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Efficacy of pulmonary rehabilitation in patients with post-acute COVID-19

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Abstract. – OBJECTIVE: The most important cause of mortality and morbidity of COVID-19 is lung involvement. In this study, the effects of pulmonary rehabilitation (PR) in the post-acute COVID-19 period on lung functions, functional capacity, dyspnea, quality of life, and psychiatric state were investigated.

PATIENTS AND METHODS: Patients were admitted to a PR program after discharge when their general condition had stabilized. The patients' scores of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio, maximum vital capacity (VCmax), peripheral arterial oxygen saturation (PaO2), 6-minute walking distance (6MWD), Medical Research Council Dyspnea Scale (MRC), St. George Respiratory Questionnaire (SGRQ), and Hospital Anxiety and Depression Scale (HADS) before and after pulmonary rehabilitation were compared. The patients were divided into three groups, mild, moderate, and severe, according to their thorax CT findings.

RESULTS: A total of 52 patients [mean age: 46.7 ± 12.5 (range: 19-76) years] were included in the study. Nineteen patients were in the mild group, 16 in the moderate group, and 17 patients comprised the severe group. Comparing the parameters before and after PR, significant improvement was observed in all three groups in the evaluation parameters after treatment including FVC, FEV1, FEV1/FVC, 6MWD, and MRSC; SGRQ symptoms, activity, effects and total scores; HADS depression, anxiety, and total scores ($p<0.05$ for all).

CONCLUSIONS: PR is a beneficial treatment for patients with COVID-19 with lung involvement for improving lung functions, eliminating dyspnea, and improving functional capacity, psychological status, and life quality of the patient.

Key Words:
COVID-19, Pulmonary rehabilitation, Pulmonary functions, Depression and anxiety scales

Introduction

Coronavirus disease-2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. The first case in the world was seen in Wuhan, China in December 2019 and it was declared as a pandemic by the World Health Organization (WHO) at March 2020[2].

COVID-19 does not cause significant problems in the majority of cases, but it can cause more life-threatening problems, especially in those with co-morbidity, the elderly, and men. Lung involvement is currently the most important cause of mortality and morbidity. Acute respiratory distress syndrome (ARDS) developing in the lung may cause structural damage and fibrosis, and lead to progressive dyspnea[3-6]. In the acute phase, immunosuppressive treatments are often given to suppress the developing hyperinflammatory state. However, after the infection, many problems of the patients, especially the respiratory system, may continue. For example, fatigue, cognitive dysfunction, and dyspnea are ongoing problems in 20-30% of hospitalized patients[7]. Dyspnea may develop due to fibrotic sequelae of COVID-19 infection on the lung parenchyma[8,9]. Age, disease severity, length of stay in the intensive care unit, duration of mechanical ventilation, smoking, and chronic alcoholism seem to be the main risk factors for the development of fibrosis[10]. In addition to standart treatment of COVID-19, some antifibrotic agents such as nintedanib and pirfenidone have been found useful in the prevention and treatment of pulmonary fibrosis[11,12].

In addition to pharmacologic measures, it is suggested that taking the patient to pulmonary

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rehabilitation (PR) during the post-acute period will have a positive effect on the patient's prognosis[13-15]. Providing pulmonary rehabilitation from a multidisciplinary approach, while focusing on making improvements to respiratory, physical, and psychological impairments will address the deficits highlighted by patients with COVID-19[16-19].

In the literature, the number of studies reporting that rehabilitation is required due to residual damage in the lungs and negativities in function tests and that PR positively affects the prognosis of COVID-19 lung involvement has started to increase recently[20-23].

In this study, we aimed to contribute to the literature by investigating the effects of PR on pulmonary function tests, functional capacity, dyspnea, quality of life, and psychological symptoms in the post-acute period of COVID-19 pneumonia and to set an example as a design for other future studies on this subject.

Patients and Methods

Between December 1st, 2020, and June 31st, 2021, adult patients who were hospitalized due to COVID-19 and pulmonary involvement were included in the study. Demographic and clinical features of the patients such as age, sex, body mass index (BMI), smoking status (as smoker or nonsmoker), and comorbidities (e.g. diabetes mellitus, hypertension) were recorded. COVID-19 diagnosis was based on positive nasopharyngeal polymerase chain reaction (PCR) and thorax computed tomography (CT) imaging. Patients were divided into three groups according to the lesions on the thorax CT, mild, moderate, and severe[24].

