of three repeated PRs

Out of the 190 patients having performed two PR2, 62 (33%) patients repeated PR a third time 10-14 months after PR2. **Eighty-nine percent were readmitted to PR following pulmonologist's prescription of a yearly follow-up program.**

The BMI of these 62 patients did not change over time (results not shown). FEV1 showed a non-significant ($p = 0.12$) reduction at pre-PR2 ($46 \pm 12\%$) and pre-PR3 ($44 \pm 13\%$) compared to pre-PR1 ($50 \pm 13\%$). Data from the 6MWT pre and post-PR1, PR2 and PR3 are shown in Table 5 and Figure 2. The patients started each PR with almost the same walked distance. The

mean change in 6MWD following PR3 was $+55 \pm 58$ m, which was not significantly different from neither PR2 ($+52 \pm 64$ m, $p = 0.73$) nor PR1 ($+73 \pm 70$ m; $p = 0.35$). The percentage of non-responders to PR based on changes in 6MWD was not significantly lower post-PR1 (20%) compared to post-PR2 (37%) and post-PR3 (31%) ($p = 0.17$). The change in response between each PR program is presented in Figures 4 and 5. We observed that the majority of the patients showed clinically significant response to PR3 no matter their responses to PR1+PR2. Only 3 patients (5%) were non-responders to all three PR, and 37% were responders to all three PR.

DISCUSSION

The main result of this study is that among a large population of 190 COPD patients having performed 2 PRs, 54% of non-responders to PR1 become responders if PR2 was to be repeated after 10-14 months. Also, only 3% of the 62 patients having performed three PR did not show any clinically significant increase in 6MWD to any of the three programs. We were able to identify 4 different classes of repeated-PR response trajectory, showing that staying a responder or a non-responder over several PR is not a systematic trajectory, but that the patients the most likely to remain non-responders were those under LTOT and very dyspneic. In addition, this study showed that: i) the increase in 6MWD post-PR is partially lost during the following 12 months and ii) the improvement in 6MWD after each repeat PR is of smaller amplitude on average compared to PR1 despite remaining clinically significant (≥ 30 m MCID on average).

Repeat PR can be offered to patients because the effect of PR diminishes after 1–2 years.¹¹⁻¹³ Our results agree with these studies since we showed that the increase in 6MWD post-PR1 is partially lost during the 12 months but the walking capacity pre-PR2 did not drop below the pre-PR1 walked distance. **It should be emphasized however that to alleviate the cost of repeated**

PR on healthcare resources and to attenuate the long-term decline in PR outcomes, other care plans should be considered in future studies, including patient education, follow-up interventions and telemedicine¹⁷.

The preservation of functional capacity over a year in these patients may illustrate an attenuation of disease progression due to PR. Indeed, FEV1 did not significantly decline from year to year, nor did BMI change. This shows a stabilization of the disease progression, possibly because the disease's increasing impact on walking capacities (higher dyspnea, etc) may have been averted. These results need to be confirmed with future studies including a control group of patients who did not take part in any PR program.

We also showed that the effect on 6MWD of PR2 was lower than the effect of PR1 but remained statistically and clinically significant (≥ 30 m on average). Current ATS/ERS pulmonary rehabilitation guidelines state that PR2 offers similar gains in exercise capacity to PR1² based on small observational studies^{8,18} and two small randomized controlled trials.^{7,11} In our study, a third PR in the subgroup showed similar effect of PR3 compared to PR2, suggesting that beyond PR1, patients can expect a similar significant 6MWD response to PR. To our knowledge, we present the largest published cohort of patients with COPD undergoing a second and a third PR, which demonstrates the ongoing benefits of completing repeated PR. Although the reduced benefits may be attributed to advancing airflow obstruction over time, recent studies have demonstrated a reduced magnitude of improvement in 6MWD post-PR2 despite no overall change in spirometric values.¹⁹ It is also possible that advancing age may have contributed to an overall age-related decline in 6MWD.²⁰ However, in the National Emphysema Treatment Trial, COPD patients who had completed prior PR and had smaller improvement in 6MWD post-PR2, had no difference in age or lung function.²¹ We speculate that the worsening of airflow obstruction over the years, increasing comorbidities in COPD patients²², the ageing

process²⁰, and a potential learning effect from previous PR²¹, may all contribute to the reduced outcome of repeated PR.

