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Research Article

Pulmonary Rehabilitation for Post/Long Covid Patients: A Serial Cross-Sectional Study in a Resource-Limited Outpatient Setting in Bangladesh

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Abstract

Long COVID is a major health problem all over the world after the COVID-19 pandemic. Increasing evidence suggests that pulmonary rehabilitation (PR) effectively reduces the symptoms, leads to health benefits and improves the exercise tolerance of patients with post-COVID-19. That evidence, however, has been generated so far among patients from the indoor settings of hospitals. The present study was conducted to investigate the benefits of an outdoor-based PR program on the exercise performance and respiratory function of post-COVID-19 patients. A total of 99 COVID-19-positive patients from an OPD-based PR centre were enrolled in a prospective study with a serial cross-sectional design. All the subjects followed an 8-week comprehensive multimodal and multidisciplinary pulmonary rehabilitation schedule. Spirometry and endurance shuttle walk tests (ESWT) were performed before and after the rehabilitation program. The minimal clinical important difference (MCID) was used as an indicator for the response of individual subjects to the PR program. A proportion of 75% and 55% of subjects were improved by walk distance and time in ESWT respectively. On spirometry, 57% of FVC (L), 61% of FVC (%), 48% of FEV1 (L) and 31% of FEV1 (%) subjects were improved after the PR program by MCID among the 91 subjects. On pooling all data together, 36% of subjects were found to show clinically meaningful improvements in pulmonary function [FVC (%)] when a 10% increase was taken as the cut-off point. A negative association was evident on the adjustment of the effects of age and BMI during multiple regression analysis with 'post-PR % predicted FVC' as the outcome variable. The present data suggest that an OPD-based pulmonary rehabilitation program, even with a relatively short duration, has a beneficial effect on exercise endurance and pulmonary function among subjects affected by long-term COVID problems.

Keywords: *Post-COVID; Long COVID; Pulmonary Rehabilitation; Lung Function; Bangladesh*

Abbreviations

ESWT: Endurance Shuttle Walk Tests; MCID: Minimal Clinically Important Difference; FEV: Forced Expiratory Volume; FVC: Forced Vital Capacity

Introduction

The COVID-19 pandemic has affected millions of people across the world, creating a global burden for long-term care among survivors [1]. The lasting symptom burden and impact of COVID-19 on patients have been interchangeably referred to as long COVID and post-COVID syndrome [2,3]. 'Long COVID' is now recognised as a major problem among a substantial number of COVID-19 survivors all over the world [4]. It creates the risk of long-term sequelae including respiratory, neuropsychiatric, cardiovascular, hematologic, gastrointestinal, renal, and endocrine manifestations [5-7]. The pathological mechanisms underlying the disease and the differences in clinical presentations remain largely unknown. Persistent inflammation is a key mediator in the multifactorial genesis of the long-term sequelae [7,8]. Fatigue, breathlessness, muscle weakness, and psychological distress rank among the most frequent symptoms of long COVID [9,10]. In light of the fast-increasing disease burden of long COVID, strategies are urgently needed to improve the long-term patient benefits. Currently, guidance statements and some research papers suggest acute and long-term rehabilitation for people living with COVID-19 [11-14].

Pulmonary rehabilitation (PR) is known to enhance exercise capacity, reduce depression and anxiety, and improve health-related quality of life QoL (HRQoL in a wide range of respiratory disorders [15] such as chronic obstructive pulmonary disorder [16], idiopathic pulmonary fibrosis [17], interstitial lung disease [18] and lung cancer [19]. The first experiences of PR in post-COVID-19 patients revealed promising findings in improving physical performance and subjective health status regardless of previous ventilation [20]. The increased aerobic capacity resulting from PR could lead to short-term improvement of the immune and respiratory systems in COVID-19 patients [21] and enhance their ability to maintain adequate muscle strength [22].

