Timing of Pulmonary Rehabilitation in Readmitted Patients with Severe Chronic Obstructive Pulmonary Disease: a Randomized Clinical Trial

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Abstract

Early pulmonary rehabilitation (PR), started during hospitalization or within the first month after discharge, has been shown to reduce exacerbations and improve health-related-quality of life (HRQoL) and exercise capacity. However, no randomized clinical trials (RCT) have compared the efficacy of PR started during hospitalization (DHPR) to PR initiated one month post-hospitalization (PHPR). We conducted an RCT to compare DHPR to PHPR in severe patients with COPD readmitted for exacerbations in a tertiary hospital setting. Patients were randomized to receive three months of DHPR or PHPR. Outcomes were assessed at completion of the PR programme and at months 3 and 9. A total of 53 patients (26 DHPR and 27 PHPR) were included. There were no between-group differences in the number of exacerbations (mean, 3.62 vs. 3.04 in the DHPR and PHPR groups, respectively; p=0.403). Dyspnoea in activities of daily living, exercise capacity, and all HRQoL parameters improved in the PHPR group. In the DHPR group, improvement was observed only for some HRQoL parameters. All gains in both groups were lost during follow-up. More adverse events were observed in the DHPR group (20 vs 5, p=0.023), although none of these were clinically significant. In this sample of patients with severe COPD readmitted to the hospital for exacerbations, both approaches to PR were safe, but PHPR yielded better outcomes overall. These findings suggest that, PR should be initiated in patients with severe COPD only after hospital discharge when the patients' clinical condition has stabilized.

242 Words

Key words: Severe COPD patients; Hospital Pulmonary Rehabilitation; Home Pulmonary Rehabilitation; Exacerbations**.**

INTRODUCTION

In patients with chronic obstructive pulmonary disease (COPD), exacerbations are associated with deterioration in the patients' condition and a worse prognosis, thus significantly increasing healthcare costs [1]. Published reports [1] estimate that one-third of patients hospitalized for COPD are readmitted at least once within the first year after discharge, and many are readmitted more than once. The efficacy of pulmonary rehabilitation (PR) in patients with COPD is supported by a strong body of evidence [2]. PR has been shown to reduce symptoms, increase exercise capacity, and improve health-related quality of life (HRQoL) [2,3]. In addition, some evidence (moderate strength) suggests that PR may reduce exacerbations, thereby lowering treatment-related costs [4].

The optimal time to initiate PR to achieve maximal efficacy is unknown, and this uncertainty presents an important challenge for clinicians [2,3]. Although clinical guidelines recommend waiting at least 3-4 weeks after hospital discharge before starting PR [5], in recent years, several authors have suggested that it could be more effective to begin PR earlier, while the patient is still hospitalized or shortly after discharge [6-11]. However, the results of this approach have been mixed and therefore controversial. One systematic review found that PR initiated during hospitalization yielded the same benefits—fewer exacerbations, improved HRQoL, and increased exercise capacity—as PR started four or more weeks after discharge [6]. That review also found that this approach was associated with few adverse events, none of which were serious. More recently, a meta-analysis [7] that included 13 randomized controlled trials (RCT) found similar results for early PR, including a decrease in mortality rates, leading the authors to recommend early PR programmes. However, PR was initiated during hospitalization in less than 40% of the patients in those studies (versus 60% who started PR within 4 weeks of hospital discharge). By contrast, the largest RCT [8] conducted to date to compare moderately extensive PR administered during hospital admission to usual care found that PR in hospitalized patients did not reduce the risk of readmission, nor did it improve physical function over the following 12 months. Importantly, all of the aforementioned studies compared PR with usual care at different time points after exacerbations, but only two RCTs [9, 12] have compared PR programmes initiated at different timepoints, and neither found that timing of PR had any effect on outcomes.

In this regard, most of the published data supporting early PR in patients with COPD are based on studies conducted in patients with moderate disease [6,7]. In patients with severe COPD, there is a notable lack of data and thus it is not clear whether patients with severe COPD would benefit from early PR or not.