Most importantly, we showed that 54% of non-responders to PR1 became responders to PR2 despite that, as previously emphasized, the effect of PR2 on the 6MWD is on average lower than the effect of PR1. This is promising for patients failing to show clinically significant improvement in 6MWD after PR1 who should not avoid repeating PR since they may show larger functional benefit. Meanwhile, when comparing the classes of response to repeated PR, we found that those under LTOT and the most dyspneic, were most likely to stay non-responders to repeated PR. Interestingly, we showed that a third PR can lead to a significant clinically response to PR in this population. **While in the present study it could be hypothesized that patients with severe dyspnea during exercise and under LTOT may have difficulties to perform exercise training during PR and therefore to show significant improvement in 6MWD post-PR, others have found that these patients showed larger multidimensional benefits (including symptoms, exercise performance, health and mood status) following PR²³. Overall, the mechanisms underlying non-response to PR in patients remain to be further elucidated²⁴⁻²⁵ in order to optimize the effect of PR in the COPD management strategy.**

A strength of our study is that it focused on a homogeneous population of COPD patients only who performed within the standardized setting of a single PR center up to three PR programs. We are the first to describe classes of response trajectories showing that a response to repeated PR is not systematically **identical**. A limitation of our study was that we focused on the 6MWT only to evaluate the effect of PR. **Other important outcomes of PR such as quality of life should be also considered in future studies in order to take into account the multidimensional response to PR²³.**

This study demonstrates that there are clinically significant benefits of repeated PR for patients with COPD, with improvements in functional exercise capacity following a second and a third PR in the majority of the patients. We validated our hypothesis that a large proportion of COPD patients non-responders to a first PR can become responders if PR were to be repeated. Further studies are needed to take into account other parameters than the 6MWT to characterize the effects of PR.

Guarantor: YAC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

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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FIGURE LEGEND

Figure 1. Flow chart showing the inclusion process for the analysis.

Figure 2 Mean (\pm standard deviation) 6-min walking distance (in % predicted) pre and post each pulmonary rehabilitation (PR) program: Panel A with 2 PRs over 2 years (n=190), and Panel B with 3 PRs over 3 years (n=62). Every point represents pre- or post-PR values. *significantly different compared to pre-PR1, +significantly different compared to post-PR1, \$significantly different compared to pre-PR2 (p < 0.05)

Figure 3. Alluvial plot showing distinct trajectories of 190 patients having performed two pulmonary rehabilitation (PR) programs based on their post-PR changes in 6-min walking distance (responder \geq 30 m, non-responder < 30 m).

Figure 4. Alluvial plot showing distinct trajectories of 62 patients having performed three pulmonary rehabilitation (PR) programs based on their post-PR changes in 6-min walking distance (responder \geq 30 m, non-responder < 30 m) compared to PR1 and PR2.

Figure 5. Alluvial plot showing distinct trajectories of 62 patients having performed three pulmonary rehabilitation (PR) programs based on their post-PR changes in 6-min walking distance (responder \geq 30 m, non-responder < 30 m) compared to PR1 + PR2.