All patients were enrolled in an outpatient program at a unit reserved for PR. Patients with a history of lung disease (obstructive type and restrictive type lung diseases) that would affect respiratory functions, patients with spinal disease that could affect thoracic mobility (e.g., spondyloarthropathy, kyphoscoliosis, diffuse idiopathic skeletal hyperostosis), those with other musculoskeletal problems, patients with neurologic, cardiac, and renal involvement due to COVID-19, and patients with angina pectoris, recent myocardial infarction, and severe cardiac arrhythmia were excluded from the study. Patients with a mini-mental score of 25 and above were included.

The patients were evaluated according to the parameters detailed below:

1. Lung Function: All patients were evaluated using standard pulmonary function testing with a spirometer (Wyntus One; Vyaire Medical Inc., Mettawa, IL, USA) to assess forced vital capacity (FVC, L), forced expiratory volume in the first second (FEV1, L), FEV1/FVC ratio, and maximum vital capacity (VCmax, L)[25]. Oxygen saturation (SO_2) was evaluated using pulse oximetry.
2. Functional capacity: The 6-minute walking distance (6MWD) was used to determine functional capacity. The 6MWD is a part of the 6-minute walking test developed in 1963 and is a functional test that measures the distance a person walks in meters in 6 minutes. Contraindications and termination criteria reported by the American Thoracic Society (ATS) were followed in the application of the test[26].
3. Dyspnea: The Medical Research Council Dyspnea Scale (MRC) was used in the evaluation of dyspnea. The MRC is a 5-item scale based on various physical activities that cause dyspnea. The patient was asked to select the most appropriate option describing respiratory distress by reading the scale options. On the scale, 0 indicates no dyspnea, and 5 indicates worst dyspnea[27].
4. Quality of Life: To assess quality of life, the St. George Respiratory Questionnaire (SGRQ) was used. Scoring was calculated in three areas as symptoms (8 items), activity (16 items), and psychosocial influence (26 items), and a total score was obtained. Scoring is made between 0-100 in this survey; 0 points mean 'excellent' and 100 points indicate 'poor' results[28].
5. Psychological Evaluation: The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the anxiety and depression levels of the patients. HADS consists of 14 items related to anxiety and depression. Each item is scored between 0-3 points. Higher scores from the questionnaire indicate that the level of anxiety and depression is more severe. There are Turkish validity and reliability studies of the SGRQ and the HADS[29,30].
6. Rehabilitation: All patients were admitted to the outpatient pulmonary rehabilitation program for 4 weeks, once per day/5 days per week. Before this, the patients were given an education program including lung anatomy, physiology, physiopathology, bronchial hygiene techniques, and exercise techniques. The

rehabilitation program consisted of nutritional assessment and support, occupational therapy, psychosocial support, joint range of motion exercises, aerobic exercises, energy control techniques, strengthening exercises, breathing exercises, and stretching and relaxation exercises. The range of motion exercise consisted of a single set of 10 repetitions for the neck, waist, upper and lower extremities given before the aerobic exercise. Aerobic exercise was performed under a monitor on a treadmill (15 min) and static bike (10 min) for a total of 25 minutes, with 60-70% of PVO2 and heart rate reserve, at a slightly difficult (13-14 on the Borg scale) exercise intensity. Strengthening exercises were applied to the pectoralis major, triceps, biceps, latissimus dorsi, abdominal muscles, quadriceps, hamstrings, and gastrocnemius muscles at mild to moderate difficulty (Borg 13-14 level) with 15 repetitions, one set, 500-2000 grams. Breathing exercises to strengthen inspiratory and expiratory respiratory muscles (voluntary isocapneic hyperpnea, inspiratory resistive loading, inspiratory threshold loading), controlled breathing exercises (pursed lip breathing, segmental breathing, diaphragmatic breathing, slow and deep breathing, the air turning technique, frog breathing, abdominal girdle exercise) included bronchial hygiene techniques. At the end of each exercise session, stretching exercises involving the hamstrings, quadriceps, and pectoral muscles for 15-30 seconds/2-4 times and progressive muscle relaxation with the Jacobson technique were applied to the patients[16].