The evidence so far generated on the effect of PR on post-COVID physical and mental health is based on data mainly generated from in-patient interventions and, also, the study designs are mostly retrospective or case series in nature [23]. Only one prospective study [24] has reported the benefits of an outdoor-based 3-week PR program. However, it was conducted on a relatively younger group of subjects (mean age 46 years) and thus the findings may not apply to the aged subjects who are the main victims of the post-COVID problems. Under this perspective, the present study was designed to prospectively investigate the benefit of a shorter (8 weeks) outdoor-based PR program on the exercise performance and respiratory function of COVID-19 patients with relatively higher ages.

Materials and Methods

Study design

It was a prospective study with a serial cross-sectional design, conducted from July 2021 to July 2022. Exercise performance and respiratory function were the primary outcome variables and those were assessed among the post-COVID patients at Baseline (immediately before the starting of PR) and after the OPD-based PR program.

Study setting

The study was conducted in an OPD-based PR centre in Dhaka, Bangladesh.

Study subjects

Patients with post-COVID symptoms were the subjects in this study depending on inclusion criteria. Following WHO [25] we defined post-COVID subjects as individuals with a history of confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that lasted for at least 2 months and cannot be explained by an alternative diagnosis. Patients of both sexes with more than 22 years of age who complained of symptoms of chronic cough, shortness of breath, unable to discontinue oxygen and or simple weakness and asthenia after 2 weeks of test positivity, were recruited consecutively from a Pulmonary Rehabilitation Centre as per the advice of a Chest Physician or Consultant who is a staff member in the pulmonary rehabilitation Centre. Patients were informed by a flyer regarding the design of the study including the rationale of the study and ensuring the procedure of Intervention process. A hard copy of patient-reported outcome measures was provided. They were allowed to discuss the study further if they had any queries at their initial appointment, or by telephone.

Inclusion criteria:

- Patients of more than 22 yrs age and any sex who complain of symptoms of post-COVID-19.

Exclusion criteria:

- Subjects with prior COPD or other respiratory disease, moderate or severe heart disease, severe ischemic hemorrhagic stroke, and neurodegenerative diseases.
- Subjects who were unable to walk for any reason(s).
- Unwilling to take part in the study.

Sample size

All eligible post-COVID-19 patients attending the PR centre during the study period were invited to take part in the study. All eligible subjects (as per inclusion and exclusion criteria) were relatively more likely to take part and, accordingly, they were enrolled in this study. The total number of subjects enrolled was 99.

Intervention procedures

Patients participated in an 8-week comprehensive multimodal and multidisciplinary OPD-based pulmonary rehabilitation program. The program included 5-day training sessions per week of which 2 were supervised 1.5 hr-training sessions and 3 were home-exercise sessions up to 30 to 40 minutes. The program is further detailed in annex 1.

Outcomes were measured

Assessments were performed before and after the eight weeks of the rehabilitation program. The outcomes were evaluated by exercise capacity and lung function. Exercise capacity was assessed by MCID (Minimal clinical importance difference, with a cut-off value of 47.5 meters) and Time (cut-off value 174 sec) on the Endurance shuttle walk test (ESWT). Respiratory function was assessed by spirometry using the following variables: FVC (L), FVC (% of predicted), FEV1 (L), FEV1 (% of predicted), FVC/FEV1 ratio (% of predicted), and SpO_2 (% of predicted).

Ethical considerations

This study was approved by the Ethical Review Committee (AKMMC/2021/01) of the Anker Khan Modern Medical College and Hospital, Dhaka, Bangladesh. Informed written consent was taken from each participant.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) for normally distributed data. Non-normally distributed variables were shown as median [interquartile range (IQR 25, 75)]. Categorical variables were presented as frequency (%). Statistical analysis was conducted using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 26.0 [26]. A chi-square test was used to analyze categorical variables. The differences in the non-normally distributed variable between groups were compared using the Mann-Whitney test. A paired sample t-test was used to explore the correlation of the Pre-PR baseline with the post-PR outcome variables. Statistical significance was set at a two-sided p-value < 0.05.

