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Assessment of a Domiciliary Integrated Pulmonary Rehabilitation Program for Patients with a History of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective 12-Month Observational Study

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Background: Integrated pulmonary rehabilitation (PR) in chronic obstructive pulmonary disease (COPD) may prevent acute exacerbations of COPD (AECOPD). The aim of this study was to evaluate the effectiveness, before and 12 months after, the use of an integrated PR program in patients discharged from hospital for AECOPD.

Material/Methods: A retrospective observational clinical study included patients diagnosed with COPD who participated in a domiciliary integrated PR program that included a weekly phone interview supervised by a respiratory team. A six-minute walk test (6MWT), COPD assessment test (CAT), and the modified Medical Research Council scale (mMRC) were evaluated every three months.

Results: Of the 303 eligible patients, 267 patients (88.1%), with a mean age of 64.9±8.7 years, a mean FEV_1 percentage predicted of 48.8±12.9%, successfully completed the 12-month study program and achieved a significant improvement in their clinical performance with a significantly reduced frequency of episodes of EACOPD (3.1±1.7 *vs.* 2.0±1.4) (p<0.001), a significant reduction in emergency department visits (2.5±1.5 *vs.* 1.2±1.1) (p<0.001), and significantly reduced episodes of hospitalization (2.0±1.2 *vs.* 1.4±1.2) (p<0.001). Significant patient benefits were found during the 12-month study, on CAT, mMRC, and patient well-being when compared with the end of the study after 12 months (p<0.001).

Conclusions: A multidisciplinary integrated PR program maintained a significant clinical improvement, in patients with COPD by reducing episodes of AECOPD, CAT, mMRC, emergency hospital admissions, and improved patient well-being, for the duration of the program.

MeSH Keywords: Activities of Daily Living • Disease Progression • Patient Care Management • Pulmonary Disease, Chronic Obstructive

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Background

According to the 2018 Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) guidelines [1], chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation caused by chronic inflammation of small airways, resulting in chronic respiratory symptoms. COPD is not only a disease of the lungs but is also associated with recognized co-morbidities and systemic diseases [2]. In 2007, the prevalence of COPD was estimated to be 8.2% in the population aged 40 years or more in China [3]. Recently, COPD has been reported to rank as the third most common cause of death in China, according to the results of Global Burden of Disease Study [4]. The main reason for the increased morbidity and mortality from COPD in China might be due to an acute exacerbation of COPD (AECOPD), which is mainly triggered by the viral infection of upper respiratory tract [5], bacterial infections of the trachea and bronchi [6], as well as environmental air pollution and atmospheric particulate matter (PM2.5) [7]. To reduce the burden of the disease, it is important to develop comprehensive healthcare strategies in communities to prevent the AECOPD and the associated morbidity and reduced quality of life, increase in hospital admissions, and patient mortality.

Based on evidence from previously published studies, an integrated pulmonary rehabilitation (PR) program has been recommended for patients with stable COPD and should be provided following AECOPD, within two weeks of hospital discharge of the patient to their home environment [8,9]. In 2015, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published their policy statement on the delivery of pulmonary rehabilitation, including the type of session of integrated PR required in different clinical stages of COPD, emphasizing the importance of an individual patient-tailored program [10]. Traditional PR strategies are currently used in hospital-based outpatient departments, and are feasible and of value for the majority of patients with COPD [11]. However, there are some barriers to patient participation in hospital-based outpatient programs, particularly associated with the requirement to travel to the hospital during episodes of AECOPD [10]. Therefore, the recent ATS/ERS international statement has also recommended that a PR program should be individually developed and able to adapt to different patient conditions [10]. To improve the effectiveness of chronic disease management for patients with COPD, improved components of PR, and of patient monitoring in COPD has been called for [12].

A recently published clinical study, which included patients with AECOPD, showed that the use of multidisciplinary integrated PR programs did not show clinical effectiveness, and the study was terminated due to increased patient mortality [13]. However, other studies have resulted in differing results, leading to the conclusion that the outcome of comprehensive integrated PR studies in patients with COPD might vary due to the population being studied, the severity of COPD, the type and duration of the study, the duration of the study follow-up, and the methods of patient evaluation and evaluation of COPD [14]. Currently, the assessment of the long-term effectiveness of patient management and the outcome of integrated PR programs for patients with COPD remain unclear.