Ethics committee approval was obtained (Altınbaş University Clinical Research Ethics Committee, no 13722), and all patients read and approved the informed consent form.

Statistical Analysis

The results were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA). The Chi-square test was used to compare categorical variables according to groups. One-way analysis of variance (ANOVA) was used for normally distributed data and the Kruskal-Wallis Test was used for data not normally distributed in the comparison of quantitative variables according to groups. The paired two-sample *t*-test was used to compare normally distributed data before and after treatment, and the Wilcoxon test was used to compare other data. Whether the data were normally distributed was tested using the Kolmogorov-Smirnov test. Analysis results are presented as mean+standard deviation (minimum-maximum) for quantitative data, and frequency (percent) for categorical data. *p*-values of less than 0.05 were accepted as significant.

Results

A total of 52 patients were included in the study, 16 (31%) women and 36 (69%) men. The mean age of the patients was 46.7±12.4 years. Only two (3.8%) patients were active smokers, the others were nonsmokers (four patients had stopped smoking at least 2 years ago). No additional disease was found in 42 patients, but 10 patients had hypertension and/or diabetes, or hypothyroidism. The demographic and clinical characteristics of the patients are shown in Table I.

The patients were divided into three groups according to their thorax CT findings, mild (n=19), moderate (n=16), and severe (n=17). There were no significant differences regarding the age, BMI, and sex distributions between the groups ($p > 0.05$ for all) (Table I).

Comparing the parameters before and after PR, a significant improvement was observed in all three groups in the evaluation parameters after

Table I. Demographic and clinical features of the patients.

	N:	%
Gender		
Men:	36	69.2
Woman	16; 31%	30.8
Age	46.7 ± 12.4	(19-76)
BMI (kg/m^2)	27.7 ± 4.5	27.5 (16-36.9)
Smoke		
Nonsmoker	50	96.2
Active smoker	2	3.8
Co-Morbid Diseases		
No:	42	80.8
Hypertention	6	11.5
Diabetes Mellitus	2	3.8
Hypertention + Diabetes Mellitus	1	1.9
Hypothyroidism	1	1.9
Thorax CT		
Mild	19	36.5
Moderate	16	30.8
Severe	17	32.7

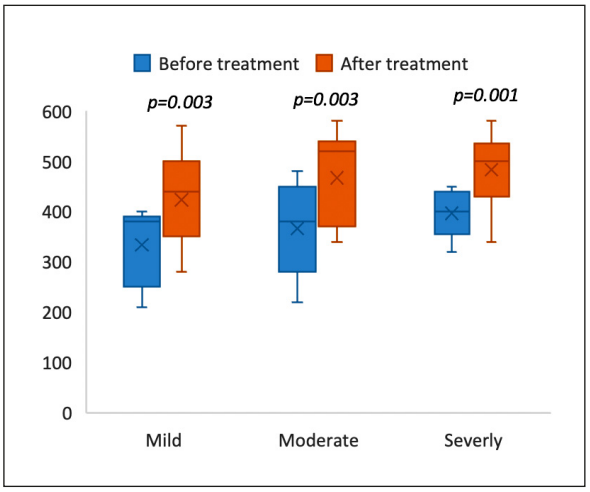

Figure 1. Box plot for 6 min walking distance.

treatment including FVC (L), FEV1 (L), FEV1/FVC (%), VCmax (L), 6MWD, MRSC, SGRQ symptoms, SGRQ activity, SGRQ effect, SGRQ total score, HADS depression, HADS anxiety, and HADS total score (Figures 1-8, Table II).

For VCmax, only the severe group had a significant difference before and after PR, but no significant difference was found for the mild and moderate groups before and after PR (Table II).