In this context, the aim of the present clinical trial was to compare the effects of PR initiated during hospitalization (DHPR) to PR initiated one month post-hospitalization (PHPR), which is the recommended approach in most clinical guidelines. Our main aim was to determine whether the timing of pulmonary rehabilitation influenced exacerbations, exercise capacity, functional status, HRQoL, and adverse effects in patients with severe COPD readmitted to hospital due to an acute exacerbation.

MATERIAL AND METHODS

Study design

In this clinical trial, patients admitted to our tertiary care hospital for an acute exacerbation of COPD were randomized to receive three months of pulmonary rehabilitation initiated during hospitalization (DHPR) or at one month post-hospitalization (PHPR).

Inclusion criteria were as follows: 1) diagnosis of severe COPD (stage III or IV, GOLD criteria [1]) readmitted to the hospital for acute exacerbation and 2) hospitalized at least twice in the previous year (between July 2014 and April 2016). Patients were enrolled in the trial on the first day of admission to the Pneumology Department. Exclusion criteria were as follows: 1) participation in a PR programme in the previous 6 months, 2) inability to properly perform the physical exercises prescribed in our PR programme (e.g., due to severe comorbidities or end-of-life situations), 3) cognitive impairment, 4) residence located outside of the hospital's health care service area, or 5) hospitalization in another ward.

The hospital's clinical research ethics committee approved the study (approval code: IIBSP-EXA-2013-04). All patients provided written informed consent. Randomized clinical trial registered at ClinicalTrials.gov (identifier NCT02190461).

Pulmonary rehabilitation programme

The programme for both groups consisted of two educational sessions to provide patients with basic knowledge of pulmonary disease (COPD), and 23 sessions of respiratory physiotherapy, including aerobic strength training.

Patients randomized to the DHPR group started daily PR sessions on the second day after admission and continued until discharge to home, after which they continued receiving PR at home until completing the full 12-week PR programme. Patients randomized to the PHPR group started the physiotherapy sessions at home one month

after discharge and continued the sessions until they had completed the 12-week programme. In both groups, the home PR programme was supervised by a trained physiotherapist. Patients in the DHPR group who were readmitted to the hospital during the 12-week programme continued to receive PR, regardless of their location (i.e., hospitalized or at home). By contrast, patients in the PHPR group received PR only at home, not during the hospitalizations, but completed all 23 sessions (for details, see the study schedule in the supplementary material).

Outcomes

Study variables were assessed at admission (baseline), immediately after completion of the PR programme (PR0), and at months 3 (PR3) and 9 (PR9) after completing the PR programme. At each evaluation point, we assessed and registered the following variables: 1) Number of exacerbations according to GOLD criteria [1], classified as severe (requiring hospitalization) or non-severe. The main study outcome measure was severe exacerbations during follow up. Exacerbations were detected by checking patient medical records (hospital and primary care records), and also verified during the patient interviews conducted during trial-related hospital visits; 2) dyspnoea during activities of daily living (ADL), which was assessed with the original Chronic Respiratory Questionnaire (CRQ) [13]. The CRQ allows the patient to indicate the five ADLs that induce dyspnoea. A change of 0.5 or more points was considered to be the minimal clinically important difference (MCID) [14]; 3) Exercise capacity, assessed with the 6-minute walking test (6MWT) in accordance with the American Thoracic Society guidelines [15]. For this variable, the MICD was defined as an increase of ≥ 26m on the 6MWT [16]; 4) HRQoL, measured with the COPD Assessment Test (CAT) [17] and the self-administered standardized Chronic Respiratory Questionnaire (SAS-CRQ) [18]. For the CAT, the MCID was a change ≥ 2 points. On the SAS-CRQ, the MCID was a change ≥ 0.5 points per area [14]; 5) Functional status was assessed with the Barthel index [19] at three time points: prior to hospital admission (obtained retrospectively from patient interviews conducted during the stable phase of the disease), at admission, and at completion of PR (PR0); and 6) adverse events, defined as any event (patient-reported symptoms or observations or measurements made by the physiotherapist) that required interruption of PR. In all cases, outcomes were assessed by the same trained

nurses and physiotherapists during scheduled visits to the hospital. These professionals were not blinded to the treatment allocation.

