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THE EFFECTS OF A PULMONARY REHABILITATION PROGRAMME ON FUNCTIONAL CAPACITY AND STRENGTH OF RESPIRATORY MUSCLES IN PATIENTS WITH POST-COVID SYNDROME

UČINEK PROGRAMA PLJUČNE REHABILITACIJE NA FUNKCIONALNO SPOSOBNOST IN MOČ DIHALNIH MIŠIC PRI BOLNIKIH Z DOLGIM COVIDOM

Lana VRANIĆ [1], **Zrinka BILOGLAV** [2], **Petar MEDAKOVIĆ** [3], **Jasminka TALAPKO** [4], **Ivana ŠKRLEC** [4*]

[1] Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, 10000 Zagreb, Croatia
[2] Department of Medical Statistics, Epidemiology and Medical Informatics, School of Public Health Andrija Štampar, University of Zagreb School of Medicine, 10000 Zagreb, Croatia
[3] Department of Radiology, Polyclinic Croatia, 10000 Zagreb, Croatia
[4] Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Crkvena 21, 31000 Osijek, Croatia

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ABSTRACT

Aim: The aim of this study was to estimate the effects of a pulmonary rehabilitation programme (PR) on the functional capacity and respiratory muscle strength of patients with post-COVID syndrome.

Methods: A cross-sectional study was conducted using hospital data on patients who participated in a pulmonary rehabilitation programme at the Clinic for Lung Diseases, University Hospital Centre Zagreb, Croatia, between January 2021 and December 2022. Data on the spirometry, respiratory muscle strength, and functional exercise capacity of patients were collected at baseline and three weeks after the start of rehabilitation. The study included 80 patients (43 females, 37 males) with a mean age of 51±10 years.

Results: A significant increase in respiratory muscle strength ($P<0.001$) was observed after pulmonary rehabilitation, with effect sizes ranging from small to large (Cohen's d from 0.39 to 1.07), whereas the effect for PImax expressed as a percentage was large (Cohen's d=0.99). In addition, the pulmonary rehabilitation programme significantly improved the parameters of the six-minute walk test in patients, and the parameters of lung function, FVC, FEV1, and DLCO also improved significantly after PR ($P<0.05$).

Conclusion: The results showed that the pulmonary rehabilitation programme has clinically significant effects on functional capacity and respiratory muscle strength in patients with post-COVID syndrome.

Keywords:
Dyspnea
Post-COVID syndrome
Pulmonary function tests
Pulmonary rehabilitation
Respiratory muscle strength

IZVLEČEK

Cilj: *Cilj te študije je bil oceniti učinek programa pljučne rehabilitacije na funkcionalno sposobnost in moč dihalnih mišic pri bolnikih z dolgim covidom.*

Metode: *Opravili smo presečno študijo na podlagi bolnišničnih podatkov o bolnikih, ki so med januarjem 2021 in decembrom 2022 sodelovali v programu pljučne rehabilitacije v Kliniki za pljučne bolezni v Univerzitetnem bolnišničnem centru v Zagrebu. Podatke o spirometriji, moči dihalnih mišic in funkcionalni zmogljivosti za telesno aktivnost bolnikov smo zbrali ob izhodišču in tri tedne po začetku rehabilitacije. Študija je vključevala 80 bolnikov (43 žensk, 37 moških) povprečne starosti 51±10 let.*

Rezultati: *Ugotovili smo bistveno povečanje moči dihalnih mišic ($P < 0,001$) po pljučni rehabilitaciji, pri čemer so bile velikosti učinka od majhnih do velikih (Cohen d od 0,39 do 1,07), učinek za PImax, izražen v odstotku, pa je bil velik (Cohen d = 0,99). Poleg tega je program pljučne rehabilitacije precej izboljšal parametre 6-minutnega sprehoda pri bolnikih, parametri pljučne funkcije FVC, FEV1 in DLCO pa so se po pljučni rehabilitaciji prav tako znatno izboljšali ($P < 0,05$).*

Zaključek: *Rezultati so pokazali, da ima program pljučne rehabilitacije pri bolnikih z dolgim covidom klinično pomemben učinek na funkcionalno sposobnost in moč dihalnih mišic.*

Ključne besede:
dispneja
dolgi covid
testi pljučne funkcije
pljučna rehabilitacija
moč dihalnih mišic

***Correspondence:** iskrlec@fdmz.hr

1 INTRODUCTION

In late 2019, the WHO declared a COVID-19 pandemic (1), with the severity ranging from asymptomatic to mild forms of the disease, to multiple organ failure and death (2).

In addition to the acute phase, a distinction is also made with regard to post-COVID syndrome or long COVID. This refers to a duration of disease symptoms – such as shortness of breath, fatigue, chest pain, and cough – for more than two months after onset (3, 4). SARS-CoV-2 virus reduces respiratory muscle strength independently or in combination with other factors, resulting in shortness of breath in patients in acute and post-COVID phases (5). Pathophysiological mechanisms include direct myopathic effects on respiratory muscles (4) or damage to neurological control of breathing (6).