Discussion

COVID-19 has continued to occupy the world agenda for a while. Although the last variant, Omicron, had a mild course, it had higher conta-

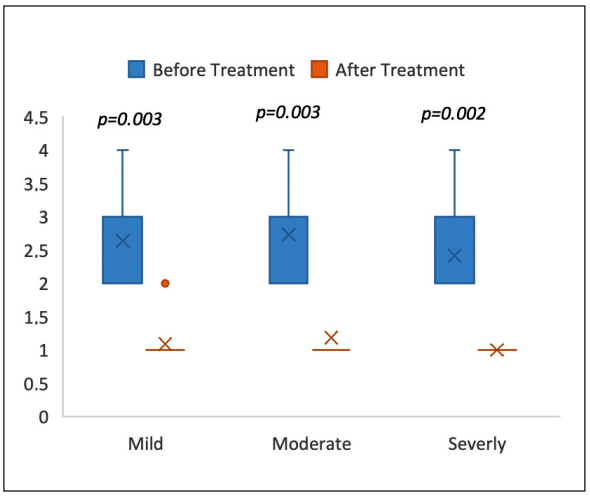

Figure 2. Box plot for MRSC.

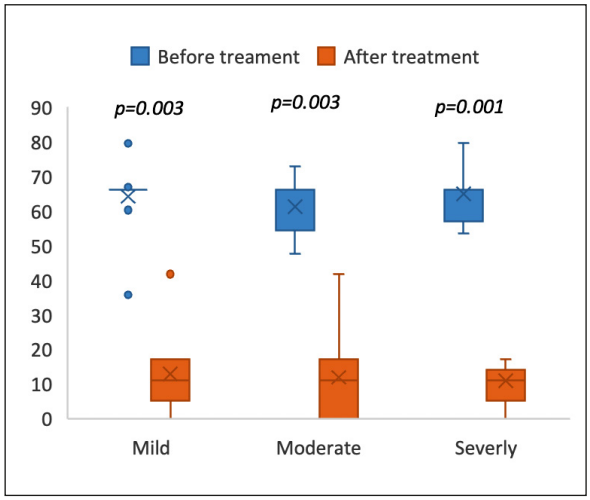

Figure 3. Box plot for SGRQ Activity.

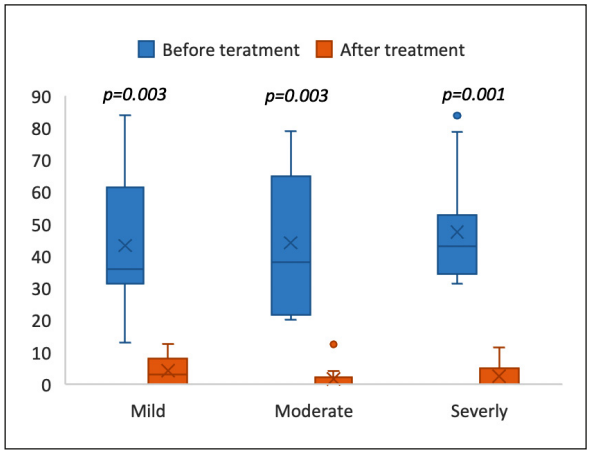

Figure 4. Box plot for SGRQ Effect.

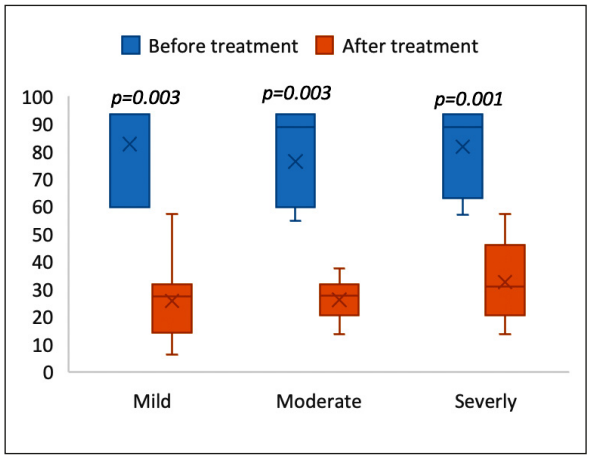

Figure 5. Box plot for SGRQ Symptom.