Statistical analysis

The sample size was calculated according to the expected reduction in hospital admissions due to COPD exacerbations (study endpoint). To detect a mean difference of ≥ 1.07 exacerbations with a common standard deviation of 1.40 [20,21] and a loss to follow-up of 10%, a total of 30 subjects were required per group. An external statistician (not involved in the study) used the R statistical programme v.3.3 to generate a balanced simple random allocation sequence in blocks. During the recruitment period, patients were centrally allocated, on a 1:1 basis, to receive DHPR or PHPR. Clinicians were informed of the treatment allocation by telephone at the time of assignment on the first day of admission. The study investigators, outcome evaluators, and participants were aware of the administered treatment.

The analysis was carried out on an intention-to-treat basis. To compare variables within and between groups, we used paired and independent bivariate tests, respectively. Mixed linear regression models adjusted for baseline covariates were used to compare the groups in terms of changes in the study variables. We used the log-rank test and Cox proportional hazards risk analysis methods to compare the time to the first exacerbation. Multivariate analyses were adjusted for the covariates that differed significantly between groups at baseline (i.e., age; smoking status; length of hospital stay; smoking during PR; BI score at admission; CRQ emotional function; and CRQ fatigue). We used the R statistical software programme, v. 3.3 to perform all analyses.

RESULTS

Of the 185 patients identified as potential candidates for study inclusion, 132 did not meet all inclusion criteria. The 53 patients who met the inclusion criteria were randomized to undergo DHPR (n=26) or PHPR (n=27) (Figure 1). The most common reasons for exclusion were: 1) residence outside the catchment area (n=58), 2) presence of very severe comorbidities that impeded the patient's capacity to exercise (n=33), 3) cognitive disorders (n=15), and 4) refusal to sign the informed consent form (n=9).

Of the 53 patients initially included in the trial, nine were excluded from the final analysis because they did not complete the PR programme (due to death, withdrawal, or onset of severe disease) programme. The final analysis included 21 of the 26 patients (80.8%) initially included in the DHPR group and 23 of the 27 patients (85.2%) in the PHPR group. These 44 patients all completed the minimum number of PR sessions. Overall, patients in both groups completed a mean of 21.1 (1.44) home sessions over a mean of 3.0 (0.34) months. During the course of the PR programme, 24 (54.6%) patients required temporary interruptions due to hospitalization, respiratory symptoms that prevented PR, or absence from home. There were no significant differences between the groups with regard to the number of PR sessions.

Several patients in both groups (3 and 4 patients in the DHPR and PHPR groups, respectively) missed some of follow-up appointments. The final assessment (performed at the end of the follow-up period) was completed by 18 patients in the DHPR group and 19 in the PHPR group. Mean follow-up was 11.5 (2.89) months versus 12.6 (2.27) months in the DHPR and PHPR groups, respectively. The overall mortality rate at the end of follow-up was 7.7% and 11.1%, respectively, in the DHPR and PHPR groups (p=0.67).

Table 1 shows the baseline characteristics of the 44 patients who completed the PR programme. In both groups, patients had severe airflow obstruction (FEV_1 < 35%, high residual volume), multiple comorbidities, dependence for ADL, and poor HRQoL. More than 50% of patients were on long-term oxygen therapy. At baseline, the groups did not differ significantly in terms of age, sex, spirometry results, exercise capacity, or number of exacerbations in the previous year. However, at the start of PR, the DHPR

group had worse Barthel index scores and worse scores on the fatigue and emotional function domains of the CRQ.

Table 2 shows the exacerbations registered during follow-up. Exacerbations were common in both groups, but without significant between-group differences. Compared to the previous year, there were no significant differences within or between groups in the mean number of total or severe exacerbations per patient.

Figure 2a shows the Cox regression model comparing the time to the first exacerbation among patients in the two groups. Half of the patients had at least one exacerbation after 2.57 months (DHPR group) and 2.33 months (PHPR group); these differences were not significant before or after adjusting for baseline differences: the adjusted hazard ratio (95% confidence interval) for a first exacerbation in the DHPR group versus the PHPR group was 0.454 (0.192-1.077; p=0.073). The pattern of exacerbations during follow-up was similar in the two groups.