TABLES

Table 1. Characteristics of the population pre-PR1 (n = 190)

		n (%) or median [Q1;Q3]
Sex	Male	89 (47)
	Female	101 (53)
Age (years)		66 [59;75]
LTOT (n, %)		45 (24)
BMI (kg·m ⁻²)		24.3 [20.8;31.2]
BMI classification	Underweight < 18.5	24 (13)
	Normal [18.5-25[77 (41)
	Overweight [25-30[36 (19)
	Obese [30-35[26 (14)
	Very obese ≥ 35	27 (14)
TLC (% predicted)*		109 [95;129]
FEV1 (% predicted)*		46 [33;63]
GOLD classifications*	Mild ≥ 80	14 (10)
	Moderate [50-80[57 (39)
	Severe [30-50[46 (31)
	Very severe < 30	30 (20)
Comorbidities	Arterial hypertension	71 (37)
	Other cardiovascular disease	33 (17)
	Chronic renal failure	33 (17)
	Sleep apnea	27 (14)
Reason for admission	Yearly follow-up	166 (87)
	Exacerbation	15 (8)
	Before or after surgery	9 (5)
Current smoker		26 (14)
Physically active		21 (17)
6MWD (m)		387 [310;470]
6MWD (% predicted)		65 [50;76]
Minimal SpO ₂ (%)		89 [85;92]
Maximal HR (bpm)		112 [100;121]
End-of-test dyspnea		5 [4;7]

Data are presented as n (%) or median [Q1;Q3]. LTOT, long term oxygen therapy, BMI, body mass index, TLC, total lung capacity, FEV1, forced expiratory volume in 1 s, **Physically active, score to the Ricci and Gagnon questionnaire ≥ 18**, 6MWD, 6-min walking distance; SpO₂, pulse oxygen saturation, HR, heart rate. *lung function data available for 147 patients.

Table 2. Six-minute walking test responses before and after the first and second pulmonary rehabilitation programs (n = 190)

	Pre-PR1	Post-PR1	Pre-PR2	Post-PR2
6MWD (m)	387 [310;470]	469 [378;535] *	395 [290;480] +	442 [370;526] * [§]
Minimal SpO ₂ (%)	88 [85;92]	87 [84;91]	88 [84;92]	87 [83;92]
Maximal HR (bpm)	112 [100;121]	118 [109;129]	113 [103;123]	117 [106;129]
End-of-test dyspnea	5 [4;7]	5 [3;7]	6 [4;7]	5 [4;7]

Data are presented as median [Q1;Q3]. 6MWD, 6-min walking distance; SpO₂, pulse oxygen saturation; HR, heart rate. * Significantly different compared to pre-PR1, + significantly different compared to post-PR1, [§]significantly different compared to pre-PR2 (p < 0.05)

Table 3. Results of the multivariable analysis of response to PR2 (n = 190)

	OR (CI95%)	p-value
Use of oxygen during the pre-PR1 6MWT	0.55 [0.31;0.97]	0.03
Being responder to PR1	21.1 [11.29;39.45]	< 0.01

OR, odds ratio; PR, pulmonary rehabilitation; 6MWT, 6-min walking test.

Table 4. Characteristics of the four classes based on repeated-PR responses.

	NR1-NR2 n = 18 (10 %)	NR1-R2 n = 23 (12%)	R1-NR2 n =44 (23%)	R1-R2 n =105 (55%)	p- value
Sex	13M/5F	8M/15F	19M/25F	49M/56F	0.10
Age (years)	66 [58;72]	68 [59;77]	70 [60;77]	65 [59;74]	0.55
LTOT (n, %)	8 (44)	7 (30)	11 (25)	22 (21)*	0.03
BMI (kg·m ⁻²)	24 [18;27]	23 [19;29]	26 [21;31]	24 [21;31]	0.52
TLC (% predicted)	117 [103;132]	111 [95;122]	105 [98;131]	109 [92;126]	0.60
FEV1 (% predicted)	40 [29;59]	45 [29;63]	52 [41;65]	49 [33;65]	0.41
<u>6-min walking test pre-PR1</u>					
6MWD (m)	348 [309;546]	450 [349;513]	388 [290;440]	377 [310;455]	0.23
6MWD (% predicted)	66 [49;76]	76 [49;88]	65 [53;74]	63 [50;75]	0.24
Minimal SpO ₂ (%)	89 [85;93]	90 [86;93]	87 [84;91]	89 [85;92]	0.11
Maximal HR (bpm)	122 [104;137]	115 [97;127]	108 [98;120]	109 [101;118]	0.13
End-of-test dyspnea	6 [5;7]	6 [4;7]	5 [3;6]	5 [4;7]	0.04