The pulmonary rehabilitation (PR) programme, based on 2013 recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS), aims to improve the health status of patients with chronic respiratory diseases (7). Patients with chronic obstructive pulmonary disease commonly use PR, but it is effective with many other pulmonary diseases, such as COVID-19 and post-COVID syndrome. In the long term, it improves the physical and psychological health of patients with chronic lung diseases (7). It improves the quality of life by improving cardiorespiratory and bone-muscular function, reducing dyspnea and fatigue intensity (8). During rehabilitation, the patient's condition is regularly assessed. Exercises are adjusted with a gradual increase in load, and the same tests are performed at the beginning and end of PR programme (9).

Exercises to strengthen respiratory muscles are an important part of PR programme for post-COVID patients (10). Various respiratory muscle strengthening devices are used in rehabilitation, such as an inspiratory muscle training (IMT) device, positive expiratory pressure device (PEP), and Respifit S (an inspiratory muscle training device). The IMT device increases the strength of the patient's respiratory muscles and is more effective than breathing exercises (11), while IMT exercises improve respiratory muscle strength and lung function in COPD patients (12). The efficacy of these exercises has already been demonstrated in patients with some other diagnoses. Morgan et al. examined respiratory muscle-strengthening exercises in post-COVID-19 patients, and their review found that pulmonary function improved in all but one of included studies, and dyspnea and quality of life improved significantly (13). This led to a hypothesis that PR programmes positively affect functional capacity and respiratory muscle strength in patients with post-COVID syndrome. This study aimed to investigate a PR programme's effects on lung functional capacity and respiratory muscles strength in patients with post-COVID syndrome.

2 MATERIALS AND METHODS

2.1 Patients

This cross-sectional study was approved by the Ethics Committee of University Hospital Centre Zagreb (No.02/013AG). It was conducted in accordance with guidelines for the safety of subjects participating in such studies, including the Declaration of Helsinki. It included analyses of data collected during routine PR.

Patients who had recovered from COVID-19 and, after clinical evaluation by a specialist, had participated in and fully completed the PR programme at the Clinic for Lung Diseases Jordanovac University Hospital Centre Zagreb from January 2021 to December 2022, were eligible for this study. They had been infected with SARS-CoV-2 over two months before starting rehabilitation. All the patients were required to present a test upon arrival to exclude current SARS-CoV-2 infection. All the data for the study were obtained from the hospital information system.

The study included 80 patients aged 25 to 68 (Table 1). The proportion of women was higher, at 53.8% vs. 46.3%.

Table 1. Characteristics of patients (N=80, 43 females, 37 males).

Variable	All patients	Females (n=43)	Males (n=37)
Mean age (years)	50.96±10.22	50.46±10.53	51.54±9.97
Age (interval)	25–68	25–68	28–68
Age (mode)	49	49	52
Age (median)	51.5	51	52
BMI>30kg/m2*	37 (46.3%)	17 (39.5%)	20 (54.1%)
Comorbidity	56 (70%)	32 (74.4%)	24 (64.9%)

*BMI–body mass index

2.2 Rehabilitation programme

During the three-week PR programme, the patients attended rehabilitation sessions five times a week. They participated in a three-hour rehabilitation activity each session, including tests, education, exercises, and check-ups. Since the PR programme occurred during the pandemic, all the patients were required to present a negative test upon arrival to rule out SARS-CoV-2 infection. Staff and patients wore protective clothing during the exercises and pulmonary function tests.

The patient was first examined by a specialist who determined whether there were any clinical contraindications to performing PR tests. If there were no contraindications, then the tests followed. Pulmonary function tests (spirometry, diffusion, PImax, PEmax) were performed first. The pulmonary function tests were performed sitting with the feet flat on the floor. The patient wore comfortable clothing that did not constrict them anywhere, and thus made breathing difficult. After 10 minutes, when the patient had rested sufficiently, the six-minute walk test (6MWT) began.

The PR programme took place in a room specially equipped for exercise with all the necessary devices. The PR programme was held at two times, at 8 am and noon, and each session lasted three hours. During this time, the patients learned diaphragmatic breathing exercises, exercises to strengthen the muscles of the extremities with the help of supports, and exercises to strengthen the respiratory muscles with the help of various devices (IMT, PEP, Respifit S), they also performed endurance exercises (cycling, walking on treadmill) and learned Nordic walking techniques. Nurses and physiotherapists supervised the patients during all the exercises. In addition to correct execution, during each activity the patients' blood oxygen saturation and pulse rate were monitored, so that they would not be subjected to an effort that was too intense for them at that moment. PR aims to ensure that patients learn the correct breathing techniques and use them daily to improve their quality of life.

Patients who trained on an IMT or PEP device were later given this device to continue training after the PR programme. In contrast, the Respifit S was used exclusively during rehabilitation and under the supervision of medical staff.

2.3 Pulmonary function tests and respiratory muscle strength

Pulmonary function tests were performed with a Schiller LFX8 spirometer according to the ATS and ERS standards using the standardized quality control protocol ERS93&GLI2017 (14, 15). The following parameters were compared: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and ratio of FEV1/FVC, i.e., the Tiffeneau index and diffusion capacity of lungs for carbon monoxide (DLCO) to evaluate the effects of PR on lung function (16). Patients had to have at least three technically correct measurements for the results to be acceptable. The results were then compared with the expected values for patient age, sex, height, and weight. Values greater than 80% for FEV1, FVC, and DLCO and >70% for the Tiffeneau index were considered normal (17).