Figure 2b shows the intensity of dyspnoea during ADL over the follow-up period. In the PHPR group, decreases in dyspnoea intensity beyond the MCID were observed at PR0 and PR3. The decrease in dyspnoea intensity in the DHPR group did not reach the MCID.

In the six-minute walk test, patients in the PHPR group reached the MCID for mean distance walked at PR0 and PR3; by contrast, the MCID was not reached in the DHPR group (Figure 2c).

The CAT score at PR0 showed a decrease in respiratory symptoms in both groups, but only the PHPR group reached the MCID (Figure 3). At PR3 and PR9, neither group reached the MCID for improvement in CAT scores. In the DHPR group, improvements in the mean values on the CRQ reached the MCID for fatigue and emotional function at PR0 and PR3, as well as in mastery at PR0 and PR9. In the PHPR group, increases in the mean values exceeded the MCID for dyspnoea and fatigue at PR0, emotional function at PR0 and PR3, and mastery at PR0, PR3, and PR9.

Baseline functional status (pre-hospitalization Barthel index scores) was similar in the two groups, but lower in the DHPR group at the start of PR (Table 1). At the end of PR, the DHPR group showed virtually no functional improvement while the PHPR group presented some functional gain. Therefore, the between-group difference was greater at completion of the full PR programme, with a lower Barthel index, in the DHPR group ($p=0.024$).

Adverse events were observed programme in 13 patients, mostly in the DHPR group (n=9 patients). More adverse events, especially dyspnoea and desaturation, were observed in the DHPR group ($p=0.023$) (Table 3). None of the adverse events required discontinuation of PR.

Discussion

This trial was performed to compare PR initiated during hospitalization (DHPR) versus PR started one month after discharge (PHPR) in patients with severe COPD readmitted for an acute exacerbation. Our findings show that PR performed during hospitalization did not reduce the number of exacerbations versus post-hospitalization PR, nor did early PR improve dyspnoea during ADL, exercise capacity, functional status, or HRQoL measured with the CAT. PR performed during hospitalization yielded benefits only on a few HRQoL dimensions of the SAS-CRQ questionnaire (e.g. fatigue, emotional function and mastery) up to 3 months after completion of the PR programme. PR started after hospital discharge did not reduce the number of exacerbations, but did lead to better, longer-lasting results in secondary outcome measures (dyspnoea intensity during ADL, six-minute walk test, functional gain, CAT global score, and SAS-CRQ dimensions of dyspnoea and mastery). The good adherence to the PR programme and the minimal clinical impact of adverse effects in both groups were noteworthy.

This trial was performed to compare PR initiated during hospitalization versus PR started one month after discharge in patients with severe COPD readmitted for an acute exacerbation. Our findings show that PR performed during hospitalization produced greater functional gains than PR after discharge only in several HRQoL variables (e.g. fatigue, emotional function and mastery) up to 3 months after completion of the PR programme. However, PR did not reduce the number of exacerbations, nor did it improve dyspnoea during ADL, exercise capacity, or functional status. The good adherence to the PR programme and the minimal clinical impact of adverse effects in both groups were noteworthy.

The recently published guidelines of the European Respiratory Society (ERS)/American Thoracic Society (ATS) [5] noted the unmet need to establish the optimal time at which PR should be initiated to achieve the greatest benefit. However, until now, no studies have sought to determine the best time to start PR in patients admitted for exacerbations. To our knowledge, this is the first RCT to specifically compare PR during hospitalization to PR one month after hospitalization. In the existing systematic reviews [6,7], most of the trials started PR two or more weeks after hospital discharge, and most compared early PR to usual care. To our knowledge, the only study similar to

ours was the trial carried out by Kjaergaard et al. [9], who compared PR programmes initiated at two time points after hospital discharge (2 weeks vs. 2 months).