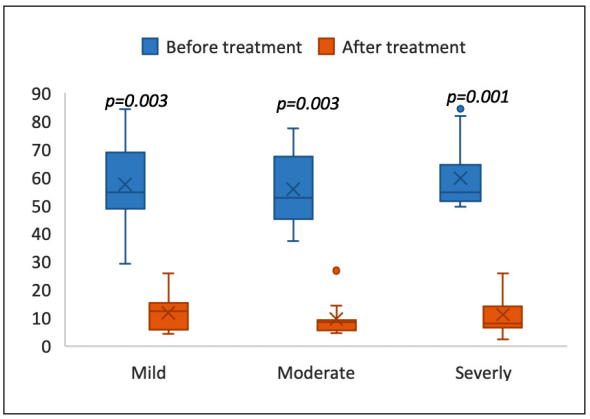

Figure 6. Box plot for SGRQ Total.

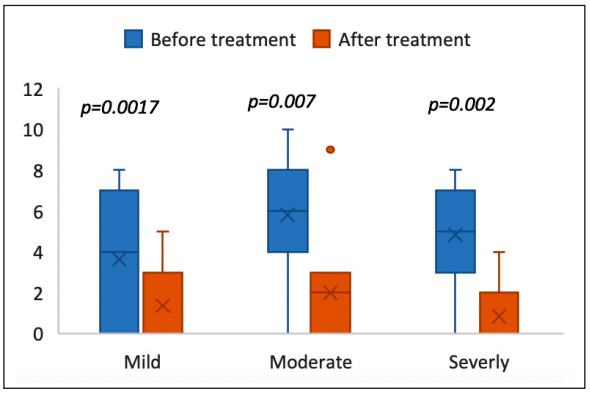

Figure 7. Box plot for HADS HD.

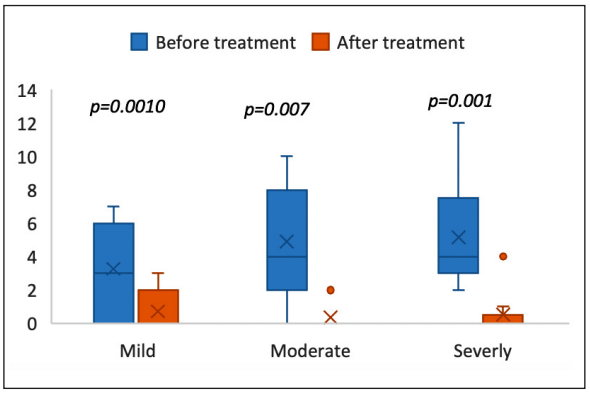

Figure 8. Box plot for HADS HA.

giousness and could infect people despite being vaccinated. COVID-19 lung, which is a rare complication of this disease, but has become very widespread, is a candidate to become a public problem. Although the virus is eradicated in patients recovering from COVID-19, removal of the cause of the lung injury does not in itself prevent the development of progressive, fibrotic irreversible interstitial lung disease[31]. Moreover, even a relatively small degree of residual but nonprogressive fibrosis can result in significant morbidity and mortality in older patient populations with COVID-19, many of whom will have pre-existing lung conditions.

It is of vital importance to provide pharmacologic and non-pharmacologic supportive treatments to patients. Unfortunately, there is no definitive medical treatment for COVID-19 lung yet. Although some antifibrotic drugs have been found useful, they are far from being a definitive solution and are very expensive[11,12]. Recently, lung transplantation, which is an aggressive way of treatment, was successfully performed in selected patients with severe lung involvement due to COVID-19[32]. The importance of supportive treatments that can be offered to patients is obvious. On the other hand, many cognitive dysfunctions and mental problems that develop after COVID-19, most of which are evaluated in the long COVID spectrum, especially in patients hospitalized in the ICU, also reduce the quality of life of patients. In the long term, post-COVID-19 infection patients have mental and cognitive fatigue, sleep and mood disorders, persistent cognitive problems, and difficulty restarting work[23].

PR protects against lung functions and supports mental health in patients with chronic lung diseases[33,34]. PR may also be useful in COVID-19 due to the long-term damage it causes. Many centers around the world have approached the issue of PR seriously and have developed various proposals. Leading organizations such as the Italian Association of Respiratory Physiotherapists (ARIR), the Respiratory Rehabilitation Committee of the Chinese Association of Rehabilitation Medicine (CARM), and the Cardiopulmonary Rehabilitation Group of the Chinese Society of Physical Medicine and Rehabilitation (CSPMR) have published various sets of recommendations for this purpose[35-38].