Respiratory muscle strength was determined, with PImax indicating the maximal inspiratory pressure and PEmax the maximal expiratory pressure. Measurements for both values were taken at least twice. Any result >80% of patient's reference value, as determined by age, sex, height, and weight, was considered the lowest normal value for PImax and PEmax.

2.4 Six-minute walk test and grade of dyspnea

The 6MWT determines the functional exercise capacity of patients with moderate to severe lung disease (18), based on the maximum distance a patient can walk in a given period (19). The patient's vital signs at rest (arterial pressure, peripheral blood oxygen saturation (SpO2), and pulse) were measured at the test's beginning and end. The degree of dyspnea at rest was determined using the modified Borg scale from 0 to 10, where 0 indicated complete absence of dyspnea and 10 the most severe dyspnea (20). At the end of the 6MWT test, measurements were repeated to determine whether vital signs had changed or SpO2 had decreased during fast walking.

2.5 Statistical methods

Data are presented as the arithmetic mean and standard deviation (SD), arithmetic mean difference, and 95% confidence interval (95%CI). The differences in pulmonary function tests before and after completion of the PR programme were calculated using Student's t-test for paired samples. The comparison of proportions was assessed with a chi-square test. Differences between PR initiation time after COVID-19 were tested by one-way ANOVA. Effect sizes were calculated for all differences in measured outcomes after the PR programme using Cohen's d index. The SPSS statistical programme (26.0, SPSS, USA) was used for statistical analysis, and $P<0.05$ was considered significant.

3 RESULTS

Most patients (71.3%) started the rehabilitation programme more than four months after having COVID-19 (Figure 1).

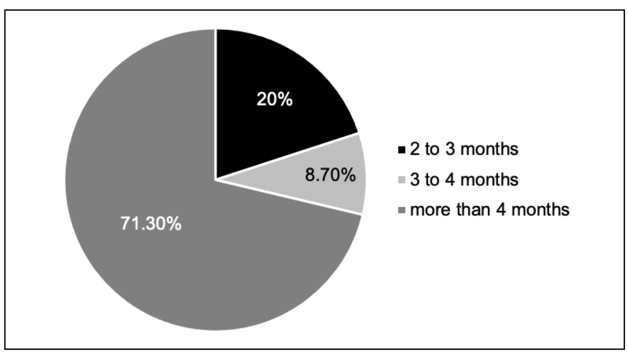

Figure 1. The distribution of patients depends on the time of initiation of PR after COVID-19 (N=80, 43 females, 37 males).

Over half of the patients had decreased respiratory muscle strength (<80%) and functional capacity before the PR programme. After rehabilitation, 51.3% and 16.3% of patients had PI_{max} and PE_{max} values <80% of the predicted threshold, respectively, whereas only 21.3% had a 6MWT distance <80% of the predicted reference value (Table 2).

The effects of PR on patients' respiratory muscle strength (Table 3) showed significant differences (P<0.001), with small to large effect sizes. The effect and difference are very large for PImax. The mean value of PImax increased by 18.16 cmH2O and PEmax by 8.50 cmH2O. The results for all other pulmonary function parameters in patients with COVID-19 syndrome showed significant improvement after PR (P<0.05), except for the Tiffeneau index. However, the effect sizes of PR ranged from very small to small, with a Cohen's d index from 0.18 to 0.48. PR significantly improved functional capacity as measured by 6MWT, with a large effect size. Peripheral oxygen saturation improved significantly, but the effect size was small. A significant reduction in dyspnea, as measured on the modified Borg scale, was observed after PR, with a small effect.

Table 2. Pathological values of pulmonary parameters and respiratory muscle strength before and after the PR programme (N=80, 43 females, 37 males)

Variable	Baseline n(%)	After PR n(%)	P*	Cohen's d
PI_{max}<80%	57 (71.3)	41 (51.3)	**<0.001**	0.89
PE^{max}<80%	28 (35)	13 (16.3)	**<0.001**	0.15
FVC<80%	14 (17.5)	8 (10)	0.251	0.06
FEV1<80%	19 (23.8)	14 (17.5)	0.338	0.59
FEV1/FVC<70%	16 (20)	18 (22.5)	0.699	0.41
DLCO<80%	15 (18.8)	13 (16.3)	0.677	0.26
6MWT<80 %	44 (55)	17 (21.3)	**0.007**	0.65

*Chi-square test.

Table 3. The effects of the PR programme on muscle strength (N=80, 43 females, 37 males).