In our trial, nearly 90% of the patients had at least one exacerbation (mean ≥ 3) during follow-up. The exacerbations started early and occurred uniformly (i.e., without any definable pattern) over the follow-up period. However, we did not observe any significant trend toward more exacerbations in the DHPR group. Compared to the year prior to the intervention, there was no significant trend towards fewer severe exacerbations, especially in the DHPR group. Greening et al. [8] conducted a clinical trial to compare PR started within 48 hours of hospital admission to usual care, finding that early PR did not decrease the risk of readmission. A systematic review [6] carried out to evaluate the impact of early PR vs usual care on exacerbations found that PR had a significant but variable impact on exacerbations, with a high degree of heterogeneity between studies. A more recent meta-analysis [7] concluded that early PR reduces the risk of mortality and hospital readmissions. However, more than 50% of the studies in that meta-analysis started PR ≥ 2 weeks after hospital discharge whereas "early" PR in our study was initiated during hospitalization in all patients in that group. To our knowledge, only two RCTs have compared PR programme at two different time points. In one study, Kjaergaard et al. [9] compared PR initiated 2 weeks after discharge to PR started 2 months post-discharge. In another study, Puham et al. [12] compared PR initiated before hospital discharge vs. PR initiated at 6 months post-discharge. Both of those studies found no between-group differences in survival or readmissions.

One concern about early PR is the risk of higher mortality rates. Greening et al. [8] found that 12-month mortality rates were higher in patients who received early PR versus those who received usual care. However, this finding was controversial because the higher mortality was not clearly associated with early PR given that the deaths occurred 5 months after patients had completed the PR programme [5]. The mortality in our cohort was within the ranges reported in similar studies and systematic reviews [6,7,9]. We found no significant differences in mortality between the groups, suggesting that mortality rates are probably more closely related to the severity of disease itself rather than to the specific PR programme or the timing thereof.

In our study, we found that the DHPR group had less favourable outcomes than the PHPR group in terms of dyspnoea during ADL, exercise capacity, respiratory symptoms, self-perceived dyspnoea, and mastery. Although the reasons for this difference are not clear, we hypothesize that they could be attributable to overtreatment related to the early initiation of PR before the patients had achieved clinical and functional stability, and from continuing PR even during exacerbations. These findings, together with the trend towards more consistent benefits in the PHPR group, suggest that it may be more efficacious and safer to delay PR until one month after hospital discharge in patients with severe COPD.

The scant clinical improvement observed in both groups in our study contrasts with the large benefits of early PR reported by other authors [6-10]. However, this difference can probably be explained by the important differences between our patients and those included in other studies, in which the patients were, on average, significantly younger (mean age 68 vs. 74 years) with less severe COPD (FEV_1 >36% vs. 32%). The greater disease severity in our sample is further evidenced by the number of hospital admissions (≥ 2) in the year prior to the study, the high proportion (>50%) on home oxygen therapy, and the high comorbidity rate in our sample. As Franssen et al. [22] demonstrated, comorbidities can reduce patients' capacity to respond to PR, which is why many studies exclude patients with comorbidities [23]. Moreover, whereas most other studies have focused on assessing the effects of high-intensity PR programmes, we applied a low-to-moderate intensity programme due to the severity of COPD in our cohort. Thus, it seems reasonable to conclude that the small benefits observed in our sample can be primarily attributed to two factors: 1) the greater disease severity and 2) the use of low intensity PR. Based on our findings in the context of the published literature, we agree with the recommendations of the main clinical guidelines [5] that PR should be started from 3 to 8 weeks after hospital discharge following an exacerbation.

In patients in our study with stable COPD before hospitalization, functional status (Barthel index) was similar in the two groups. However, at initiation of PR, functional status was lower in the DHPR group, probably because these patients were still hospitalized when PR started. At completion of the PR programme, there was no significant improvement in functional status in the DHPR group; by contrast, the

Barthel index scores in the PHPR group were consistent with those observed in patients with stable disease. Furthermore, the PHPR group showed greater clinical improvement on the 6MWT. These findings provide further support suggesting that it is better to wait until patients have stabilized before starting PR.