Results and Discussion

The mean age of the subjects in this study was above 55 years (Table 1); 36% of them were within the normal weight range, 51% were overweight and 13% were obese. One or more comorbidity was present among 76% of cases where diabetes mellitus (DM) was the most prevalent one (30%) followed by hypertension (22%) and a combination of DM with hypertension (20%). A large proportion of patients

(62%) had one or more symptoms which were mainly cough, chest pain and weight loss. About 75% of patients were nonsmokers and 23% were ex-smokers. Restrictive features on spirometry were diagnosed in 80% of subjects and 13% of subjects were normal.

Characteristics	**n (%)**
Age in years (M ± SD)	55 ± 11.3
BMI (M ± SD)	26 ± 4.2
Gender	
Male	64 (65)
Female	35 (35)
Occupation	
House Wife	29 (29)
Business	22 (22)
Private Service	30 (30)
Govt Service	7 (7)
Unemployed	11 (11)
Symptoms	
No Symptoms	38 (38)
Cough	28 (28)
Weight Loss	8 (8)
Chest Pain	7 (7)
Cough and Weight Loss	6 (6)
Cough and Chest Pain	12 (12)
Comorbidities	
Normal	24 (24)
Hypertension	22 (22)
DM and HTN	20 (20)
Diabetes	29 (30)
Ischemic Heart Disease	2 (2)
DM, CKD and HTN	2 (2)
Smoking History	
Smoker	2 (1)
Non-Smoker	74 (75)
Ex-Smoker	22 (23)
Type of Lung Disease	
Normal	13 (13)
Restrictive Lung Disease	79 (80)
COPD	2 (2)
Restrictive and COPD	5 (5)

Table 1: *Socio-demographic and clinical characteristics of study subjects.*

Data are expressed as numbers (percentage).

On the endurance shuttle walk test (ESWT), the mean post-PR walk distance was found to be almost double as compared to the Pre-PR value (Table 2). The Level of ESWT was also higher in the post-PR state.

Parameters in EWT	Pre-PR value (M ± SD)	Post-PR value (M ± SD)	p-value
Distance (m)	641.4 ± 485	1133 ± 495	< 0.001
Level	9.9 ± 3.9	10.9 ± 3.4	0.031

Table 2: *Pre- and Post-PR EWT parameters among the study subjects.*

Data are expressed as M ± SD. Statistical differences between device and analyzer values were analyzed by paired t-test.

All post-PR variables related to exercise capacity showed significant improvement as compared to the pre-PR values. The mean walk distance was nearly doubled after the intervention ($p < 0.001$). Based on the cut-off value of MCID as 47.5 m, 75% of the participating patients showed improvement by more than MCID, 4% of patients showed improvement by less than MCID; 3% showed no change, and 14% showed some worsening among which 3% patients worsened by less than MCID (Figure 1).

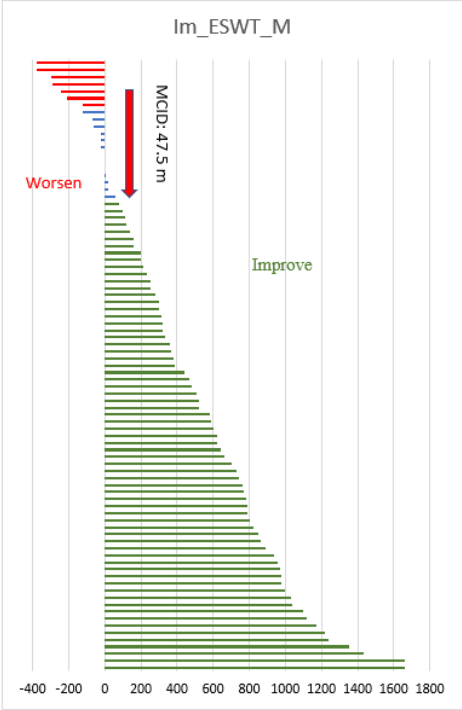

Figure 1: *Plots the individual changes of walk distance in ESWT.*

The ESWT time was also higher in the post-PR state as compared to the pre-PR one (Table 2). Based on the cut-off value of MCID for ESWT time as 174 sec, 55% of the participating patients showed improvement by more than the MCID, 20% of patients showed improvement by less than the MCID; 12% showed no change, and 9% showed some degree of decline. This is illustrated in figure 2 which plots the individual changes in FEV1 (%).