Variable	Baseline M±SD	After PR M±SD	Mean difference (95%CI)	P*	Cohen's d
PI_{max}	69.90±26.49	88.06±26.23	18.16 (-21.94-(-14.38))	**<0.001**	1.07
PI_{max}(%)	64.74±25.01	80.84±24.57	16.10 (-19.72-(-12.48))	**<0.001**	0.99
PE_{max}	92.16±30.03	100.66±30.49	8.50 (-12.78-(-4.22))	**<0.001**	0.44
PE_{max}(%)	90.80±27.26	99.78±25.82	8.98 (-14.13-(-3.82))	**0.001**	0.39
FVC	4.14±1.28	4.33±1.29	-0.14 (-0.21-(-0.07))	**<0.001**	0.48
FVC(%)	98.16±18.28	100.49±16.97	-2.92 (-4.64-(-1.19))	**0.001**	0.39
FEV1	3.04±0.93	3.15±0.96	-0.08 (-0.13-(-0.04))	**0.001**	0.42
FEV1(%)	90.61±18.97	92.16±18.58	-2.36 (-3.76-(-0.97))	**0.001**	0.39
FEV1/FVC	74.28±11.62	73.47±11.93	0.68 (-0.18-1.54)	0.122	0.18
DLCO	24.34±7.58	24.96±7.81	-1.17 (-2.02-(-0.33))	**0.007**	0.35
DLCO(%)	95.23±21.57	95.88±21.72	-4.03 (-7.11-(-0.95))	**0.011**	0.33
6MWT(m)	442.76±96.22	503.11±105.15	-66.92 (-84.01- (-49.82))	**<0.001**	0.91
6MWT(%)	77.72±16.06	87.68±13.86	-9.66 (-11.78-(-7.55))	**<0.001**	1.08
SpO_2 (before 6MWT)	96.59±2.10	97.14±1.64	-0.64 (-1.09-(-0.19))	**0.006**	0.33
SpO_2 (after 6MWT)	94.15±4.89	94.60±4.29	-0.56 (-1.09-(-0.04))	**0.036**	0.25
Dyspnea (Borg)	3.53±2.32	2.63±1.94	0.95 (0.44-1.45)	**<0.001**	0.44
Heart rate	81.43±12.67	113.65±18.27	-32.22 (-36.39)-(31.99))	**<0.001**	1.75

*Student's t-test for paired samples.

In Table 4, we compared the outcomes after PR between patient groups according to the time elapsed between onset of COVID-19 and start of rehabilitation. Significant differences ($P<0.05$) were observed for higher PI_{max} in patients who started rehabilitation after two to three months than in those who started rehabilitation more than four months after the onset of COVID-19. The lowest values of PI_{max} were measured in patients who started rehabilitation more than four months after disease onset. Post-hoc analysis showed that PI_{max} in terms of cmH2O was significantly higher in patients who started PR two to three months after disease onset than in patients who started rehabilitation more than four months after it (Tukey P=0.024). The same was true for PI_{max} in percentage terms (Tukey P=0.012). For PI_{max}, no significant difference was found between patients who started PR two to three months after COVID-19 and patients who started rehabilitation three to four months after COVID-19 (Tukey P=0.369). For PE_{max}, there was no significant difference with regard to the time when rehabilitation started after COVID-19. The time elapsed from disease onset to initiation of PR had no significant effect on other spirometric pulmonary function test results or DLCO, 6MWT, and dyspnea. A post-hoc analysis showed that patients who started PR two to three months after disease onset had a significantly higher heart rate than patients who started rehabilitation more than four months after it (Tukey P=0.038).

4 DISCUSSION

COVID-19 and post-COVID syndrome, relatively new clinical entities for acute and chronic patients' health problems, have become subject of numerous studies. The results of this study support the clinical use of a PR programme with post-COVID-19 patients, since it significantly improved most indicators of pulmonary function.

At the end of rehabilitation, the values of FEV1, FVC, DLCO, 6MWT, and respiratory muscle strength improved significantly, with effect sizes ranging from small to large (Cohen's d from 0.35 to 1.08). In contrast, the Tiffeneau index remained unchanged, as both the numerator (FEV1) and denominator (FVC) improved significantly. Lung function increased in litres from 4.14±1.28 to 4.33±1.29 for FVC and from 3.04±0.93 to 3.15±0.96 for FEV1. Functional capacity increased in metres from 442.76±96.22 to 503.11±105.15, with an increase in the predicted value from 77.7% to 87.7%. In addition to the significant effects of PR on lung function, a previous study of older adults who had recovered from COVID-19 confirmed a positive impact on other areas of health, such as quality of life and anxiety. In that study, a six-week PR programme included 10-minute exercises twice weekly to strengthen respiratory muscles and the diaphragm, as well as stretching exercises (21). After hospitalization, post-COVID patients usually have muscle weakness and difficulty breathing after exercise.

Table 4. Differences in outcomes of the PR programme according to the time elapsed between disease onset and the beginning of rehabilitation (N=80, 43 females, 37 males).

Variable	2 to 3 months (n=16) M±SD	3 to 4 months (n=7) M±SD	More than 4 months (n=57) M±SD	P*	Cohen's d
PI_{max}	21.44±24.07	17.86±14.38	17.28±15.05	**0.032**	3.36
PI_{max}(%)	19.88±22.78	16.43±13.29	15.00±14.51	**0.021**	3.29
PE_{max}	7.56±21.62	2.86±25.24	9.46±18.01	0.180	3.30
PE_{max}(%)	8.38±20.33	0.57±23.32	10.18±24.00	0.785	3.86
FVC	0.31±0.34	0.02±0.27	0.11±0.28	0.363	3.33
FVC(%)	5.47±6.69	1.29±8.75	2.40±7.45	0.269	5.92
FEV1	0.15±0.21	0.02±0.18	0.08±0.19	0.124	3.29
FEV1(%)	3.87±4.82	1.00±6.71	2.38±6.14	0.812	4.96
FEV1/FVC	1.48±4.89	2.35±5.04	0.23±3.10	0.327	6.16
DLCO	2.99±3.59	3.61±5.04	0.29±2.91	0.275	3.20
DLCO(%)	8.33±10.36	14.86±15.12	1.14±11.12	0.709	4.41
6MWT(m)	525.87±105.47	468.43±146.46	501.21±99.61	0.483	4.78
6MWT(%)	88.07±11.06	91.17±17.52	87.16±12.68	0.798	6.33
SpO2 (before 6MWT)	97.60±0.99	97.43±1.40	96.96±1.81	0.374	59.08
SpO2 (after 6MWT)	94.40±3.38	93.71±3.15	94.78±4.68	0.813	22.07
Dyspnea	1.97±1.64	2.93±1.43	2.78±2.07	0.332	1.35
Heart rate	84.19±16.14	81.71±10.45	80.57±11.87	**0.047**	6.43

*ANOVA test.