Data are presented as n (%) or median [Q1;Q3]. R, responder; NR, non-responder; LTOT, long term oxygen therapy; BMI, body mass index; TLC, total lung capacity; FEV1, forced expiratory volume in 1 s; 6MWD, 6-min walking distance; SpO₂, pulse oxygen saturation; HR, heart rate. * The difference is significant vs NR1-NR2 (p < 0.05 with Bonferroni correction).

Table 5. Six-minute walking test responses before and after 3 pulmonary rehabilitation programs (n = 62)

	Pre-PR1	Post-PR1	Pre-PR2	Post-PR2	Pre-PR3	Post-PR3
6MWD (m)	415 [325;480]	479 [410;520]*	418 [346;477]	465 [400;518]*	415 [330;463]	468 [393;520]*
Minimal SpO ₂ (%)	88 [84;91]	88 [83;91]	89 [83;92]	87 [82;91]	90 [81;93]	87 [82;91]
Maximal HR (bpm)	113 [103;122]	119 [111;131]	116 [104;124]	123 [111;128]	114 [108;125]	120 [108;129]
End-of-test dyspnea	6 [4;7]	5 [4;7]	6 [4;7]	6 [4;7]	6 [5;7]	6 [4;7]

Data are presented as median [Q1;Q3]. 6MWD, 6-min walking distance; SpO₂, pulse oxygen saturation; HR, heart rate. * Significantly different from pre-PR p < 0.05 with Bonferroni correction

Figure 1.

