Original Article

Cardiopulmonary rehabilitation programme improves physical health and quality of life in post-COVID syndrome

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Background: Many patients with previous COVID-19 infection suffer from prolonged symptoms after their recovery: cough, dyspnea, chest pain, shortness of breath, fatigue, anxiety or depression, regardless of milder or severe coronavirus infection. Review of the literature demonstrates underrepresented complex cardiopulmonary rehabilitation of patients with post-COVID syndrome. The aim of our quasi-experimental study was to evaluate the effectiveness of complex cardiopulmonary rehabilitation and to assess the quality of life, functional parameters before and after a 14-day specific cardiopulmonary rehabilitation and two months later.

Methods: Sixty-eight patients participated in rehabilitation at Semmelweis University's Department of Pulmonology. Respiratory function: forced expiratory volume in 1 second (FEV_1%pred), 6-minute walk test (6MWT), chest kinematics (CK), quality of life [EuroQol-5D (EQ-5D), Post-COVID-19 Functional Status (PCFS)] and Modified Medical Research Council (mMRC) dyspnea scale were measured at the beginning and end of the programme and two months after the rehabilitation.

Results: The 14-day rehabilitation programme resulted in significant improvement of 6MWT {492 [interquartile range (IQR), 435–547] *vs.* 523 (IQR, 477–580) m; P=0.031}, mMRC [1 (IQR, 0.25–1) *vs.* 0 (IQR, 0–1); P=0.003], EQ-VAS score [75 (IQR, 65–80) *vs.* 85 (IQR, 75–90); P=0.015], and PCFS [1 (IQR, 1–2) *vs.* 0.5 (IQR, 0–1); P=0.032]. Respiratory function and chest kinematics also improved, FEV_1(%pred) [86 (IQR, 73–103) *vs.* 91 (IQR, 80–99); P=0.360], chest kinematics [3.5 (IQR, 2.75–4.25) *vs.* 4 (IQR, 1–5.25) cm; P=0.296], and breath-holding test (BHT) [33 (IQR, 23–44) *vs.* 41 (IQR, 28–58) s; P=0.041].

Conclusions: Complex cardiopulmonary rehabilitation improved workload, quality of life, respiratory function, complaints and clinical status of patients with post-COVID syndrome. Personalized complex pulmonary rehabilitation can be beneficial and recommended for patients suffer from post-COVID syndrome, who have good potential for recovery and are able to participate in the two weeks complex pulmonary rehabilitation.

Keywords: Coronavirus disease (COVID-19); pulmonary rehabilitation; dyspnea; fatigue; quality of life

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus that emerged in 2019 (1), causing coronavirus disease (COVID-19) with a predominantly respiratory manifestation (2,3). In addition, many other organs can also be affected, particularly the cardiovascular system and the central nervous system (4) with complications such as venous thromboembolism (5), cardiac arrhythmias (6), myocarditis, acute coronary syndrome, stroke, cerebral small vessel disease (7-9) and cognitive impairment (4). Older adults are at a higher risk of developing severe symptoms and increased mortality (10-14). The underlying mechanisms involve an age-related decline in immune functions (15-17), age-associated decreases in cellular resilience, dysregulation of angiotensin-converting enzyme 2 (ACE2) (18-20), changes in haemostasis and thrombocyte function (21), nutritional factors and an increased prevalence of co-morbidities (22-25).

Alongside medication, early rehabilitation is a key part of a treatment, playing a role throughout the disease (26), helping to improve exercise tolerance and activities of daily living, quality of life and overall recovery itself (27). The more severe is the course of the disease, the more important is a well-planned complex (includes physical and mental health assessment, social support, educational and exercise training) and individualized (activities adapted to the needs of the individual and the active participation of the patient to be rehabilitated) cardiopulmonary rehabilitation to facilitate the recovery of patients with COVID-19, and this should be a major focus of clinical practice (28).