For them, rehabilitation is crucial to improving fitness and muscle strength because the muscles of whole body are weakened in addition to respiratory muscles (22).

PR significantly improved PImax, PEmax, and respiratory muscle strength. A total of 71.3% of patients had a pathological value <80% of the predicted value for PImax at the first measurement, and 51.3% of them at the last measurement. For PEmax, pathological values were found in 35% of patients at the first measurement and in 6.3% of them at the last measurement. Vieira da Costa et al. confirmed the improvement of respiratory muscle strength after PR in a study of nine post-COVID patients with different clinical presentations, dry cough, shortness of breath, and chest pain (23). In addition to improving lung function and respiratory strength, the endurance of the respiratory muscles and diaphragm, main respiratory muscle, and quadriceps all improved (23). Villelabeitia-Jaureguizar et al. studied SARS-CoV-2 patients who were treated with invasive mechanical ventilation in an intensive care unit, and then performed low-intensity respiratory muscle exercises after discharge (24). The results suggest that low-intensity respiratory muscle training improves respiratory strength and quality of life associated with health status and shortness of breath.

In this study the COVID-19 patients who took part in the PR programme recovered better and faster than those who did not participate in it. Their muscle strength, balance, and psychosocial status also improved significantly compared to patients who suffered only respiratory failure. Long-term ICU treatment significantly damages muscle function in the short term, limits physical performance, and reduces quality of life. Al Chikhania at al. suggest that PR programmes may reduce posttraumatic stress (25). The increased PImax and PEmax values after PR indicate that improved inspiratory and expiratory muscle strength is associated with greater mobility of the chest wall and diaphragmatic movements (10, 26). Respiratory muscle training improves muscle strength, airway resistance, and diaphragm thickness. It also reduces dyspnea, as weakness of the respiratory muscles is associated with shortness of breath (10).

The development of fibrosis is partly genetically determined. The angiotensin-converting enzyme-2 gene is expressed in the myofiber membrane of the diaphragm, allowing infiltration of the SARS-CoV-2 virus and increasing gene expression involved in fibrosis (4,27). COVID-19 also changes the function of the diaphragm and decreases its thickness (27). A decrease in diaphragm muscle significantly increases the risk of pneumonia, and low thickness and density at CT are predictors for a severe form of COVID-19 (28). Diaphragm thickness at the end of expiration decreased In COVID-19 patients, and the thickening proportion increased (29). Various pathophysiological mechanisms are involved in the damage to the respiratory muscles that occurs with COVID-19, such as the decreased contractility of the respiratory muscles, myopathy of the respiratory muscles caused by the virus, unilateral paralysis of diaphragm due to unilateral injury of the phrenic nerve, severe atrophy and weakness due to dysfunction of the diaphragm, and baseline respiratory muscle weakness (4). COVID-19 may also affect neural control of breathing and cause unilateral diaphragm paralysis, unrelated to mechanical ventilation and normal lung parenchyma (6, 30).

Fibrous abnormalities and lung fibrosis affect about one-third of COVID-19 patients (31). Risk factors include older age, chronic comorbidities, use of mechanical ventilation during the acute phase of COVID-19, and female gender. The development and progression of pulmonary fibrosis is influenced by each individual's genetic background, i.e., the genes involved in innate antiviral defence, inflammatory lung injury, and the ABO system of blood groups (31, 32). Aging increases lung parenchyma stiffness and facilitates pulmonary fibrosis progression (33). For all these reasons, it is obvious why exercise in PR alleviates the severe symptoms of post-COVID-19 pulmonary fibrosis (34).

The results are consistent with a systematic review, which showed that PR significantly improved exercise tolerance as determined by 6MWT (35). PR improves the pulmonary function parameters and reduces anxiety, depression, and symptoms of dyspnea and fatigue. Moreover, the lung function parameters and respiratory muscle strength were significantly better in patients who took part in a PR programme than in patients who did not (35).

The time between onset of COVID-19 and start of PR had no significant effects on most of the parameters of lung function, except PImax, suggesting that the time of starting PR is not as important clinically as simply starting rehabilitation in terms of achieving faster recovery and improvement in quality of life in post-COVID syndrome patients.