Currently, many centers offer this service to their patients. However, there is insufficient data on the time to start rehabilitation and the duration and frequency of the rehabilitation program in patients with COVID-19. Generally, it is recommended to initiate PR after the patient's condition stabilizes (if fever decreases, dyspnea decreases, respiratory rate decreases below 30 per minute, oxygen saturation exceeds 90%, and virus load decreases)[39-41]. Patients who are hospitalized in

Table II. Distributions of pulmonary functions before and after pulmonary rehabilitation.

	Mild	Moderate	Severe	All patient
BAPO2 Before PR	94.73 ± 2.24* (90-98) *	95.55 ± 2.25 (92-98)	95.69 ± 1.18 (94-98)	95.34 ± 1.91 (90-98)
BAPO2 After PR	97.27 ± 1.1 (95-98)	98 ± 1 (96-99)	98.23 ± 0.73 (97-99)	97.86 ± 1 (95-99)
p	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
FEV1 Before PR	2.64 ± 0.92 (1.05-4.38)	3.31 ± 1.01 (1.25-4.82)	3.35 ± 0.72 (1.99-4.33)	3.12 ± 0.92 (1.05-4.82)
FEV1 After PR	2.87 ± 0.95 (1.13-4.95)	3.67 ± 1.01 (1.61-4.87)	3.68 ± 0.8 (2.25-4.81)	3.42 ± 0.97 (1.13-4.95)
p	**0.004**	**0.001**	**0.002**	**0.001**
FVC Before PR	2.94 ± 1.12 (1.19-5.41)	3.81 ± 1.14 (1.43-5.3)	3.7 ± 0.86 (2.23-4.65)	3.5 ± 1.08 (1.19-5.41)
FVC After PR	3.22 ± 1.12 (1.34.5.94)	4.15 ± 1.15 (1.82-5.49)	4.07 ± 0.84 (2.35-5.51)	3.83 ± 1.09 (1.34-5.94)
p	**0.006**	**0.003**	**0.001**	**0.001**
FEV1/FVC before PR	100.45 ± 14.76 (81-120)	99.55 ± 10.65 (82-116)	104.62 ± 11 (86-117)	101.7 ± 12.06 (81-120)
FEV1/FVC After PR	115.45 ± 7.39 (102-129)	109 ± 5.88 (96-117)	109.85 ± 12.77 (79-129)	111.34 ± 9.59 (79-129)
p	**0.001**	**0.006**	**0.039**	**0.001**
$VC_{max.}$ before PR	2.95 ± 1.07 (1-5)	3.37 ± 1.07 (1-5)	3.24 ± 0.83 (2-4)	3.15 ± 0.99 (1-5)
$VC_{max.}$ after PR	3.58 ± 1.02 (2-6)	3.94 ± 0.85 (2-5)	3.82 ± 0.85 (2-5)	3.78 ± 0.91 (2-6)
p	0.2	0.79	0.033	0.001

*Mean ± standart deviation. (Minimum-maximum).

the ward can be discharged after 3 days of a fever-free period and after two consecutive negative PCRs[42].

From this period, patients are eligible to be admitted to rehabilitation centers, but publications are showing that stool contamination can continue for up to 10 days; therefore, isolation precautions should be considered during the rehabilitation process[43,44]. Kurtaiş Aytür et al[37] recommended a useful PR guide for patients with COVID-19 in many different disease states such as in the acute and post-acute periods, those in the hospital, at home, and patients who are mobile or bedridden. In light of these recommendations, a separate unit was allocated in our hospital for our study. All patients and physiotherapists were equipped with equipment in accordance with isolation precautions, and sterilization was performed after each patient. The patients did not use public transportation in order not to put society at risk and came to treatment using their own vehicles or on foot. Again, PFTs were performed in a separate room, the personnel and patients performing the test wore protective equipment, filters and equipment were changed for each patient, and the environment was disinfected after each patient. Due to these measures, our working time has been extended. When necessary, the rehabilitation program of the patients can be supported with video calls, but all patients were treated at the hospital[19,45].