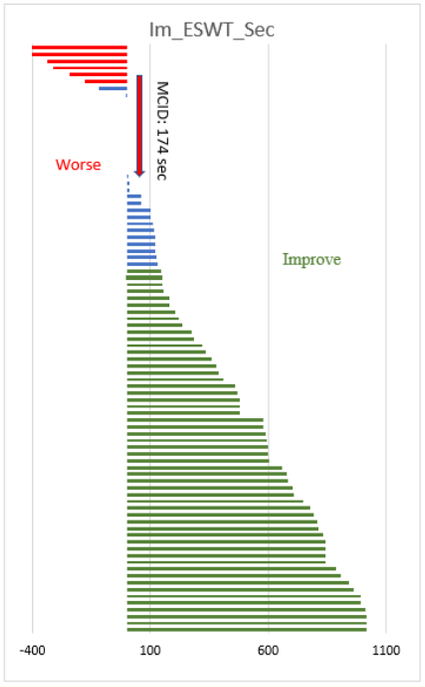

Figure 2: *Plots the individual changes of time in ESWT.*

In parallel to the exercise capacity, almost all the lung function-related variables were found to be significantly improved after the PR program. With 0.02 as the cut-off value for MCID of FVC (L), 57% improved by more than MCID, 16% improved by less than MCID, 12% of patients had the slight cure, and 8% patients showed deterioration among whom 7 worsened by less than MCID (Figure 3). With a cut-off value of 4% for MCID of FVC (%), 61% improved by more than MCID, 14% improved by less than MCID, 23% of patients showed some decline, and 9% of patients worsened by less than MCID (Figure 4). With 0.2 as the cut-off value for MCID of FEV1 (L), 48% of the participating patients improved by more than MCID, 22% improved by less than MCID, 4% showed no improvement, and 24% patients showed deterioration of 13% patients worsened by less than MCID (Figure 5). With 12% as the cut-off value for MCID of FEV1 (%), 31% of the participating patients improved by more than MCID, 37% improved by less than MCID, 7% showed no improvement, and 21% showed deterioration of whom 20% worsened by less than MCID (Figure 6).