The PR programme is effective in patients recovering from severe acute respiratory syndrome (SARS). In these patients, pulmonary abnormalities are present in up to 75.4% of patients six months after onset of the disease (36), and abnormalities in pulmonary function are present in one-third one year after SARS (37). Some studies reported reductions in DLCO scores ranging from 11% to 45% among patients after one year, while the 6MWT results improved (38). Wu et al. showed radiological abnormalities resembling pulmonary fibrosis seven years after SARS (39). The results of studies on SARS patients, in whom the consequences of damage to pulmonary function are visible seven years after onset of the disease, point to the importance of a timely PR programme in post-COVID-19 patients. Although the short-term consequences of COVID-19, such as weakened lung function, decreased muscle strength, and reduced mobility, are described in detail, further studies are needed to determine whether

COVID-19 permanently impairs lung function. In this way, rehabilitation programmes in the acute and later phases of the disease can be maximally individualized and thus enable the best possible quality of life for each person (40).

In the context of all the previously mentioned studies on patients who have recovered from COVID-19, the use of the PR programme has been shown to have numerous positive effects, with sufficient supporting evidence. This complex programme includes physical activity and breathing exercises that increase respiratory muscle strength and lung function. The results are clinically significant since, at the end of rehabilitation, the patients had the ability to walk a greater distance with a lower grade of dyspnea. The use of the correct breathing patterns and exercises helped the patients to make tremendous efforts and achieve a higher workload with less breathlessness. This underscores the importance of referring patients in the post-COVID phase for PR. Learning the correct breathing patterns, strengthening specific limb muscles, increasing fitness, strengthening the respiratory muscles, improving the pulmonary function parameters, and increasing the functional capacity all help to improve the quality of life. Corral et al. have shown that an inspiratory and expiratory muscle training programme effectively improves the quality of life of people with long-term COVID-19 symptoms (41). In addition, a systematic review with a meta-analysis found that rehabilitation interventions are associated with significant improvements in quality of life, functional exercise capacity, and dyspnea in post-COVID patients (42).

It should be noted that the programme investigated in this study is neither financially nor technically demanding for medical personnel. A clinical psychologist was included in the PR programme and had an important role in treating people with post-COVID syndrome, since anxiety and depression are not uncommon in this population (43). However, psychological monitoring of patients during PR has shown that this medical intervention can improve mental health.

4.1 Study limitations

One of the limitations of this work is that it is a single-centre study. All patients who met the inclusion criteria and had a clinical indication for participation in a PR programme were included in the study. Given such a sampling frame, which implies consecutive sampling, it was impossible to estimate the required sample size before study was conducted. Moreover, data are lacking on the patients' premorbid respiratory status, which might have influenced the measured parameters of lung function and respiratory muscle strength even before the disease, and whether SARS-CoV-2 infection was responsible for their worsening or was a clinical course of another, underlying condition. Nevertheless, these limitations could not significantly affect the study's results because most patients (91.3%) who participated in PR had not previously received pulmonary treatment. The collected data did not include information on the clinical presentation of COVID-19 and hospitalizations. In the Croatian health system, secondary and tertiary medical institutions are not linked by a single hospital information system, and it is impossible to conduct multicentre studies. Although the severity of clinical presentation could be associated with other comorbidities affecting respiratory muscle strength and functional capacity, it could not be subsequently categorized based on secondary use of the collected data. Undoubtedly, further research is needed to determine whether clinical improvement in post-COVID syndrome is attributable to the natural course of the disease, or if PR is crucial in improving the patient's quality of life. However, identifying and quantifying the consequences of COVID-19 and its dynamics over time requires a longitudinal study, extensive clinical follow-up, and many participants. Still, the methodological approach adopted in the current work makes it possible to compare the results with those of previous studies, although the statistical associations that it obtained have some limitations, usually due to the cross-sectional research design.

5 CONCLUSION

PR significantly strengthens the respiratory muscles in patients with post-COVID syndrome, particularly in terms of PImax, by 18.16 litres, it improves lung functional capacity–FVC by 0.14 and FEV1 by 0.08, and reduces dyspnea by 0.95. Besides statistical significance, these positive effects on respiratory muscle strength have clinical relevance. The pulmonary function parameters of FVC, FEV1, and DLCOS significantly improved in the patients, as did endurance based on the results of the 6MWT test. The time elapsed between disease onset and starting the PR programme was not found to be significant in improving lung function, but it did affect respiratory muscle strength.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from the Ethics Committee of the University Hospital Centre Zagreb (No. 02/013 AG).

Informed consent: The manuscript does not contain any individual person's data in any form.

AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study were collected from the hospital's information system and are available upon reasonable request.

CONTRIBUTIONS

All the authors contributed equally to the manuscript, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