Alawna et al[46] reviewed 11 studies and presented a safe aerobic exercise prescription for patients with COVID-19. Exercises with an intensity of 60-80% of maximum heart rate and 55-80% of VO2 max, lasting 18-60 minutes in total, including walking, cycling, and running, should be performed 2-3 days a week, but if the patients are active and do not feel fatigued during the exercise, it is said that it can be done every day. It has been shown that an increase in aerobic capacity improves immune functions by increasing serum

immune cells and immunoglobulins, reducing free radical production and oxidative damage, increasing lung tissue flexibility and pulmonary muscle strength, reducing symptoms such as chronic cough, and increasing airway clearance[46]. In our study, aerobic exercises were performed 5 days per week on a treadmill (15 minutes) and a static bike (10 minutes) under a monitor for a total of 25 minutes, 60-70% of PVO2 and heart rate reserve, at mild-moderate intensity (13-15 on the Borg scale) exercise intensity, similar to the recommendation in the current publication[46].

In this study, we examined the pulmonary functions, quality of life, and the effect of PR on depression and anxiety scales in the post-acute period of patients with COVID-19 and pulmonary involvement after a short-term follow-up. For this purpose, we measured the depression and anxiety scale and functional capacity and quality of life of our patients before and after the special PR program, as well as pulmonary function tests. In terms of FVC, FEV1, FEV1/FVC, 6MWD, MRSC, SGRQ symptom, SGRQ activity, SGRQ effect, SGRQ total score, HADS depression, HADS anxiety, and HADS total scores of patients showed significant improvement after PR (p<0.005) for all. Vc Max, on the other hand, improved significantly in severe COVID-19 cases. Seven of our patients remained in the ICU and received mechanical ventilation support (about 4 days on average), and then continued their treatment in the ward with oxygen support. A statistically significant improvement was observed in all evaluation parameters after treatment. We suggest that the reason for this success in the treatment results is the young age of our patient group, the low rate of additional diseases, the low rate and sort duration of stay in the ICU, and the good management of the rehabilitation process. So much so that some of our patients did not have a habit of exercising in the past, but at the end of the treatment, they took the equipment to their homes and continued the exercises. We saw that the decrease in dyspnea and the increase in functional capacities of the patients at the end of the treatment process facilitated their daily life activities and relieved their depression and anxiety. In a randomized controlled trial by Liu et al[14] who applied PR in the form of telerehabilitation to 36 of 72 post-acute COVID-19 older patients for 6 weeks, the authors found significant improvement in respiratory function, quality of life, and anxiety, as in our study. Gloeckl et al[13] conducted a prospective observational cohort study on 50 patients, 24 with mild/moderate and 26 with severe/critical COVID-19, and a 3-week PR program was applied in the post-acute period. It was suggested to be effective, safe, and beneficial in improving exercise performance, lung function, and quality of life in patients with persistent sequelae due to a mild to critical course of COVID-19. In the prospective observational cohort study of Curci et al[15], 32 post-acute older patients with COVID-19 who were discharged from the ICU and hospitalized were divided into two groups according to their fractionated oxygen levels (FiO2 21-40% and 40-60%). The PR protocol was for 2 to 3 weeks. The authors expressed that their protocol might be useful in the clinical practice of patients with COVID-19 at the early stages of recovery. A limited number of clinical studies regarding post-acute respiratory rehabilitation following COVID-19 infection have been published in the literature[13,45,46].

Limitations

The lack of a control group, the small number of patients, and the absence of long-term follow-up results are limitations of our study, but it provides preliminary information for future controlled double-blind studies.

Conclusions

PR is a supportive and beneficial treatment for patients with COVID-19 with lung involvement for improving lung functions, eliminating dyspnea, and improving the functional capacity, psychological status, and life quality of the patient. It should be recommended to all patients, including those who are isolated or unable to leave the house.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

All the investigators ensure that the study has been conducted according with the Declaration of Helsinki Guidelines. Ethics committee approval was obtained (Altınbaş University Clinical Research Ethics Committee, no. 13722).

Informed Consent

All patients read and approved the informed consent form.

Availability of Data and Material

The study data are available at Bahcelievler Medicalpark Hospital archive.

Authors' Contribution

Data colletion, Conceptualization (A.O.H, S.K, M.S), methodology and writing — original draft preparation (A.O.H, S.K, S.S.B, M.S) writing — review & editing and supervision (A.O.H, M.S.). All authors have read and agreed to the last version of the manuscript.

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