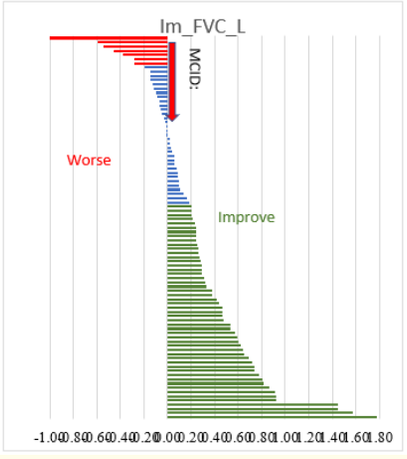

Figure 3: *Plots the individual changes of FVC (L) in spirometry.*

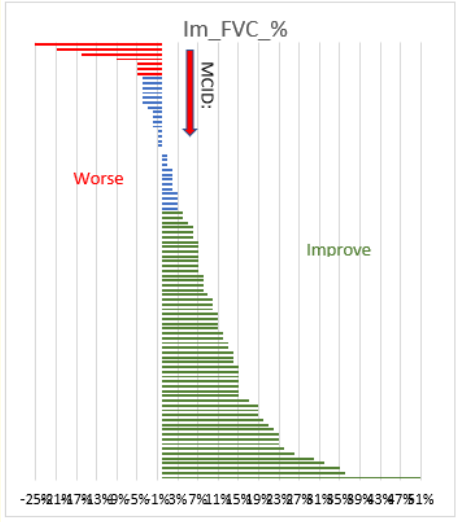

Figure 4: *Plots the individual changes of FVC (%) in spirometry.*

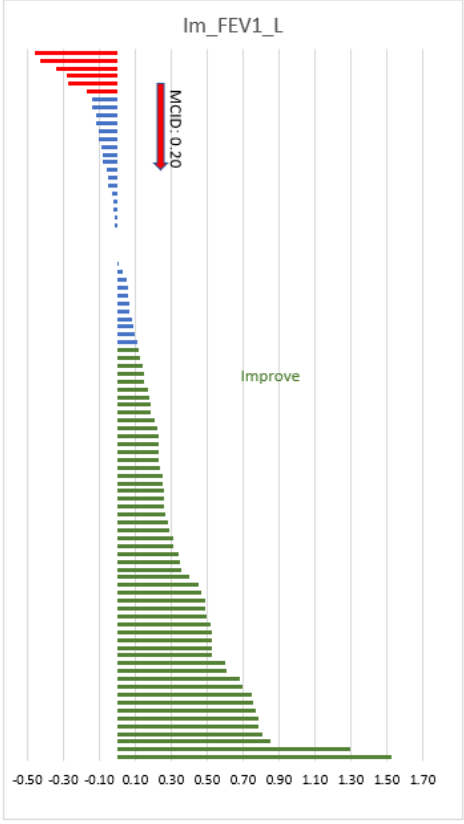

Figure 5: *Plots the individual changes of FEV1(L) in spirometry.*

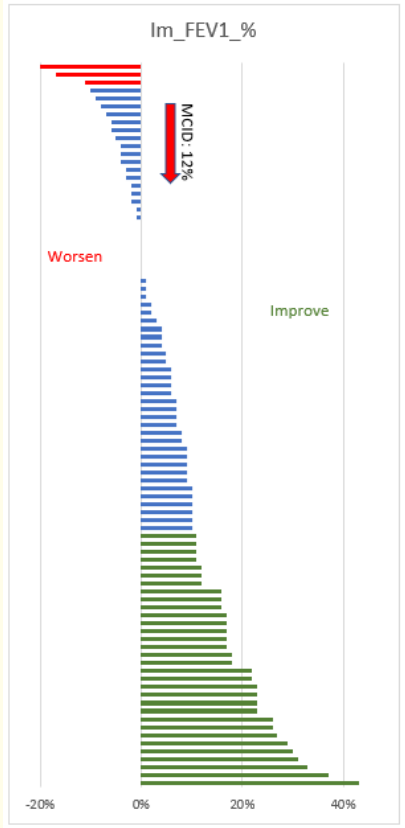

Figure 6: *Plots the individual changes of FEV1 (%) in spirometry.*

Among the respiratory function parameters, the SpO_2 value did not show any significant change after the PR-program (SpO_2, % of predicted, Pre-PR 98.3 ± 0.9 vs Post-PR 97.9 ± 4.4; p = 0.45).

On pooling together data pre and post PR, the improvement in the exercise performance was paralleled by the postbronchodilator pulmonary function where the post-PR FVC (% predicted) value was significantly higher as compared to the Pre-PR value (p < 0.001, Table 3). Taking a 10% increase in the % predicted FVC value as a cut-off point, overall, 36% of subjects were found to show clinically meaningful improvements in pulmonary function on participating in the rehabilitation program. The improvement was found to be present in all the age, BMI and smoking status groups (Table 4).

Parameters on Spirometry	Pre-PR value (M ± SD)	Post-PR value (M ± SD)	p-value
FVC (L)	2.08 ± 0.7	2.3 ± 0.7	< 0.001
FVC (% of predicted)	63.3 ± 16.3	71.3 ± 14.5	< 0.001
FEV1 (L)	1.8 ± 0.5	2.1 ± 0.6	< 0.001
FEV1 (% of predicted)	69.1 ± 16.6	77.3 ± 14.7	< 0.001
FVC/FEV1 ratio (% of predicted)	89.9 ± 6.0	88.9 ± 6.3	0.029
SpO_2 (% of predicted)	98.3 ± 0.9	97.9 ± 4.4	0.45

Table 3: *Pre- and Post-PR respiratory function among the study subjects.*

Data are expressed as M ± SD. Statistical differences between device and analyzer values were analyzed by paired t-test.