While relatively few adverse events were observed in the PHPR group, dyspnoea and desaturation were common among patients in the DHPR group. Importantly, none of these events were severe enough to require interrupting PR, and all were resolved by reducing loads and then progressively increasing them when feasible. The adverse events observed in the DHPR group may be related to the tail of exacerbation. Notably, only one of the four RCTs (Tang et al.) described in the ERS/ATS clinical guidelines [5] reported adverse events, affecting 19% of the patients but with only one serious adverse event.

In our study, adherence to the PR programme was good in both groups (80-85%, in the upper range of published studies) [6,7], most likely because PR was performed at home under the direct supervision of the physiotherapist.

Study limitations

The main limitation of this study is the sample size, which was less than estimated due to the unexpectedly large number of patients who failed to meet eligibility criteria. Consequently, this reduces the strength of the statistical analysis. Indeed, this is why the main focus of our analysis was on identifying minimal clinically-important differences between the treatment groups.

It is worth emphasizing that the clinical characteristics of the patients who withdrew from the study prior to the end of follow-up (and therefore excluded from the final analysis) were similar to those included in the final sample, except for 3 variables (more hospital stays, lower exercise capacity [6MWT], and lower emotional function scores [CRQ]), see table in the supplementary material). Finally, another potential study limitation is the COPD severity in our sample, which prevented us from administering high intensity PR, which influenced the potential benefits of this therapy and therefore the outcomes of the study.

Conclusion

This study shows that initiating pulmonary rehabilitation in patients with severe COPD and hospital readmissions during hospitalization was relatively safe. However, this approach appeared to be less effective in reducing exacerbations and improving secondary outcomes than starting PR 30 days after discharge.

These findings, considered in the context of the current body of evidence, suggest that, in patients with severe COPD and comorbidities, it is better to initiate PR after hospital discharge when the patient's clinical condition has stabilized.

3836 words

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Conflicts of interest

The authors certify that there are no conflicts of interests.

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Author Contributions

All authors played a role in the clinical investigation and in writing the manuscript. MRG was the principal investigator and developed the original idea for the study. GFF and LPDR applied the PR programme and evaluated the outcomes together with FMV. All authors contributed to data collection. IBR and DOV analysed the data.

Supplementary Material

This article includes supplement files available online.

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Table 1. Patient characteristics at baseline according to study group.

	DHPR (n=21)	PHPR (n=23)	p-value
Age, years	74.0 (7.1)	71.3 (9.1)	0.282
Sex, n (%) male	19 (81.0)	16 (78.3)	1.000
Current smoker status, n (%)	7 (33.3)	6 (26.1)	0.599
FEV_1 (%)	31.7 (13.3)	29.2 (10.8)	0.518
FVC (%)	61.3 (16.1)	65.4 (18.9)	0.438
FEV_1/FVC (%)	36.7 (12.3)	33.3 (11.3)	0.369
TLC (%)	118.5 (27.7)	114.9 (24.2)	0.674
RV (%)	173.3(63.8)	184.9 (64.8)	0.588
KCO (%)	63.6 (20.6)	59.3 (27.6)	0.433
PaO_2, mmHg	62.7 (11.2)	62.6 (12)	0.973
$PaCO_2$, mmHg	46.8 (9.6)	47.9 (11.5)	0.736
Exacerbations in the previous year	2.9 (1.7)	3.0 (2.6)	0.888
Barthel Index in stable phase	94.6 (6.8)	97.8 (5)	0.076
at the admission of PR	89.0 (7.7)	94.7 (7.4)	0.016
at the end of PR	90.6 (13.1)	97.6 (5.6)	0.024
mMRC	2.8 (0.8)	2.9 (0.9)	0.815
LTOT, n (%)	11 (55.0)	12 (54.5)	1.000
Charlson index	2.9 (1.4)	2.9 (1.7)	0.979
6MWT, meters	237.3 (94.8)	229.05 (79.7)	0.757
CAT Global Score	23.6 (6.4)	20.7 (6.5)	0.154
CRQ original dyspnoea	2.9 (1.0)	3.3 (0.9)	0.184
CRQ dyspnoea	3.6 (1.2)	3.8 (1.0)	0.484
CRQ fatigue	2.8 (1.1)	3.5 (0.7)	0.018
CRQ emotional function	3.2 (0.9)	4.1 (1.0)	0.003
CRQ mastery	3.5 (1.1)	3.8 (1.1)	0.481