The post-COVID syndrome is a multisystemic disease with several manifestations that can occur even after mild or asymptomatic COVID-19 infection (29), it can be defined as a condition among confirmed and recovered SARS-CoV-2 infected patients. Post-COVID-19 occurs usually three months after the diagnosis of COVID-19 infection and lasts at least 2 months and cannot be explained by other alternative diagnosis or condition (30). According to a US study, the prevalence of post-COVID syndrome ranges from 10% to 35% meaning that only 65% of patients returning to their previous state of health in 14–21 days after a positive COVID test (31). Causes are thought to be varied with multiple factors at play, such as persistent viremia due to an incomplete or poor antibody response (32), an inflammatory immune response (33), post-traumatic stress or other mental conditions (34), or reinfection or relapse (35). Symptoms of the post-COVID disease can range widely, including cough, chronic fatigue, fever, shortness of breath, chest pain, headache, dizziness, muscle pain, weakness, diarrhoea, weight loss, memory and learning difficulties, thromboembolic complications, metabolic disturbances, anxiety, sleep disturbances, depression, and skin rashes (36). If there are signs of lung damage, the patient should be referred to a pulmonologist and it is advised to start a pulmonary rehabilitation programme as soon as possible (37).

The aim of a complex cardiopulmonary rehabilitation is similar to the rehabilitation of other chronic lung diseases, e.g., chronic obstructive pulmonary disease (COPD), to reduce symptoms and complaints, improve quality of life, increase the strength of the respiratory muscles and auxiliary muscles, teach exhalation and inhalation techniques to help clearing airway secretions, increase physical exercise capacity and endurance by training (38). There are currently no targeted medical treatments for post-COVID syndrome, so early diagnosis and early rehabilitation are essential (39). Rehabilitation of COVID-19 patients treated in intensive care should be started there, in the intensive care unit. The

Highlight box

Key findings

- Post-COVID syndrome has a notable burden of disease that needs a complex cardiopulmonary rehabilitation.

What is known and what is new?

- Personalised post-COVID rehabilitation is beneficial for patients.
- Significant improvements in functional parameters and quality of life can be presented by individualised rehabilitation program in post-COVID syndrome.

What is the implication, and what should change now?

- To prevent the long-term effect of post-COVID syndrome, an early diagnosis is essential. More available post-COVID rehabilitation programs are needed in form of in person rehabilitation or telerehabilitation to help patients to return to their normal life.

Table 1 List of the criteria for enrolment

Inclusion criteria	Exclusion criteria
Individual 18 years or older	Unstable cardiovascular disease (uncontrolled high blood pressure (>140/90 mmHg), cognitive heart failure, angina NYHA Class III–IV, etc.)
Can understand oral and written trial information	Severe rheumatic or orthopedic disease, which limits the freedom of movement
Previous diagnosed COVID-19 infection (≥3 months)	Mental illness
Weakness and/or reduced physical performance expressed after 6 weeks of COVID-19 infection	Unstable diabetes
Constant dyspnea at rest or during light exercise	Exacerbation of pre-existing chronic disease

NYHA, New York Heart Association.

first published results in this field of pulmonary rehabilitation are very promising, with significant improvement in almost all aspects, providing evidence for the importance of pulmonary rehabilitation, the main elements of which are respiratory exercises, physiotherapy, expectorant management, education, dietary advice, psychological and social support, as well as robotic therapy (40).

Pulmonary rehabilitation can be recommended on an individual basis for appropriate symptomatic post-COVID patients, with the involvement of trained professionals, who are familiar with multidisciplinary long COVID care and rehabilitation. The aim of our study is to investigate the effects of a 2-week complex cardiopulmonary rehabilitation on respiratory function, chest kinematics, exercise tolerance, quality of life in patients with post-COVID syndrome. We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1143/rc).

Methods

Study design and population

An observational quasi-experimental study was performed on post-COVID patients at the Department of Pulmonology, Semmelweis University from 01 April 2021 to 01 April 2022. The study protocol was approved by the Ethics Committee of Semmelweis University (No. 160/2021), and it complies with the Helsinki Declaration (as revised in 2013). Patients were given oral and written information prior to the assessment, and then they signed a statement of consent. Patients were involved at least 6 weeks after a negative PCR test result according to our criteria. Participants met the criteria were invited to the rehabilitation programme through their pulmonologists (*Table 1*).

After recovering from COVID-19 infection, the patients visited their specialist for a medical check-up, which included a physical exam, blood- and imaging tests. If a person's general health was adequate for an intensive, comprehensive rehabilitation could apply for our study. The rehabilitation programme started usually at least 3.5 months after the COVID-19 infection. After a physiatrist examined all the applicants using physical examination and questionnaire, 68 patients were involved in our study. Demographics such as age, gender, body mass index and smoking habits, as well as the vaccination status, co-morbidities and current persistent symptoms were collected during a face-to-face interview lead by a physiatrist.