The aim of this retrospective observational clinical study was to evaluate the feasibility and effectiveness, as well as the exacerbation rate before, and 12 months after, an integrated, personalized PR program in patients with COPD who were discharged from hospital for AECOPD.

Material and Methods

Patients, ethics, and study design

This retrospective longitudinal observational study was conducted at the Respiratory and Critical Care Medicine Department of Tianjin Chest Hospital, which is a tertiary hospital offering highly specialized medical care for patients with pulmonary and cardiovascular disease in Tianjin, China. The hospital admissions for chronic obstructive pulmonary disease (COPD) or acute exacerbation of COPD (AECOPD) in this department had increased gradually, from 900 to 1,200 per year during the past five years (70–100 patients per month). An exacerbation of COPD has been defined as "*a worsening of respiratory symptoms, which is beyond normal daily variation and requires additional treatment*" [15]. This study and its design were approved by the Ethics Committee of Tianjin Chest Hospital. All patients provided written informed consent to participate in the study.

Clinical data were retrospectively analyzed from patient follow-up records for the three years from January 2013–December 2015. The total number of patients discharged from the department during that time was 19,749. Among the previously discharged patients, there were 3,611 patients discharged from hospital following admission for AECOPD. From these patients, 303 patients with former AECOPD received an initial eight-week integrated pulmonary rehabilitation (PR) program at home within two weeks of hospital discharge.

The patient exclusion criteria included a diagnosis of COPD combined with obstructive sleep apnea syndrome (OSAS), based on a combination of patient history (unexplained sleepiness in the daytime, snoring, headache during the morning, insomnia, difficulty with concentration, and mood changes), polysomnography tests, and oxygen saturation monitoring by oximetry [16]. Patients were also excluded from the study who had a diagnosis of cancer, Alzheimer's disease, depression or anxiety disorders, or who had suffered from emotional trauma in

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the previous six months (for example, death of a relative, or divorce). Patients who left the program due to AECOPD during the integrated PR program, patients with poor study adherence, and patients with incomplete medical records or follow-up data were also excluded.

In this study, patient adherence to the PR program was assessed by evaluating the proportion of completed sessions. The study required three sessions per week of aerobic training and upper body resistance training, respectively; seven sessions per week of respiratory training, with the scheduled total number of study sessions in eight weeks being 104. Patients were categorized as showing study adherence if they completed more than 50% of the scheduled sessions. The integrated PR program was performed at home with a weekly phone call supervised by a specialized respiratory therapy team.

The integrated pulmonary rehabilitation (PR) program

The training program began when the patient was in hospital and continued for an initial eight weeks. This initial eight-week integrated PR program consisted of the following five training components and the following eight assessment components.

Five training components of the integrated PR program

1) Aerobic training: Initially, all patients were evaluated by a treadmill test to identify the maximum walking speed according to their target heart rate, which was between 70–85% of the maximum heart rate [17], and on three occasions, before they were discharged from hospital. Also, patients performed tailored aerobic training with outside walking at home for eight weeks. After routine warm-up and being given general information about PR by a physiotherapist, patients began the test with a speed of 1 km/hr, and an increment 0.2 km/hr every 10 minutes, until they complained of breathlessness or muscle weakness. The maximum speed was recorded during the test, which was performed three times per week. Aerobic training began for 5 minutes and then increased to 20 minutes. Patients adjusted the speed of training to their symptoms and real-time heart rate. The clinical signs for stopping aerobic training included chest pain, breathlessness, profuse sweating, an increase in systolic blood pressure above 180 mmHg, and a pulse oximetry oxygen saturation measurement of less than 85%.

2) Upper body resistance training: Resistance training of the arms was used with weights of 0.5 kg for 5 minutes, or as long as the patient did not experience muscle pain, cramps, or dyspnea. This training component also required patients to hold their inhaled breath for 5 seconds at the end of inspiration and then to expire slowly. The 5-minute training period was repeated three times a week for an initial eight weeks and was also supervised by a physiotherapist before discharge from the hospital.

3) Respiratory training: Half-closed lip abdominal respiratory training and exhalation training was performed for 30 minutes, once every day for eight weeks.

4) Health education: This component of the program emphasized the importance of smoking cessation, long-term oxygen therapy, the correct use of any prescribed respiratory medicine, breathlessness, emotional and anxiety management, and nutrition, which was offered by respiratory nurses. Recognition of exacerbations of COPD, information for the family and social support were also provided by respiratory nurses. Also, respiratory physicians regularly reviewed the medications of all patients.