Values are given as means (standard deviation) or numbers (percentages) as appropriate.
DHPR: Pulmonary Rehabilitation (PR) initiated during hospitalization; PHPR: PR initiated post-hospitalization; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; TLC: Total lung capacity; RV: Residual volume; Kco: capacity of diffusion oxygen; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure; mMRC: Modified Medical Research Council; LTOT: Long-term oxygen therapy at home; 6MWT: Six minute walking test; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; CRQ: Chronic respiratory questionnaire.

Table 2. Exacerbations during the 12-month follow-up period by study group.

	DHPR (n=21)	PHPR (n=23)	p-value
Total exacerbations			
Patients with ≥1 exacerbation, n (%)	19 (90.5)	21 (91.3)	0.368
Total number of exacerbations, (n)	76	70	---
Exacerbations per patient, mean (SD)	3.6 (2.2)	3.0 (2.3)	0.403
Increase from previous year, mean (SD)*	+0.7 (2.2)	+0.04 (3.0)	0.407
Severe exacerbations			
Patients with ≥1 severe exacerbation, n (%)	16 (69.6)	13 (61.9)	0.291
Total number of severe exacerbations, (n)	38	30	---
Severe exacerbations per patient, mean (SD)	1.8 (1.5)	1.3 (1.7)	0.311
Increase from previous year, mean (SD)*	-0.2 (1.9)	-0.7 (1.9)	0.427

Values are given as numbers (n) and (percentages), or means and (standard deviations, SD) as appropriate. PR= pulmonary rehabilitation.
DHPR: Pulmonary Rehabilitation (PR) initiated during hospitalization; PHPR: PR initiated post-hospitalization.
* p-values for inter-annual intragroup mean differences were not statistically significant.

Table 3. Adverse events observed during pulmonary rehabilitation, by study group.

	DHPR (n=21)	PHPR (n=23)	p-value
Patients with AE, n (%)			
At least one	9 (42.9)	4 (17.4)	0.262
0	12 (57.1)	19 (82.6)	0.432
1	4 (19.0)	3 (13.0)	
2	3 (14.3)	1 (4.4)	
>3	2 (9.5)	0 (0.0)	
AE, n / mean (SD)	20 / 1.0 (1.4)	5 / 0.2 (0.6)	0.023
Type of AE, n / mean (SD)			
Dyspnoea	12/ 0.6 (0.9)	1/ 0.04 (0.2)	0.007
Saturation < 90%	10/ 0.5 (0.8)	2/ 0.1 (0.4)	0.037
Pain	5/ 0.2 (0.7)	1/ 0.04 (0.2)	0.210
Diaphoresis	0.0 (0.0)	0.0 (0.0)	---
Paleness	1/ 0.1 (0.2)	0.0 (0.0)	0.301
Fading	1/ 0.1 (0.2)	1/ 0.04 (0.2)	0.949
FC max	0.0 (0.0)	0.0 (0.0)	---
Others	4/ 0.2 (0.4)	2/ 0.1 (0.3)	0.329

Values are numbers (n), percentages (%), means and standard deviations (SD) as appropriate.
DHPR: Pulmonary Rehabilitation (PR) initiated during hospitalization; PHPR: PR initiated post-hospitalization; AE: Adverse events. FC max: achievement of the maximum heart rate.

Titles of figures:

Figure 1. Flow chart of the study.

Figure 2. Comparison of clinical results among patients in the two intervention groups.

Figure 2a. Time to first exacerbation after completion of the pulmonary rehabilitation programme (lines), and repeated exacerbation episodes (dots), by study group.

Figure 2b. Dyspnoea in activities of daily living (dyspnoea area in the original CRQ original dyspnoea) during follow-up, by treatment group.

Figure 2c. Exercise capacity during follow-up (6-minute walking test), by study group.

Figure 3. Health-related quality of life during follow-up (CAT and SAS-CRQ).