The process of complex pulmonary rehabilitation

Before patients could start their 14-day comprehensive cardiopulmonary rehabilitation programme, they underwent several medical check-ups according to The Centers for Disease Control and Prevention (CDC) requirement of Assessment and Testing for Post-COVID Conditions [physical examination, general and orthostatic, vital signs, laboratory testing; e.g., inflammatory markers (C-reactive protein, ferritin), coagulation markers (D-dimer) or myocardial injury markers (troponin)] (41). Preliminary examination also included the assessment of the patients' overall physical, emotional and behavioural status, social education, nutritional and psychological counselling. After excluding all the harmful physical condition (rheumatologically conditions, coagulation disorders, myocardial injury or differentiate symptoms of cardiac versus pulmonary origin) (14,41), the intensive rehabilitation started. Including a 30-minute group exercise session two or three times daily led by a professional physiotherapist (controlled breathing technique, chest mobility-enhancing and muscle-strengthening exercises with their own body weights and dumbbells as well), and low-intensity individual training (gym bike, treadmill or arm ergometer), where age, comorbidities, and current conditions were taken into account. That was the reason of our limited number (n=68) of patients, who can participate in our rehabilitation.

During the individualized training, the pulse and the oxygen saturation were detected constantly to monitor the physiological changes and avoid harmful effects and stop the training if it is needed. Our primary goal was to assist these patients to recover from post-COVID syndrome and regain their physical and mental (emotional, psychological, and social well-being) (42) health. In line with previous research findings the most frequent comorbidities in our study were: cardiovascular disease, respiratory disease, and diabetes mellitus. Only three patients had no comorbidities at all (43,44). As pre-existing comorbidities negatively affect the course of acute COVID-19, so people with multi comorbidities are more likely to develop more severe acute COVID-19 infection, and are more likely to require rehabilitation in the future (45).

Breathing exercises could significantly improve oxygenation and help to accelerate recovery from post-COVID disease (46). The daily breathing routine included controlled breathing and stretching exercises, respiratory muscle strengthening with the essential element of inhaling through the nose and exhaling through a pursed mouth. As positive pressure could be created during exhalation, that could keep the airways open. This is one of the most vital breathing exercise to support diaphragmatic function, deep, slow breathing. Chest and shoulder expansion were found to promote lung expansion, airway secretion from the small airways, increase vital capacity and all in all improve lung function (47).

Respiratory muscle strengthening was performed twice daily with a respiratory muscle training device, patients inhaled 30 times at 40% of maximum inspiratory pressure (MIP). This part of the rehabilitation made patients to master active cyclic breathing techniques and effective coughing techniques (e.g., in post-COVID patients with COPD or bronchiectasis) and clearing phlegm with positive expiratory pressure (PEP), which was executed in tens of repetitions. Different anthropometric and functional data were recorded at the beginning and at the end of the complex pulmonary rehabilitation programme (such as respiratory function parameters, physical performance, and quality of life). The programme was considered completed if a patient took part in at least 75% of the rehabilitation sessions. No adverse events were observed during the rehabilitation and all patients completed at least 90% of the rehabilitation programme.

Examination of respiratory function

All patients underwent a baseline respiratory function test by an automated computerized spirometer for assessing respiratory function. Dynamic lung volumes were defined as the amount of air expelled in the first second: forced expiratory volume in 1 second (FEV_1%pred), forced vital capacity (FVC%pred), the degree of airway obstruction (FEV_1/FVC), inspiratory vital capacity (IVC) and percentages (IVC%pred), with Global Lung Function Initiative-defined (GLI-defined) normal spirometry (z-score) (48).

The 6-minute walk test (6MWT)

During the 6MWT patients were asked to walk down the aisle for 6 min and the maximum distance (m) walked by the patients in 6 min was recorded. 6MWT measures the distance can be walked quickly on a hard, flat surface in 6 min. This distance in meter is the final result of the test (49).

Modified Medical Research Council dyspnea questionnaire (mMRC-modified questionnaire)

The mMRC Dyspnea Scale stratifies the severity of dyspnea and consists of five statements; it almost completely covers the whole spectrum of respiratory distress, from having no problems (grade 0) to completing respiratory failure (grade 5). Patients could be scored between 0–5; all questions are related to everyday activities and are easy to understand for patients. The score can be calculated in a few seconds, with the score being the number that best fits the condition of the patient (50).