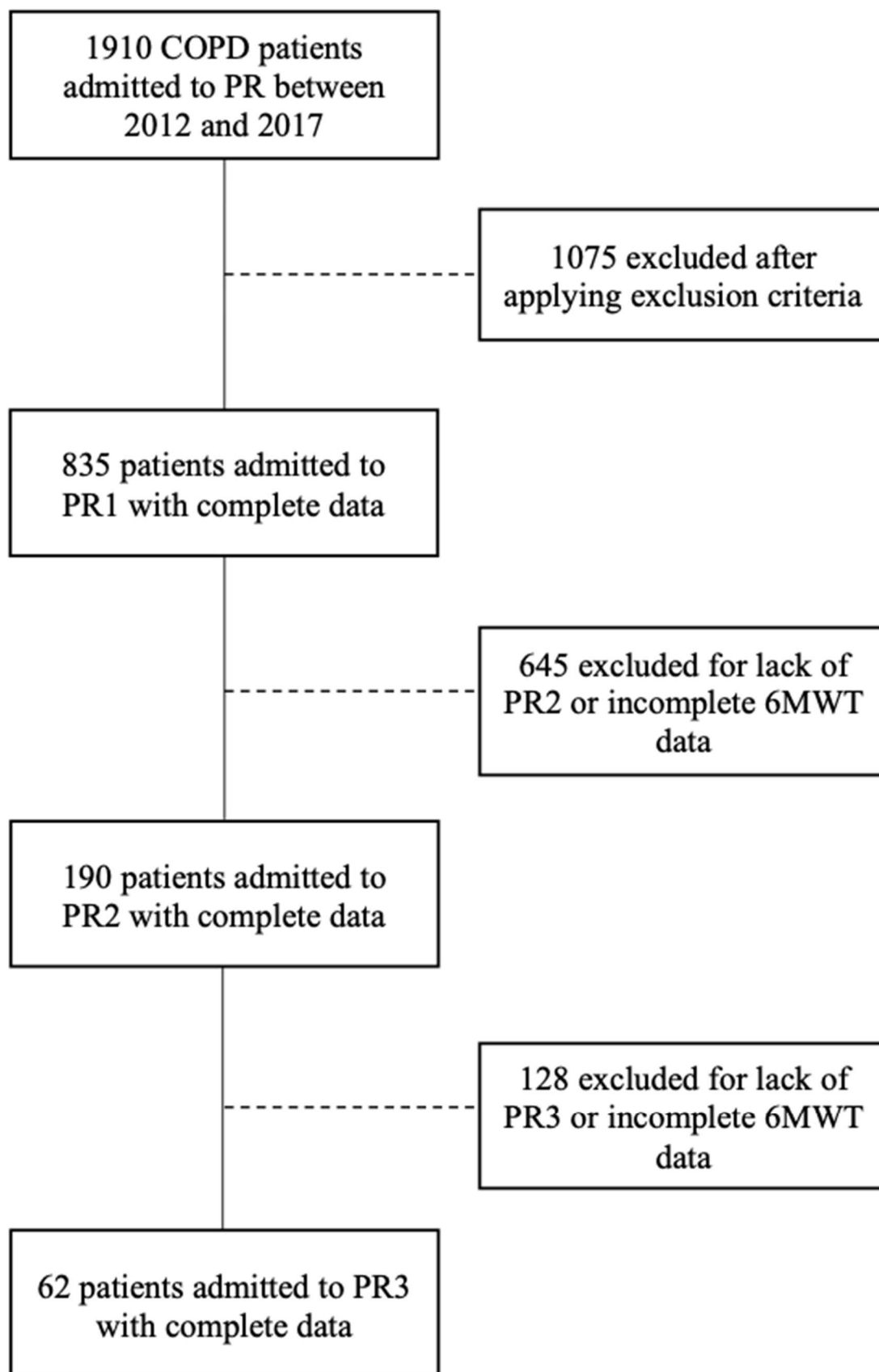


Figure 2.

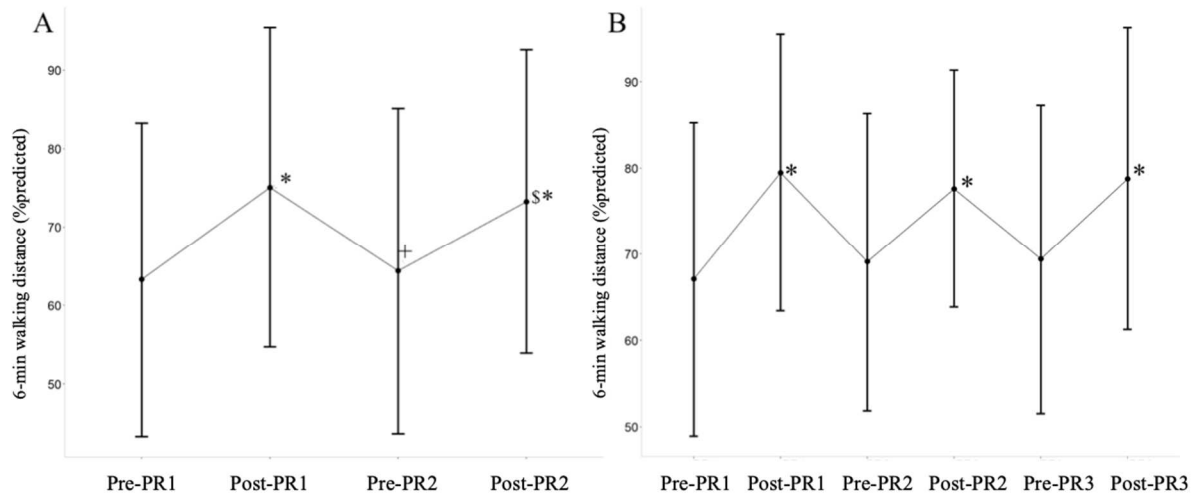


Figure 3.