ORCID

Lana VRANIĆ:
no ORCID number

Zrinka Biloglav:
https://orcid.org/0000-0002-3245-001X

Petar Medaković:
https://orcid.org/0000-0002-7173-8286

Jasminka Talapko:
https://orcid.org/0000-0001-5957-0807

Ivana Škrlec:
https://orcid.org/0000-0003-1842-930X

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomedica. 2020;91(1):157–60. doi: 10.23750/ABM.V91I1.9397.
2. Pavli A, Theodoridou M, Maltezou HC. Post-COVID syndrome: Incidence, clinical spectrum, and challenges for primary healthcare professionals. Arch Med Res. 2021;52(6):575–81. doi: 10.1016/J.ARCMED.2021.03.010.
3. Jalušić Glunčić T, Muršić D, Basara L, Vranić L, Moćan A, Janković Makek M, et al. Overview of symptoms of ongoing symptomatic and post-COVID-19 patients who were reffered to pulmonary rehabilitation - first single-centre experience in Croatia. Psychiatr Danub. 2021;33(suppl 4):565–571.
4. Severin R, Franz CK, Farr E, Meirelles C, Arena R, Phillips SA, et al. The effects of COVID-19 on respiratory muscle performance: Making the case for respiratory muscle testing and training. Eur Respir Rev. 2022;31(166):220006. doi: 10.1183/16000617.0006-2022.
5. Hockele LF, Sachet Affonso JV, Rossi D, Eibel B. Pulmonary and functional rehabilitation improves functional capacity, pulmonary function and respiratory muscle strength in post COVID-19 patients: Pilot clinical trial. Int J Environ Res Public Health. 2022;19(22):14899. doi: 10.3390/IJERPH192214899.
6. Maurie F, Godbert B, Perrin J. Respiratory distress in SARS-CoV-2 without lung damage: Phrenic paralysis should be considered in COVID-19 infection. Eur J Case Reports Intern Med. 2020;7(6):001728. doi: 10.12890/2020_001728.
7. Spruit MA, Singh SJ, Garvey C, Zu Wallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64. doi: 10.1164/RCCM.201309-1634ST.
8. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020;21(1):163. doi: 10.1186/S12931-020-01429-6.
9. McNarry MA, Berg RMG, Shelley J, Hudson J, Saynor ZL, Duckers J, et al. Inspiratory muscle training enhances recovery post COVID-19: A randomised controlled trial. Eur Respir J. 2022;60(4). doi: 10.1183/13993003.03101-2021.
10. Romaszko-Wojtowicz A, Szalecki M, Olech K, Doboszyńska A. Assessment of the function of respiratory muscles in patients after COVID-19 infection and respiratory rehabilitation. Trop Med Infect Dis. 2023;8(1):57. doi: 10.3390/TROPICALMED8010057.
11. Chung Y, Huang TY, Liao YH, Kuo YC. 12-week inspiratory muscle training improves respiratory muscle strength in adult patients with stable asthma: A randomized controlled trial. Int J Environ Res Public Health. 2021;18(6):1–17. doi: 10.3390/IJERPH18063267.
12. Figueiredo RIN, Azambuja AM, Cureau FV, Sbruzzi G. Inspiratory muscle training in COPD. Respir Care. 2020;65(8):1189–1201. doi: 10.4187/RESPCARE.07098.
13. Morgan SP, Visovsky C, Thomas B, Klein AB. Respiratory muscle strength training in patients post-COVID-19: A systematic review. Clin Nurs Res. 2024;33(1):60–69. doi: 10.1177/10547738231201994.
14. Brusasco V, Crapo R, Viegi G. Coming together: The ATS/ERS consensus on clinical pulmonary function testing. Eur Respir J. 2005;26(1):1–2. doi: 10.1183/09031936.05.00034205.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338. doi: 10.1183/09031936.05.00034805.
16. Moore VC. Spirometry: Step by step. Breathe. 2012;8(3):232–240. doi: 10.1183/20734735.0021711.
17. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, et al. Standardization of spirometry 2019 update: An official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med. 2019;200(8):E70–E88. doi: 10.1164/RCCM.201908-1590ST.