EuroQol-5D (EQ-5D) questionnaire

The EQ-5D measures the health-related quality of life of respondents on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and at three levels to choose from; 1: least, 3: most. The questionnaire is for the standardised measurement of health status, providing a simple, general measure of health status.

Table 2 Anthropometric and functional data of post-COVID patients (n=68)

Variables	Value (n=68)
Age (years)	53.5 [46.7–62.5]
Male/female	39 (57.35)/29 (42.65)
BMI (kg/m^2)	30.6 [28.1–34.7]
FEV_1%pred	86 [73–103]
FEV_1/FVC (%)	109 [102–113]
CRP (mg/L)	3.65 [1.97–8.35]
D-dimer (µg/mL)	0.44 [0.33–0.66]
IL-6 (pg/mL)	3.11 [2.28–5.86]
Ferritin (µg/L)	313.1 [276.5–664.5]
Troponin-T HS (ng/L)	6 [4–9]
Procalcitonin (µg/L)	0.03 [0.02–0.05]

Data are presented as median [IQR] or frequency (percentage). IQR, interquartile range; CRP, C-reactive protein; IL-6: Interleukin-6; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; HS, high sensitivity.

It is not cognitively demanding for the patient and takes a few minutes to complete. The EQ-5D contains two pages: the first part is the EQ-5D descriptive system: five questions and three answers, the second one is the EQ Visual Analogue Scale (EQ-VAS). EQ-VAS has values between 100 (best imaginable health) and 0 (worst imaginable health).

Post-COVID-19 Functional Status (PCFS) Scale

The PCFS Scale assesses patient-relevant functional limitations with the help of a 5-grade score (0–4), where: grade 0 reflects the absence of any functional limitation. Upward of grade 1, symptoms, pain or anxiety are present to an increasing degree. This has no effect on activities for patients in grade 1, whereas a lower intensity of the activities is required for those in grade 2. Grade 3 accounts for inability to perform certain activities, forcing patients to structurally modify them. Finally, grade 4 is reserved for patients with severe functional limitations requiring assistance with activities of daily living (51).

Examination of chest expansion

Chest circumference (cm) was measured at the level of the xiphoid process by a centimetre tape at the end of exhalation and then at the end of inhalation. The difference between these circumferences indicates the value of chest deviation. Exhalation-inhalation was repeated three times to determine chest kinematics more accurately (52).

Blood tests

A fasting blood sample was collected in the central laboratory of Semmelweis University (SYNLAB); the blood test was performed in a clinically stable, fever-free and respiratory infection-free state. We determined the blood levels of D-dimer, C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, high-sensitive troponin T (hs-TnT), and procalcitonin.

Statistical analysis

All statistical analyses were conducted with STATA SE-24.0 (StataCorp, College Station, TX). Since most of the continuous data did not follow the normal distribution (verified by Sapphiro-Wilk test), non-parametric statistical methods were used. Continuous variables were interpreted and represented by medians and interquartile ranges (IQR). Categorical data were presented with case numbers and proportions. To analyse the differences of continuous variables between the two groups we used Mann-Whitney test Frequency differences of categorical variables were tested by Fisher's exact test. 95% confidence interval was considered for all statistical tests, and the significance limit used was $P<0.05$.

Results

Before enrolling our 68 patients, general and specific examination and data recording were done. The demographic and functional characteristics of our study population are shown in *Table 2*. More than half (60.29%) of the post-COVID patients had never smoked, most of the smokers (n=27) had quit smoking, only two were current smokers. In terms of previously known comorbidities, almost half of the patients had hypertension, one-fifth of the patients had other cardiovascular disease, and more than one-third of them had COPD correlated with the smoking status (see *Figure 1*).

The most common subjective symptoms of post-COVID patients included reduced performance, fatigue, shortness of breath when climbing stairs, productive cough, dyspnea, rotatory vertigo, chest discomfort (e.g., retrosternal