5) Self-management: As an essential part of disease management targeted to help people develop skills to manage the disease more effectively, the use of a self-management strategy was encouraged. It was considered to be good for patients to control their COPD during the follow-up, including changes in health behavior, improving their mental condition, increasing physical activity as well as early recognition of symptoms and sign of an acute exacerbation (AECOPD).

Eight assessment components of the integrated PR program

Eight types of assessments were performed before and after the integrated PR program began, and then every three months at the outpatient department by the same physiotherapist during follow-up, to supervise and evaluate the change in the health status of the patients with COPD.

1) Pulmonary function testing: Tests included the forced expiratory volume in one second (FEV_1), FEV_1 percentage predicted, forced vital capacity (FVC), FEV_1/FVC%. Pulmonary function was measured at the baseline and following inhaled bronchodilator therapy, respectively.

2) Assessment of physical capacity: The six-minute walk test (6MWT) was used according to the recommended protocol of the American Thoracic Society (ATS) [18]. Patients were asked to walk as long as they could in a 30-meter straight corridor during six minutes without any interruption. The distance that each patient completed was recorded on completion of the test.

3) The Chronic Obstructive Pulmonary Disease Assessment Test (CAT): The CAT was used to evaluate the health-related quality of life (HRQOL) during patient follow-up which was performed using a self-reporting format [19].

4) The Modified Medical Research Council scale (mMRC): The mMRC was used to assess the severity of breathless, being an effective and convenient method of clinical evaluation for

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assessing apnea, which can be performed under different conditions for patients with COPD [20].

5) The Beck Depression Inventory (BDI) and State-trait Anxiety Inventory (STAI): The content of the BDI included 21 items, including evaluation of nervousness, dizziness, inability to relax, and the STAI also measured the severity of anxiety and tendency to be anxious [21].

6) Activities of daily living (ADLs): The ADLs included activities and tasks that patients routinely performed in their daily life inside and outside their homes [22]. Measuring ADL was used to evaluate the condition and progress of the disease, as well as the efficacy of rehabilitation in patients with COPD.

7) Patient adherence to the PR study program: To monitor the compliance of PR, a requirement was used in this study that completion of more than 50% of scheduled maintenance training session was considered to represent patient adherence [23]. The patients had their self-reported symptom diaries integrated with the details from their telephone interviews.

8) Clinical complications and adverse events: During the study, any events of tachycardia, that were greater than the target heart rate (220–age) (0.7–0.85) [17], hypoxia with a pulse oximetry oxygen saturation (SaO_2) <10% of baseline, hypertension (blood pressure >200/100 mmHg), and syncope observed during exercise, were adverse events that caused patients to discontinue training and to be given immediate treatment.

Statistical analysis

Categorical data were expressed as frequencies (percentages), and continuous variables were presented as the mean ± standard deviation (SD). All paired variables at pre-PR and post-PR were analyzed by *post hoc* paired t-tests. Frequency changes in exacerbation, emergency hospital visits as well as hospitalization were compared before and 12 months after an integrated PR program were also tested by *post hoc* paired t-tests. Repeated measurement of analysis of variance (ANOVA) was used to test the differences over time in the 6MWT, CAT, mMRC, BDI, and STAI. Changes in exacerbation frequency type before and after the integrated PR study were analyzed with a McNemar's test. Data were analyzed using SPSS version 17.0 software. A P-value of <0.05 was considered to be statistically significant.

Results

A total of 303 eligible patients were recruited into this observational study, of which 267 patients (88.1%) completed integrated pulmonary rehabilitation (PR) program successfully.