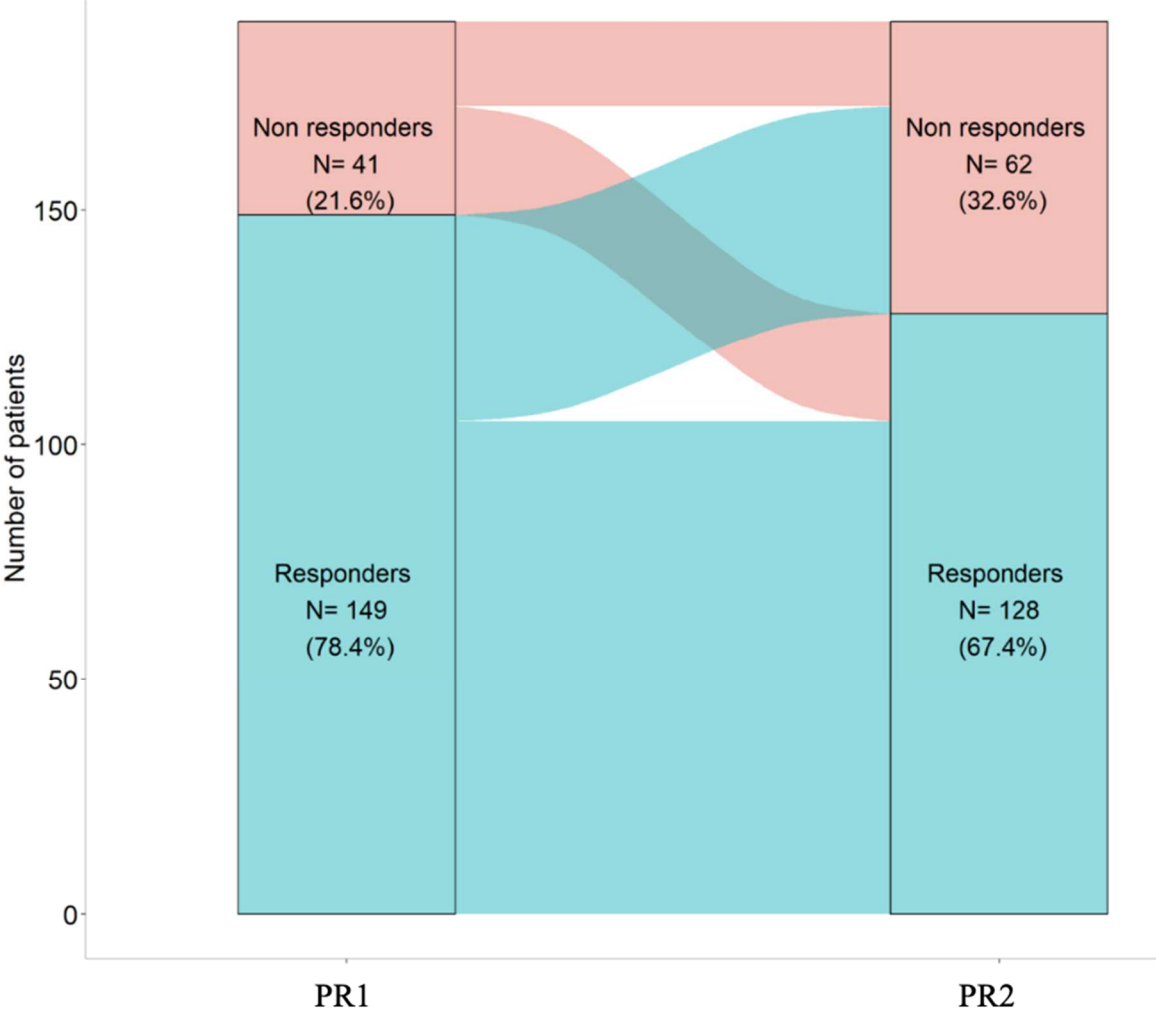


Figure 4.