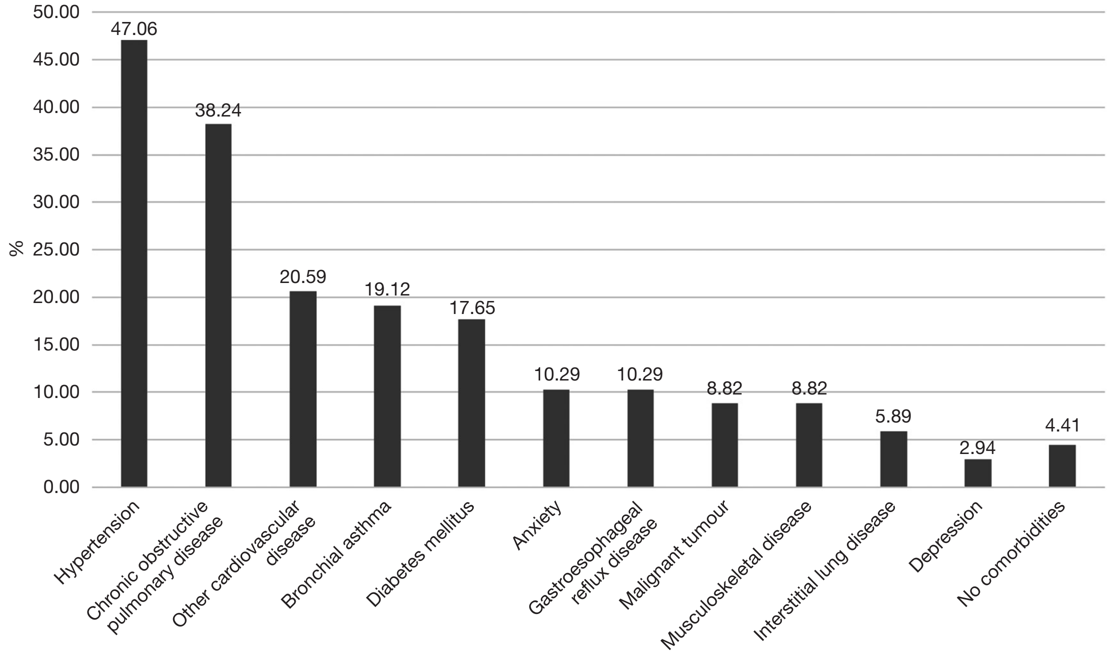

Figure 1 Prevalence of comorbidities (n=68).

pressure), increased resting heart rate, hair loss, sensation of limb numbness, menstrual irregularities, intermittent nausea, vomiting, loss of taste and/or smell, metallic taste in mouth, headache, concentration difficulties, sleep disorders, nightmares and/or mid-sleep awakenings, generalised anxiety and depression.

Several functional parameters [6MWT, FVC%pred, IVC%pred, CK, maximal expiratory pressure (PE_{max}), maximal inspiratory pressure (PI_{max}), mMRC, BHT, EQ-VAS, and PCFS] were recorded on the assessment sheet at the beginning and at the end of the programme and after 2 months. As a result of this complex cardiopulmonary rehabilitation programme, we found upgraded physical execution in chest kinematics and in general a better exercise tolerance, improved respiratory function values and respiratory mechanics parameters in our post-COVID patients, with significant improvements in 6MWT, BHT, EQ-VAS, and PCFS (*Table 3*).

In our study, we were detecting not only the changes during the pulmonary rehabilitation, but also the antecedent condition connected to their COVID-19 infection. The data showed that the majority of our patients required medical care during their acute COVID-19 infection as the following; in-patient hospital care: n=38 (55.88%), sub intensive care: n=4 (5.88%), intensive care: n=15 (22.06%). In 57 hospitalised cases 46 patients' ventilation were assisted; oxygen: n=37 (54.41%), non-invasive ventilation (NIV): n=11 (16.18%), invasive ventilation: n=6 (8.82%), extracorporeal membrane oxygenation (ECMO): n=2 (2.94%).

Despite negative microbiological test results and absence of infective symptoms, some patients had slightly elevated inflammatory markers in accordance with recent studies. IL-6 was shown to be associated with long-COVID (53,54). In our study IL-6 level was measured at the beginning of the rehabilitation programme, however, we cannot find any association between the post-COVID and the inflammatory marker. The level of IL-6 was in normal reference range. With the improved physical and mental condition, an increased level of workload, significantly decreased symptoms, and improved quality of life were detected. As EQ-5D questionnaire rates health on five different dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (55), in our study we were able to detect a positive change in all the five dimensions after the completed rehabilitation programme, moreover the improvement was significant ($P<0.05$) in the case of pain/discomfort and anxiety/depression (*Figure 2*). The pulmonary rehabilitation programme also ameliorated patient endurance, general condition, exercise capacity, chest kinematics, quality of life and increased functional reserve's values.