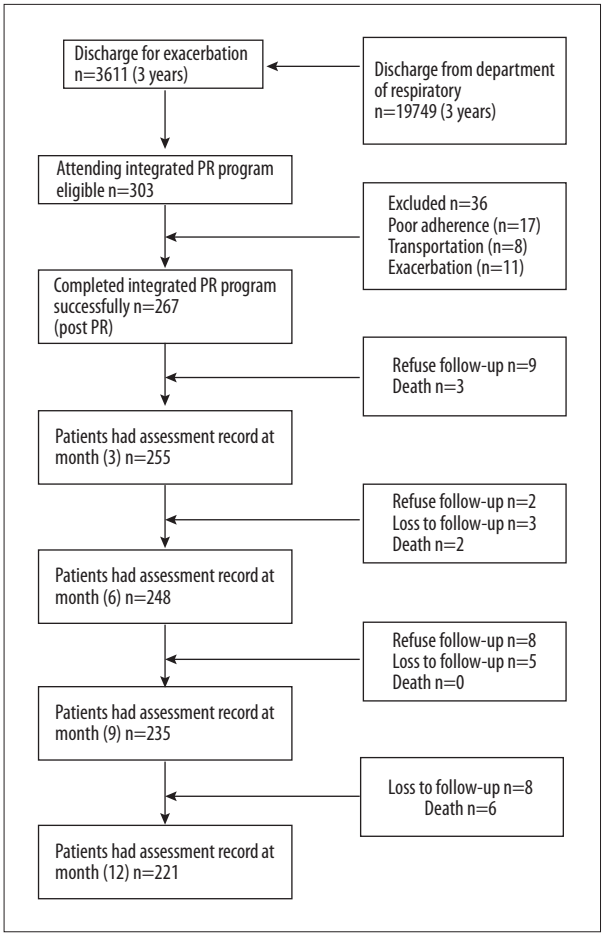

Figure 1. Flowchart of the study population.

The study adherence of 63 patients was ≥70%, the study adherence of 117 patients was ≥60–70%, and the study adherence of 87 patients was ≥50–60%. There were 221 patients who completed the follow-up (Figure 1).

The main characteristics of the patients at baseline are shown in Table 1. On average, the patients were older adults (mean age, 64.9±8.7 years), had moderate to severe chronic obstructive pulmonary disease (COPD), and the mean FEV_1 percentage predicted was 48.8±12.9%. Most of the patients had ceased smoking prior to the study. There were 101 patients (37.8%) who presented with two or more co-morbidities, including hypertension, coronary heart disease, diabetes mellitus, depression, and anxiety. Non-invasive ventilation support was applied to 94 patients (35.2%) at home. There were 44.8% (n=99) of 221 participants who completed follow-up and who underwent pharmacological therapy, including long-acting muscarinic agonist (LAMA) in 22.2% (n=49), long-acting beta-agonist (LABA) and inhaled corticosteroid (ICS) in 16.7% (n=37) and both sets of agents in 5.9% (n=13) at baseline. In contrast, the proportion of pharmacologic therapy use increased to 65.6% (n=144) at final 12-month follow-up (χ^2=44.485) (p<0.001).

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Table 1. Demographic characteristics of participants at baseline (n=267).

Variable	
Age (yr)	64.9±8.7
Male sex	203 (76)
Single (Y/N)	27/240
Work status (still work versus retired)	122/145
BMI(kg/m^2)	23.4±3.0
ADL	16.7±3.6
Education (yr)	8.7±2.9
Smoking status (cur versus ex)	35/232
Smoking(pack. yr)	32.4±18.8
FEV1 (L)	1.12±0.4
FEV1%	48.8±12.9
FVC (L)	2.41±0.62
FEV1/FVC%	46.6±10.5
Comorbidities, n (%)	
0	35(13.1)
1	131(49.1)
≥2	101(37.8)
Non-pharmacological therapy	
LTOT	135(50.6)
NIV	94(35.2)
Both	27(10.1)
None	11 (4.1)

BMI – body mass index; ADL – activities of daily living; FVC – forced vital capacity; FEV1 – forced expiratory volume in 1 s; LAMA – long-acting muscarinic agonist; LABA – long-acting beta-agonist; ICS – inhaled corticosteroid; LTOT – long-term oxygen therapy; NIV – non-invasive ventilation. For categorical variables, the results are expressed as number (percentage); for continuous variables, the results are expressed as mean ± standard deviation.

The short-term effect of integrated pulmonary rehabilitation (PR)

As shown in Table 2, analyzed by *post hoc* paired t-tests, the six-minute walk test (6MWT), (291.4±37.6 m *vs.* 334.7±47.4 m), COPD assessment test (CAT) (19.8±7.9 *vs.* 16.3±7.3), modified Medical Research Council (mMRC) test (2.4±0.9 *vs.* 1.9±1.0), Beck Depression Inventory (BDI) (10.5±5.6 *vs.* 9.9±5.4), State Anxiety Inventory (SAI) (38.7±1 0.5 *vs.* 35.4±11.6), Trait Anxiety Inventory (TAI) (43.7±10.7 *vs.* 40.6±11.2), showed statistically clinical improvements (P<0.001) after integrated PR (Table 2).