Characteristics	PR-nonimproved n (%)	PR-improved n (%)
Age (Mean ± SD)	55 ± 10	54 ± 12
BMI (Mean ± SD)	26.98 ± 4.8	25.8 ± 3.4
Comorbidities		
Normal	12 (21)	10 (26)
Hypertension	13 (23)	9 (24)
DM and HTN	14 (25)	6 (16)
Diabetes	14 (25)	12 (32)
Ischemic Heart Disease	1 (2)	1 (2)
DM, CKD and HTN	2 (4)	0
Smoking History		
Smoker	1 (2)	1 (3)
Non-Smoker	40 (71)	29 (76)
Ex-Smoker	15 (27)	8 (21)

Table 4: *Comparative sociodemographic and clinical characteristics among the PR-nonimproved and PR-improved subjects.*

Data are expressed as numbers (percentage).

Following the termination criteria, as mentioned in the methods section, no patient was required to be withdrawn from the PR program and thus from the study. Also, no adverse event was reported and no subject voluntarily opted to be withdrawn from the program or the study.

A comparative analysis of FVC between the Nonimproved and Improved Groups revealed that subjects with poorer pulmonary function at the start were more benefitted by the Rehabilitation Program (Table 5). On Spearman Correlation analysis Pre-PR FVC values did not show any significant correlation with the post-PR FVC values (Table 6). However, a negative association was evident on adjustment of the effects of age and BMI during multiple regression analysis with post-PR %predicted FVC as the outcome variable (Table 7). It may be noted that BMI also showed a marginally significant negative association with FVC in the same analysis.

Parameters of Spirometry	Pre-Intervention		U / P-value	Post-Intervention		U / P-value
	Non-Improved Median (IQR)	Improved Median (IQR)		Non-Improved Median (IQR)	Improved Median (IQR)	
FVC (L)	2.09 (1.08-4.5)	1.94 (0.92-3.73)	753.0/0.36	2.14 (1.02-4.6)	2.57(1.23-4.3)	1297.0/0.029
FVC (% of predicted)	71.0 (30-102)	55.5 (26-90)	494.0/<0.001	70.0 (37-100)	75.5(48-114)	1216.0/0.123
FEV1 (L)	1.9 (1.01-3.5)	1.7 (0.86-3.3)	813.5/0.104	1.9 (0.9-3.6)	2.3 (1.17-3.68)	1350.5/0.009
FEV1 (% of predicted)	77.5 (30-113)	63.0 (32-97)	567.5/<0.001	76 (41-116)	81.5 (55-114)	1316.5/0.02
FVC/FEV1 ratio (% of predicted)	88.9 (67.8-97.6)	93.1 (78.1-99.5)	1390.5/0.004	90.1 (67.3-99.5)	90.4 (68.5-98.6)	1121.0/0.43

Table 5: *Comparative respiratory function among the PR-nonimproved and PR-improved subjects.*

Data are presented as Median (IQR). p-values were calculated using the Mann-Whitney U test.

Variables	r value	P value
Age	-.134	0.197
BMI	1.0	...
Pre-intervention FVC (%)	0.143	0.17
Post-intervention FVC (%)	0.028	0.785

Table 6: *Correlation of post-FVC (%) with Age, BMI and pre-FVC (%) by Spearman.*

Correlation analysis was done using Pearson's correlation test.

Variables	Unstandardized Coefficients β	Standardized Coefficients β	P-value	95% Confidence Interval for β	
				Lower Bound	Upper Bound
Age (yrs.)	-.033	-.031	0.757	-.242	.176
BMI	-.509	-.185	0.049	-1.016	-.002
Smoking History	-1.305	-.052	0.570	-5.851	3.241
Comorbidities	-1.881	-.068	0.492	-7.300	3.538
Pre-intervention FVC (% of predicted)	-.351	-.476	<0.001	-.488	-.213

Table 7: *Multiple linear regression analysis of explanatory variables considering post-FVC (%) as dependent variables.*

p-values are significant at a 95% confidence interval ($p < 0.05$). Significant p-values are shown in bold. N, number.