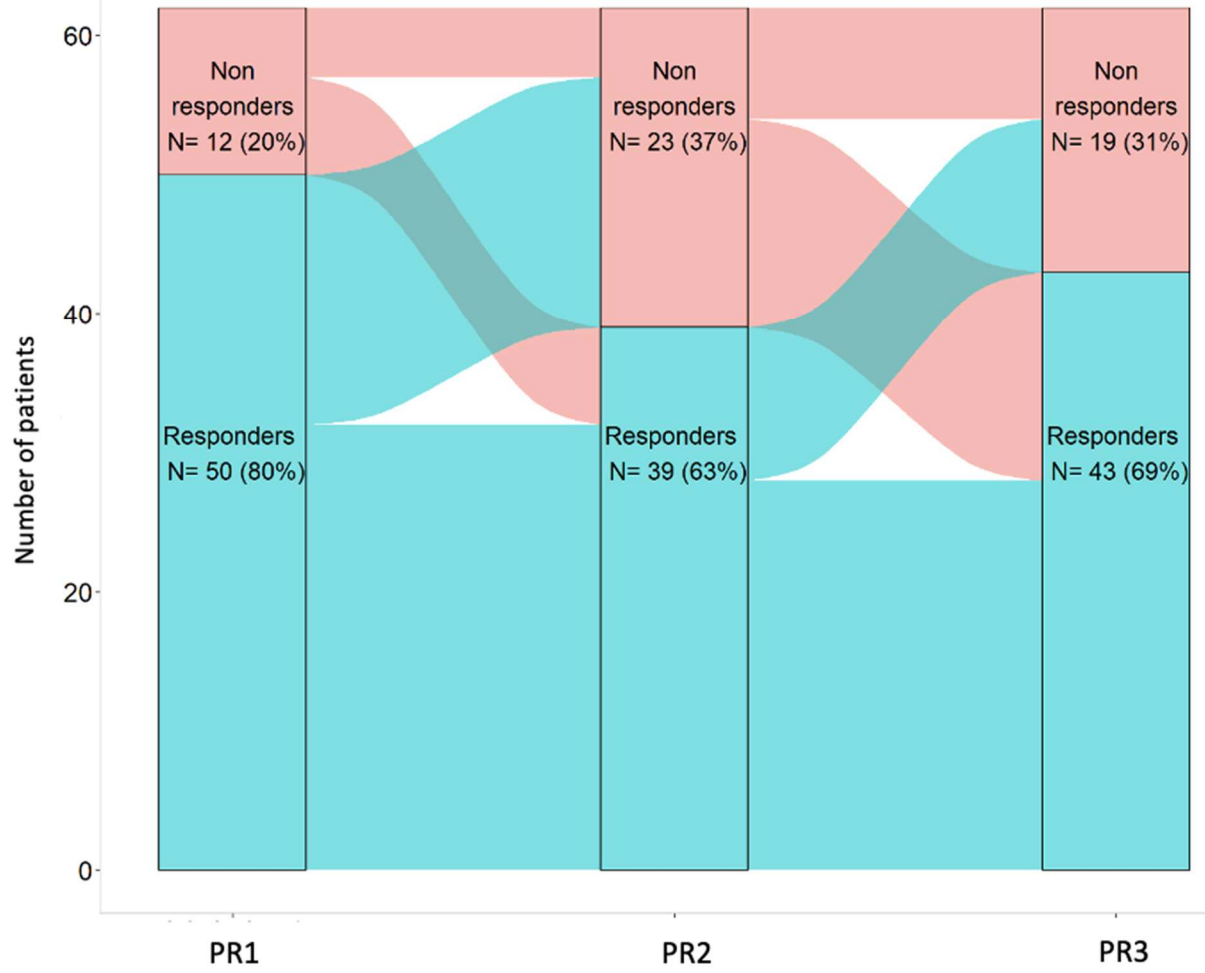


Figure 5.