The long-term effects of the integrated (PR) regimen

The results of the six-minute walk test (6MWT) showed that when compared with month 0, the results of 6MWT showed an initial significant increase at month 3 and continued to increase slightly until month 6. However, the 6MWT declined from month 6 to month 12. At the end of the 12-month study, the result of the 6MWT had returned to the level of month 0 (369.6±51, p<0.001; 383.9±39.8, p<0.001; 364.5±39.2 p<0.001; 332.3±40.9, p=0.265, respectively) (Table 3).

The CAT scores decreased gradually from month 3 to month 9 when compared with month 0 (14.8±7.7, p<0.001; 13.4±7.8, p<0.001, 14.0±7.6, p<0.001, respectively). Although, the CAT scores increased slightly from month 9 to month 12 (15.0±7.6, p<0.001), the CAT score was still lower than the level of month 0 at the end of the study (Table 3)

The modified Medical Research Council (mMRC) score showed an initial decrease from month 0 to month 6, with a slight increase over time,6 months later. However, at the end of month 12, the mMRC was also lower compared with the level at month 0. (1.6±0.9, p<0.001; 1.5±1.0, p<0.001; 1.6±1.0, p<0.001; 1.8±0.9, p=0.018, respectively) (Table 3).

During follow-up, the change in the Beck Depression Inventory (BDI) (9.0±5.6, p<0.001; 8.1±5.6, p<0.001; 9.3±5.5, p<0.001; 9.5±5.4, p<0.001, respectively) and the State Anxiety Inventory (SAI) (31.1±12.5, p<0.001; 29.3±11.8, p<0.001; 31.4±11.9, p<0.001; 31.2±11.4, p<0.001) were similar, and showed an initial decrease until month 6, with a trend toward a slight gradual increase from month 6 to month 12 until, eventually, it was still lower than the level at month 0. However, the TAI (35.2± 12.5, p<0.001; 30.6±12.8, p<0.001; 29.6±11.2, p<0.001; 32.6±11.5, p<0.001) showed a different trend with the initial decline sustained 9 months after the integrated PR program, and it slightly increased for the last three months of the study and remained lower than that at month 0 (Table 3).

Reduction in the frequency of hospitalization and emergency department visits for acute exacerbation of COPD (AECOPD) at 12-month follow-up

In comparison with the baseline, among 221 patients who completed the 12-month follow-up, the frequency of AECOPD (3.1±1.7 *vs.* 2.0±1.4, p<0.001) (Figure 2A), hospital admission (2.0±1.2 *vs.* 1.4±1.2, p<0.001) (Figure 2B), and emergency department visits (2.5±1.5 *vs.* 1.2±1.1, p<0.001) (Figure 2C) all showed a significant decline at 12 months after integrated PR, analyzed by *post hoc* paired t-tests. The McNemar's test was applied to identify the type change in acute exacerbation frequency in the study participants. The number of patients characterized by more frequent exacerbation was 71% (n=158) at

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Table 2. Comparison of clinical characters at pre-pulmonary rehabilitation and post-pulmonary rehabilitation in participants.

Variable	n=267		
	Pre-PR	Post-PR	*P*-value
BMI	23.4±3.0	24.0±2.8	**<0.001**
ADL	16.7±3.6	16.7±3.8	0.288
6MWT	291.4± 37.6	334.7± 47.4	**<0.001***
CAT	19.8±7.9	16.3±7.3	**<0.001***
mMRC	2.4±0.9	1.9±1.0	**<0.001***
BDI	10.5±5.6	9.9±5.4	**<0.001***
SAI	38.7±10.5	35.4±11.6	**<0.001***
TAI	43.7±10.7	40.6±11.2	**<0.001***
FEV1	1.12±0.4	1,11±0.4	0.284
FEV1%	48.8±12.9	49.7±13.0	0.133
FVC	2.41±0.62	2.38±0.55	0.073
FEV_1/FVC	46.6±10.5	47.3±11.1	0.955

BMI – body mass index; ADL – activities of daily living; 6MWT – six-minutes walking test; CAT – COPD assessment test; mMRC – Modified Medical Research Council scale; BDI – beck depression inventory; SAI – state anxiety inventory; TAI – trait anxiety inventory; BMI – body mass index; FVC – forced vital capacity; FEV1 – forced expiratory volume in 1 s. The results are expressed as mean ± standard deviation. A p-value less than 0.05 is considered statistically significant and indicated by an asterisk (*).