Summary of the Main Findings

The present study shows that an outdoor-based pulmonary rehabilitation program is effective and safe with a very high adherence rate. It demonstrated the beneficial effect of the 8-week program on exercise performance and respiratory function among the aged population as shown by Noop., *et al*. [24] among relatively younger subjects. To the best of our knowledge, the present study is the first prospective report investigating the effects of a comprehensive OPD-based pulmonary rehabilitation among post-COVID subjects in the Southeast Asia region. As per assessment from the present study, the level of benefits from the study is quite high for subjects having lower exercise performance and respiratory function. The findings differ from the findings from the conclusions of a recent systematic review [27] which found the level of evidence of pulmonary rehabilitation in COVID-19 patients to be low. The difference may be due to the variations in the baseline characteristics of the subjects where the presence of initial compromise in the exercise endurance and respiratory function parameters is a required prerequisite for demonstrating the improvement, as revealed in the present study. Also, the exact nature of the intervention needs to be critically examined. A simple Rehab Centre-based respiratory muscle training may not be enough. Rather, a much more comprehensive intervention is required to get the real benefit from the program. In the present study the comprehensive program, as suggested by the current British Thoracic Society/European Respiratory Society pulmonary rehabilitation statement [28], was followed.

It is noteworthy that the program is relatively more helpful to the subjects who need it more (i.e. the subjects who have poorer pulmonary function after Covid recovery. Baseline capacity as a major factor underlying the improvement has been found even after the adjustment of the effect of age and BMI. Accordingly, the program seems to be suitable for a wide spectrum of the population. This pulmonary rehabilitation Centre interventional study is relatively rare; most of the reported studies were conducted on hospitalized subjects. Evidence of the effectiveness of PR in the context of a developing country is highly important from a socioeconomic point of view.

Interpretation in the light of published paper

The present findings are in line with the data of a retrospective indoor-PR-based study by Hermann., *et al*. [20] who investigated the effects of a comprehensive PR on severe and critical patients. Gloeckl., *et al*. [23] also reported the effectiveness and safety of such a program among hospitalized patients. To the best of our knowledge, only one study [24] has been published with data on the benefits of an outdoor-based PR program among post-COVID problem-affected Austrian subjects. The authors concluded that exercise capacity, functional status, dyspnea, fatigue and quality of life improved after 6 weeks of personalized interdisciplinary pulmonary rehabilitation in patients with long COVID.

Strength and Limitations

The major strength of this study is the inclusion of patients based in an outpatient setting whose information/ data could be retrieved reliably from the records of the Centre. Also, the subjects belonged to the age group when pulmonary rehabilitation was mostly required.

The study, however, has a major limitation in regards to the lack of a randomized Control group which was not possible to include due to ethical reasons. Also, the effects of several confounders could not be analyzed by multivariate statistics due to the small size of the sample. A third limitation of our study might be a specific selection bias because COVID-19 patients mainly with a focus on lung disease were referred to our pulmonary rehabilitation programme. It is known that there are COVID-19 patients in which neural, cardiac, renal, gastrointestinal or coagulative disorders dominate [29]. This limits the generalisability of our findings.

Conclusion

In conclusion, the present data demonstrates that even a relatively short-term (8-week) pulmonary rehabilitation program has a beneficial effect on exercise endurance and pulmonary function in subjects affected with post-COVID problems. However, the PR needs to be comprehensive with all the major components properly addressed during the implementation of the program. Also, sociocultural tailored optimum protocol, duration, and long-term benefits (including cost-effectiveness) of OPD as well as Home-based PR should be worked out with additional scientific data in each specific context.

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Conflict of Interests

All authors declare that there is no conflict of interest.

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