Table 3 Changes in functional parameters and quality of life before and after 14 days and 2 months post-COVID rehabilitation (n=68)

Functional parameters	Before rehabilitation	After 2 weeks rehabilitation	P value	After 2 months rehabilitation	P value
FEV_1 (%pred)	86 [73–103]	91 [80–99]	0.360	91 [80–99]	0.360
FEV_1/FVC (%)	109 [102–113]	108 [102–113]	0.862	104 [100–109]	0.662
PEmax (kPa)	9.7 [7.3–11.7]	4.6 [4.4–4.8]	0.032	9.8 [7.0–12.4]	0.632
PImax (kPa)	7.0 [5.2–10.6]	5.0 [4.6–5.5]	0.360	9.8 [7.0–10.7]	0.452
CK (cm)	3.5 [2.75–4.25]	4 [1–5.25]	0.296	4 [1–5.2]	0.696
Breath-holding test	33 [23–44]	41 [28–58]	0.041	41 [28–58]	0.041
6MWT (m)	492 [435–547]	523 [477–580]	0.031	555 [500–564]	0.019
mMRC	1 [0.25–1]	0 [0–1]	0.003	0 [0–0]	0.001
EQ-VAS	75 [65–80]	85 [75–90]	0.015	80 [80–85]	0.011
PCFS	1 [1–2]	0.5 [0–1]	0.032	1 [0–1]	0.030
TLCO (mmol/min/kPa)	7.68 [6.58–9.78]	8.05 [6.69–9.80]	0.442	8.92 [7.95–10.25]	0.149
KLCO (mmol/min/kPa)	1.62 [1.43–1.82]	1.64 [1.43–1.74]	0.941	1.69 [1.62–1.87]	0.182

Data are presented as median [IQR]. P<0.05 means that the two indicators were significantly different before rehabilitation and 2 weeks and 2 months after rehabilitation. IQR, interquartile range; FEV_1, forced expiratory volume in 1 second; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; CK, chest kinematics; 6MWT, 6-minute walk test; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; EQ-VAS, EuroQol Visual Analogue Scale; PCFS, Post-COVID-19 Functional Status; TLCO, transfer factor for carbon monoxide; KLCO, transfer coefficient of the lung for CO.

Discussion

Patients who participated in our complex programme had common symptoms like breathlessness, fatigue, chest distress, cough, insomnia, and depression. After the 2-week rehabilitation by improving some of the functional parameters and mental scores, symptoms became less severe and had less effect on our patients' everyday life. The same beneficial effect was detected after 2 months of the successfully completed rehabilitation programme, using the learned methods regularly.

Studies showed that after a COVID-19 infection, vaccination can decrease in the odds of post-COVID (56,57). Vaccination as part of prevention can be beneficial not only against SARS-CoV-2 pathogen, but also may be advantageous to avoid serious post-COVID condition. The tendency of cumulative vaccine uptake of at least one vaccine in our study population was similar to the uptake in the total Hungarian population (cumulative uptake varied during the period, from 30% to 65.2%) (58), however not only the authorized adenovirus vector or mRNA COVID-19 vaccines were in use in Hungary (59), we cannot detect any connection between the vaccination and the severity of post-COVID condition. Despite the fact, the importance of vaccination and participating in vaccination programmes are well known and highly recommended (60,61).

Seventy-six patients who suffered from post-COVID syndrome were involved in a clinical study by Nambi *et al.*, and the effects of low and high-intensity aerobic training combined with resistance training were detected (62). Patients were divided into two groups and did low-intensity aerobic training group or high-intensity aerobic training for 30 min daily for 8 weeks. Clinical (e.g., muscle strength) and psychological (e.g., quality of life) effects were measured. After the rehabilitation programme it was shown that low-intensity aerobic training exercises (P<0.001) were more effective in post-COVID patients to improve muscle strength and quality of life (62). The outcome reinforces the conclusion of our own results, that low-intensity training is beneficial for our patients, who used different type of workout machines (treadmill for walking, stationary bicycle or rowing machine) for half an hour daily for 2 weeks under persistent professional supervision during the exercise.