Table 3. Analysis of changes in functional capacity, health-related quality of life, dyspnea and emotional function over one-year follow-up.

	Month 0	Month 3	Month 6	Month 9	Month 12	Time
	n=267	n=255	n=248	n=235	n=221	P value
6MWT	334.7±47.4	369.6±51	383.9±39.8	364.5±39.2	332.3±40.9	**<0.001***
CAT	16.3±7.3	14.8±7.7	13.4±7.8	14.0±7.6	15.0±7.6	**<0.001***
mMRC	1.9±1.0	1.6±0.9	1.5±1.0	1.6±1.0	1.8±0.9	**<0.001***
BDI	9.9±5.4	9.0±5.6	8.1±5.6	9.3±5.5	9.5±5.4	**<0.001***
SAI	35.4±11.6	31.1±12.5	29.3±11.8	31.4±11.9	31.2±11.4	**<0.001***
TAI	40.6±11.2	35.2±12.5	30.6±12.8	29.6±11.2	32.6±11.5	**<0.001***

6MWT – six-minutes walking test; CAT – COPD assessment test; mMRC – Modified Medical Research Council scale; BDI – beck depression inventory; SAI – state anxiety inventory; TAI – trait anxiety inventory for continuous variables, the results are expressed as mean ± standard deviation. For continuous variables, the results are expressed as mean ± standard deviation. A p-value less than 0.05 is considered statistically significant and indicated by an asterisk (*)

baseline, whereas, the number of less exacerbation at baseline was 29% (n=63) at 12 months. During the 12-month follow-up, 53 patients changed from more frequent to less frequent AECOPD, and 24 patients had more frequent AECOPD compared with baseline. At the end of the 12-month observational study, 58% (n=129) of the remaining 221 patients studied had frequent acute exacerbations, and 42% (n=92) of patients were defined as having less frequent exacerbations (χ^2=14.909) (P<0.001) (Figure 3).

Discussion

The aim of this retrospective observational clinical study was to evaluate the effectiveness of the use of an integrated pulmonary rehabilitation (PR) program, undertaken during 12 months, in patients with chronic obstructive pulmonary disease (COPD) discharged from hospital following an acute exacerbation (AECOPD). When compared with the baseline findings, the patients in the study showed a significant improvement of

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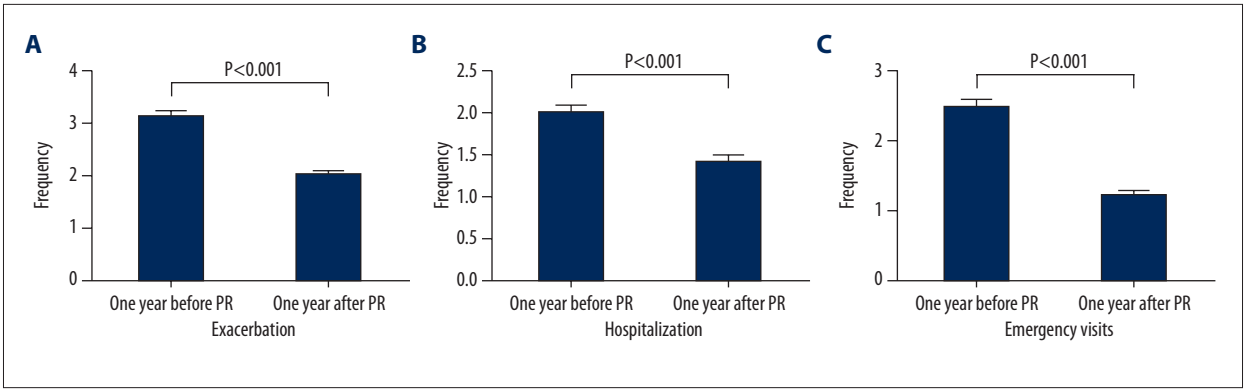

Figure 2. Comparision of exacerbation, hopistalization and emergency visit before and after PR. (**A**) Comparision of exacerbation frequency one year before and after pulmonary rehabilitation. (**B**) Comparision of hospitalization frequency one year before and after pulmonary rehabilitation. (**C**) Frequency of emergency department visit one year before and after pulmonary rehabilitation.