18. Agarwala P, Salzman SH. Six-minute walk test: Clinical role, technique, coding, and reimbursement. Chest. 2020;157(3):603–611. doi: 10.1016/J.CHEST.2019.10.014.
19. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–117. doi: 10.1164/AJRCCM.166.1.AT1102.
20. Johnson MJ, Close L, Gillon SC, Molassiotis A, Lee PH, Farquhar MC, et al. Use of the modified Borg scale and numerical rating scale to measure chronic breathlessness: A pooled data analysis. Eur Respir J. 2016;47(6):1861–1864. doi: 10.1183/13993003.02089-2015.
21. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract. 2020;39:101166. doi: 10.1016/J.CTCP.2020.101166.
22. Zhao HM, Xie YX, Wang C. Recommendations for respiratory rehabilitation in adults with coronavirus disease 2019. Chin Med J (Engl). 2020;133(13):1595–1602. doi: 10.1097/CM9.0000000000000848.
23. da Costa KV, de Souza ITC, dos Santos Felix JV, Brandão CBF, de Souza Fernandes VM, Favero ABL, et al. Efficacy of a rehabilitation protocol on pulmonary and respiratory muscle function and ultrasound evaluation of diaphragm and quadriceps femoris in patients with post-COVID-19 syndrome: A series of cases. Monaldi Arch chest Dis. 2022;93(1). doi: 10.4081/MONALDI.2022.2206.
24. Villelabeitia-Jaureguizar K, Calvo-Lobo C, Rodríguez-Sanz D, Vicente-Campos D, Castro-Portal JA, López-Cañadas M, et al. Low intensity respiratory muscle training in COVID-19 patients after invasive mechanical ventilation: A retrospective case-series study. Biomedicines. 2022;10(11):2807. doi: 10.3390/BIOMEDICINES10112807.
25. Al Chikhanie Y, Veale D, Schoeffler M, Pépin JL, Verges S, Hérengt F. Effectiveness of pulmonary rehabilitation in COVID-19 respiratory failure patients post-ICU. Respir Physiol Neurobiol. 2021;287:103639. doi: 10.1016/J.RESP.2021.103639.
26. Padkao T, Boonla O. Relationships between respiratory muscle strength, chest wall expansion, and functional capacity in healthy nonsmokers. J Exerc Rehabil. 2020;16(2):189. doi: 10.12965/JER.2040080.040.
27. Cesanelli L, Satkunskiene D, Bileviciute-Ljungar I, Kubilius R, Repečkaite G, Cesanelli F, et al. The possible impact of COVID-19 on respiratory muscles structure and functions: A literature review. Sustainability. 2022;14(12):7446. doi: 10.3390/SU14127446.
28. Parlak S, Beşler MS, Gökhan MB. Association of diaphragm thickness and density measured on chest CT with disease severity in COVID-19 patients. Am J Emerg Med. 2022;61:29–33. doi: 10.1016/J.AJEM.2022.08.029.
29. Hadda V, Raja A, Suri TM, Khan MA, Mittal S, Madan K, et al. Temporal evolution of diaphragm thickness and diaphragm excursion among subjects hospitalized with COVID-19: A prospective observational study. Respir Med Res. 2023;83:100960. doi: 10.1016/J.RESMER.2022.100960.
30. Shahid M, Nasir SA, Shahid O, Nasir SA, Khan MW. Unilateral diaphragmatic paralysis in a patient with COVID-19 pneumonia. Cureus. 2021;13(11):e19322. doi: 10.7759/CUREUS.19322.
31. Duong-Quy S, Vo-Pham-Minh T, Tran-Xuan Q, Huynh-Anh T, Vo-Van T, Vu-Tran-Thien Q, et al. Post-COVID-19 pulmonary fibrosis: facts—challenges and futures: a narrative review. Pulm Ther. 2023;9(3):295. doi:10.1007/S41030-023-00226-Y.
32. 32. Kramberger M, Biloglav Z, Talapko J, Škrlec I. The association of abo and rhd blood groups with covid-19 mortality of patients hospitalized in the COVID ward at general hospital Karlovac. Med Flum. 2023;59(2):161–169. doi: 10.21860/MEDFLUM2023_300574.
33. Lyu Q, Wen Y, Zhang X, Addinsall AB, Cacciani N, Larsson L. Multi-omics reveals age-related differences in the diaphragm response to mechanical ventilation: A pilot study. Skelet Muscle. 2021;11(1):11. doi: 10.1186/S13395-021-00267-4.
34. Reina-Gutiérrez S, Torres-Costoso A, Martínez-Vizcaíno V, Núñez de Arenas-Arroyo S, Fernández-Rodríguez R, Pozuelo-Carrascosa DP. Effectiveness of pulmonary rehabilitation in interstitial lung disease, including coronavirus diseases: A systematic review and meta-analysis. Arch Phys Med Rehabil. 2021;102(10):1989-1997.e3. doi: 10.1016/J.APMR.2021.03.035.
35. Soril LJJ, Damant RW, Lam GY, Smith MP, Weatherald J, Bourbeau J, et al. The effectiveness of pulmonary rehabilitation for post-COVID symptoms: A rapid review of the literature. Respir Med. 2022;195:106782. doi: 10.1016/J.RMED.2022.106782.
36. Ng CK, Chan JWM, Kwan TL, To TS, Chan YH, Ng FYY, et al. Six-month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. Thorax. 2004;59(10):889–891. doi: 10.1136/THX.2004.023762.
37. Ong KC, Ng AWK, Lee LSU, Kaw G, Kwek SK, Leow MKS, et al. 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. Chest. 2005;128(3):1393–1400. doi: 10.1378/CHEST.128.3.1393.
38. Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. J Rehabil Med. 2020;52(5):jrm00063. doi: 10.2340/16501977-2694.
39. Wu X, Dong D, Ma D. Thin-section computed tomography manifestations during convalescence and long-term follow-up of patients with severe acute respiratory syndrome (SARS). Med Sci Monit. 2016;22:2793–2799. doi: 10.12659/MSM.896985.
40. Boutou AK, Georgopoulou A, Pitsiou G, Stanopoulos I, Kontakiotis T, Kioumis I. Changes in the respiratory function of COVID-19 survivors during follow-up: A novel respiratory disorder on the rise? Int J Clin Pract. 2021;75(10):e14301. doi: 10.1111/IJCP.14301.
41. del Corral T, Fabero-Garrido R, Plaza-Manzano G, Fernández-de-las-Peñas C, Navarro-Santana M, López-de-Uralde-Villanueva I. Home-based respiratory muscle training on quality of life and exercise tolerance in long-term post-COVID-19: Randomized controlled trial. Ann Phys Rehabil Med. 2023;66(1):101709. doi: 10.1016/J.REHAB.2022.101709.
42. Pouliopoulou D V., Macdermid JC, Saunders E, Peters S, Brunton L, Miller E, et al. Rehabilitation interventions for physical capacity and quality of life in adults with post–COVID-19 condition: A systematic review and meta-analysis. JAMA Netw Open. 2023;6(9):e2333838. doi: 10.1001/JAMANETWORKOPEN.2023.33838.
43. Badinlou F, Lundgren T, Jansson-Fröjmark M. Mental health outcomes following COVID-19 infection: Impacts of post-COVID impairments and fatigue on depression, anxiety, and insomnia — a web survey in Sweden. BMC Psychiatry. 2022;22(1):743. doi: 10.1186/S12888-022-04405-0.