Moreover, Nopp *et al.* performed a study on 58 patients, who suffered from severe post-COVID syndrome. The authors concluded that individualized interdisciplinary rehabilitation, carried out daily for 6 weeks, could improve quality of life, help to decrease dyspnea, increase the

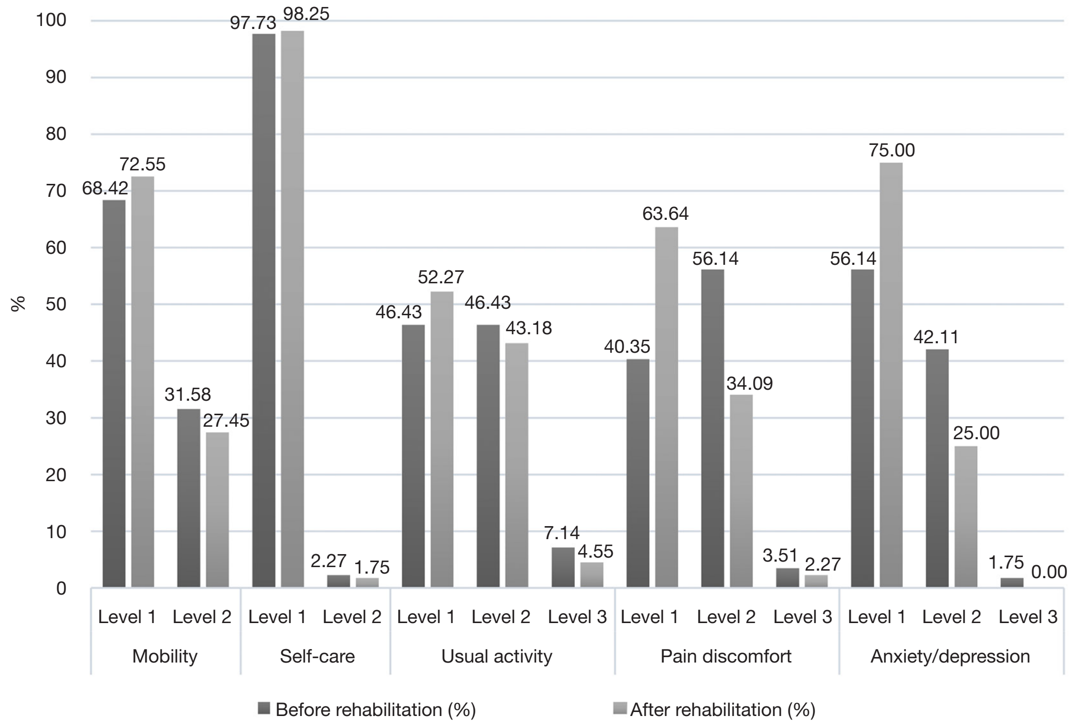

Figure 2 EQ-5D questionnaire results (n=68). EQ-5D, EuroQol-5 dimensions.

walking capacity (63). The exercises become also a useful and effective tool for further rehabilitation process at home. As a result of our individualized rehabilitation programme, with specialized breathing techniques and training, we found similar improvements in the parameters during two months follow-up.

After recovery from COVID-19 infection, patients often experience a reduction in cardiopulmonary fitness, quality of life, exercise tolerance and the unavoidable consequences of prolonged lying during treatment. There is a significant risk of impairment in survivors of critical COVID-19, who develop weakness, polyneuropathy and myopathy as a result of Post-Intensive Care Syndrome (PICS). Recovery for them is often very slow and incomplete and they require complex cardiopulmonary rehabilitation. In some cases, acute respiratory distress syndrome (ARDS) develops and they face long-term consequences. In particular, restrictive lung lesions and loss of diffusion capacity following acute lung injury contribute to long-term functional impairment and deterioration in quality of life, which may develop not only in critical but also in moderate to mild COVID-19 patients. The aim of rehabilitation is mainly to prevent the complications of inactivity by conditioning exercises, strengthening the skeletal muscles, improving diaphragm function, improving chest mobility, improving circulation and load bearing capacity (64,65). The training can be done individually or in groups—on a bike, treadmill or arm ergometer—and can be continuous training under strict supervision by physiotherapists.

The results of the first randomised controlled trial evaluating complex pulmonary rehabilitation in patients with COVID-19 infection have been published recently (66). The results showed significant improvements in respiratory function, quality of life, and reduced anxiety symptoms. Exercises included breathing and coughing exercises, diaphragm exercises, stretching exercises done daily for 6 weeks. Patient education was also part of the rehabilitation where health professionals educate patients about the benefits of physical activity and the importance of rehabilitation (67). Those exercises should be maintained after the patient has been discharged from hospital, with possible re-monitoring every 2–3 months as part of an outpatient follow-up if necessary. In our 2-month follow-up, we detected the extant beneficial effects of regular exercises.