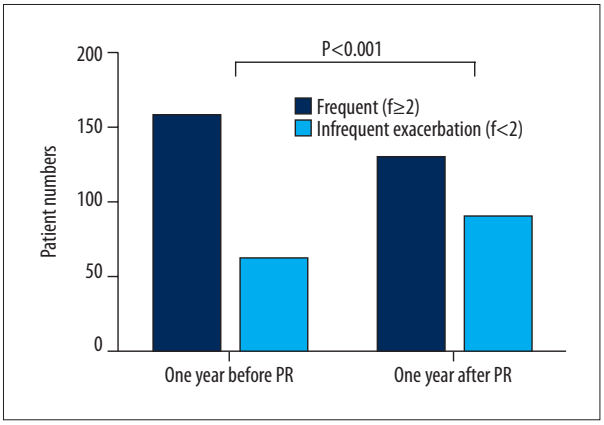

Figure 3. Comparision of frequent and infrequent exacerbation before and after PR.

their clinical performance at 12 months, the end of the integrated PR program, a finding which was consistent with the findings from a recent Cochrane systematic review [9]. However, in this study, there were no reported cardiovascular adverse events during the integrated PR program. Furthermore, following the 12-month observational study, the benefits of an initial 8-week integrated PR study showed that the clinical benefits began to appear by 6 months. Although the benefits for patients with COPD reduced gradually during the later stages of the study, some benefits of PR, although weak, were still observed until month 12, with the exception of exercise capacity, which are findings that are partially consistent with a recently published study [24]. Meanwhile, the home-based integrated PR program not only reduced the proportion of patients who were defined as having frequent acute exacerbations, but also decreased the frequency of clinical deterioration, hospitalization, and emergency hospital visits.

As previously published study concluded that, for patients with AECOPD, only short-term to medium-term and partial benefits of using integrated PR were found [24]. Furthermore, the improvements gained using an integrated PR program could not be maintained long-term without maintenance [25,26]. However, the results of this study suggested that this may not be the case, as the improvements that resulted from the use of integrated PR on the health, quality of life, and emotional state of patients with COPD was maintained at the end of the 12-month observational study.

It may be speculated that the weak progression of clinical improvements in patients with COPD may have been associated with the novel strategy used in this study, which was characterized by chronic disease management in combination with a home-based integrated PR program via telephone contact. In 2015, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) published their policy statement on the delivery of PR, and this study was designed in accordance with these recommendations, to include an integrated PR program aimed to improve the physical and psychological condition of patients with COPD in a sustained way, via patient self-management and individual therapies [10]. Consistent with the current ATS/ERS statement, the home-based study plan consisted of health education, professional consultation, and regular supervision, including facilitating smoking cessation, providing effective breathing skills, as well as optimal pharmacotherapy to help study participants to improve their health-related behaviors, lifestyle, and quality of life [12].

In particular, the improvement of breathlessness and remission in COPD in this study might have been attributed to the use of imposed pursed-lip breathing on respiratory mechanics and dyspnea at rest and during exercise, as well as chest physiotherapy, by increasing the coordination of neuromuscular and respiratory efficiency [27]. Also, this study included a convenient walking exercise test, the six-minute walk test (6MWT), and suitable upper body strengthening exercises, according

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to the individual condition of the patients, with aerobic training, which can be easily integrated into daily life and easy to implement for patients in their own homes. This type of integrated PR program has been successfully assessed in different kinds of clinical trials [28,29].

Although in this study, the long-term benefits were not maintained in the 6MWT with this integrated PR strategy, an improvement in exercise capacity was found until 9 months after the initial integrated PR program commenced. Recently, a further clinical guideline for patient management in COPD has been submitted in Australia and New Zealand indicating that a well-supervised strength maintenance strategy should be followed after integrated PR to prevent the benefits in exercise capacity declining over time [30].

Another main finding of this study was that at the end of the 12-month follow-up, the frequency of reduction of acute exacerbations, emergency hospital visits, as well as hospital re-admissions, were observed in the study participants. However, several previously published studies that have been described to include patient self-management alone did not result in consistent conclusions on the reduction of hospital re-admission [31,32]. A research study based only on telehealth monitoring failed to demonstrate its effectiveness on decreasing frequency of hospital re-admission for EACOPD but did shorten the length of hospitalization, with a high satisfaction level in patients [33]. A systematic literature review has suggested that the application of self-management-based programs alone had a beneficial effect on anxiety and health-related behavior, rather than improving exercise tolerance, depression, and patient mortality [34]. Nevertheless, given the multiple components in the design of the present retrospective observational clinical study, which included the management of COPD syndromes, early recognition clinical deterioration, a social and medical support network with support and telephone contact, it was much easier and more convenient for patients to manage their COPD symptoms, which may partially explain the reduction of acute exacerbations of COPD found during the 12 months of this study.

The integrated PR program described in this study showed the clinical effect on the patient's quality of life, and reduction of hospital re-admission in patients with COPD after acute exacerbation is supported by a previously published high-quality study [24]. Although integrated PR has been well established following AECOPD in several previous studies, it is important to note the poor patient adherence to such programs. For example, a recent observational study indicated that less than 10% of patients (11 out of 128) of participants completed a six-month integrated PR program following discharge from hospital [35]. Also, the results of a previous study that enrolled 60 patients over a three-year follow-up period without data on the rate of participation provided limited value [36]. The typical reasons for non-compliance with the integrated PR program were difficulties in transportation, self-reported breathlessness, as well as fear of the hospital environment [35]. In the present study, there were 88.1% of participants completed the integrated PR program, and more than 50% of scheduled sessions in the initial eight weeks, which was greater number compared with that reported in a previous program [35]. However, the benefits for patient health, quality of life, and emotional state, were also preserved at the end of the observational study, which may be partially attributed to the home-based, multi-component care program, and the ease of implementation of the program for participants, which can overcome geographical distance from the hospital, reduces travel costs, reduces patient anxiety, and increases patient motivation and the degree of patient participation in the program.

However, it remains unclear as to what extent the integrated PR program component would affect the reduction of AECOPD and hospital re-admission, as the application of pharmacological therapy also plays a critical role in the clinical improvement for patients with COPD. In this study, participants were re-evaluated and advised to adjust their pharmacological therapy according to recent management guidelines, which have recommended the use of a long-acting beta-agonist (LABA) or a long-acting muscarinic agonist (LAMA). Previous literature review on COPD therapy also indicated that the use of tiotropium, combination therapy of a LABA and an inhaled corticosteroid (ICS), when compared with placebo, showed significant improvement in spirometric testing, quality of health, as well as the reduction of rates of hospitalization for cases of AECOPD [37,38]. Following the use of the integrated PR strategy used in this study by nurses and physicians, including health education, the skill of administration of medication, the benefit and strategy information of pharmacology, assessment of health status, the proportion of pharmacological treatments increased from 44.8% to 65.6% by the end of the 12-month observational study. Therefore, a multidisciplinary approach to patient care in COPD, together with the application of the most appropriate pharmacologic therapy might have been a further contributor to the findings of the reduction in AECOPD seen in this study.

This study had several limitations. First, this was not a controlled study, as the use of integrated PR was not compared with usual care in our center, which means that the effectiveness of the program cannot be determined from this single study. Also, patients were excluded who did not complete the integrated PR program, but as this was part of a multidisciplinary program, the patient selection process may have affected which component contributed to the study findings relating to rates of hospital re-admission. Although the CAT is a clear and convenient questionnaire to perform when compared

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with, for example, the St George's Respiratory Questionnaire (SGRQ), CAT may be an insufficient method of assessment to identify all domains of health-related quality of life (HRQoL) in patients with COPD. Therefore, future larger, controlled, randomized, multicenter studies should be performed to evaluate the use of comprehensive, integrated PR programs for patients with COPD and AECOPD.

Conclusions

The findings of this retrospective observational clinical study showed that a multidisciplinary integrated pulmonary rehabilitation (PR) program conducted in home-based patients resulted in clinical improvement in the chronic obstructive pulmonary disease (COPD) assessment test (CAT), the modified Medical Research Council (mMRC) evaluation, and patient well-being. Also, this integrated strategy reduces the frequency of exacerbation, hospitalization, and emergency department visits for acute exacerbation of COPD (AECOPD).

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