According to a randomized controlled study by Rodríguez-Blanco *et al.*, two different exercise-based programs (strength and breathing exercises), which were carried out by telerehabilitaion (68), can also be used as a beneficial part of the pulmonary rehabilitation programme. They found that telerehabilitation brought significant improvements, e.g., in fatigue, and dyspnea; however, breathing exercises had greater benefits in dyspnea (69). Another study by Li *et al.* also claimed that an unsupervised home-based 6-week telerehabilitation programme, which included breathing and aerobic exercises, was effective in 59 patients and helped the healing process and improved muscle strength, pulmonary function and quality of life (70).

The exact physiological background of persistent dyspnea after acute COVID-19 survival is not known, but several causes are likely to be involved. Impaired lung function and inflammation of the interstitium of the lung may play a significant role, but other impairments such as cardiovascular, neurological, and psychological impairments may also contribute to the development of persistent dyspnea. Feelings of fatigue and anxiety can also be caused by prolonged physical inactivity. Some of these impairments can be positively influenced by respiratory rehabilitation (45), such as by the complex rehabilitation programme. Our complex rehabilitation programme also resulted in significant improvements in quality of life, physical performance and mMRC dyspnea scores.

The exercise tolerance of patients improved significantly during the complex rehabilitation programme, the cardiovascular system probably adapted, and the musculoskeletal system strengthened as a result of the training, and the confidence and belief of the patients returned. The domains of pain/discomfort and anxiety/depression (43) significantly improved in our present study, in line with previous research (45). Compared with patients with asthma (71) or COPD (72), the results of rehabilitation are similar and consistent (73). Considering the significant reduction in anxiety and depression, we fully agree with the results of Demeco *et al.* who recommend post COVID-19 rehabilitation programmes not only for physical but also for psychological reasons (74).

As a summary, the quality of life improved, symptoms decreased as a result of the complex pulmonary rehabilitation and patients could return to their normal everyday life. Due to the large number of patients who suffer from post-COVID syndrome we would highlight that there is an urgent need for a widely available and easy of attainment post-COVID pulmonary rehabilitation programme that can be continued at home to avoid serious health, social and economic complications.

The limitations of our study were as follows. Most importantly, our data were from an observational study, with no randomisation or randomised controlled trial (RCT). On the other hand, the recovery of the patients can be part of a natural healing process, so our results should be interpreted with caution. The third important drawback of our study is the low number of cases and the single-centre sampling. Taking all this into account, further randomised controlled trials with multicentre enrolment are needed to confirm the results of our study. Fourthly, to exclude Post-Exertional Symptom Exacerbation (PESE) and post-exertional malaise (PEM) for sure did not use the DePaul Post-Exertional Malaise Questionnaire.

Conclusions

Based on our data a comprehensive and individualised pulmonary rehabilitation programme can be recommended to symptomatic post-COVID patients, who have the potential for recovery and able to participate in and tolerate the 2 weeks rehabilitation with low-intensity exercises. With the help of appropriately trained professionals, who are specialised in post-COVID rehabilitation, primer improvement can be achieved at the end of the 2 weeks rehabilitation programme. Moreover, if the acquired exercises are performed as daily activities after the rehabilitation, it can increase the beneficial effect of the rehabilitation. An early diagnosis and proper rehabilitation interventions, are essential, as rehabilitation improves the quality of life of the patients, reduces their symptoms and allows them to return to their normal lifestyle.

Forward-looking statement

Improving patient safety and preventing adverse events DePaul Post-Exertional Malaise Questionnaire must be added to our rehabilitation protocol. A permanently continued, partly controlled exercises and training programme (e.g., daily breathing techniques or resistance training) at home after the hospital rehabilitation—would have a more long-term effect on the quality of life of our patients. In the future further follow-up is planned 1 year after the completed rehabilitation programme. We intend to measure the same parameters as the ones measured at entering and leaving the rehabilitation programme and at the 2-month follow-up. On the other hand, by increasing the number of our equipment (e.g., training tools or machines) and enlarge the number of the medical team could heighten our capacity. We would also like to extend our rehabilitation programme as a telerehabilitation programme for patients who have moderate post-COVID syndrome and those who have already done the rehabilitation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committee of Semmelweis University (No. 160/2021), and it complies with the Helsinki Declaration (as revised in 2013). Patients were given oral and written information prior to the assessment, and then they signed a statement of consent.

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