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Optimizing cardiopulmonary rehabilitation to enhance physical health and quality of life in long COVID patients: an exercise physiology approach

PhD thesis

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List of Abbreviations

Abbreviation	Definition
6MWT	Six-minute walking test
BE	Base excess
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CK	Chest kinematics
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPET	Cardiopulmonary exercise test
EQ-VAS	European Quality of Life Visual Analogue Scale
EQ-5D-3L	European Quality of Life - 5-dimension -3-level
ESS	Epworth Sleepiness Scale
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
FSS	Fatigue Severity Scale
GLI	Global Lung Function Initiative
HR	Heart rate
HRR	Heart rate reserve
hs-TnT	High-sensitive troponin T
IL-6	Interleukin-6
IQR	Interquartile range
KLCO	Transfer coefficient of lung for carbon monoxide
mMRC	Modified Medical Research Council
NIV	Non-invasive ventilation
NYHA	New York Heart Association
PCFS	Post-COVID-19 Functional Status
PCO_2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PEM	Post-exertional malaise
PEP	Positive expiratory pressure
PESE	Post-exertional symptom exacerbation
PE_{max}	Maximum expiratory pressure
PICS	Post-Intensive Care Syndrome
PI_{max}	Maximum inspiratory pressure
PO_2	Partial pressure of oxygen
PSQI	Pittsburgh Sleep Quality Index
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SpO_2	Blood oxygen saturation
TLCO	Transfer factor for carbon monoxide
VCO_2	Volume of exhaled carbon dioxide
VE	Minute ventilation

VO_{2max}	Maximal oxygen consumption
WHO	World Health Organization

1. Introduction

1.1. Background of SARS-CoV2 and long COVID syndrome

Since the global outbreak of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, healthcare systems worldwide have faced unprecedented challenges. By January 2025, over 777 million confirmed cases of COVID-19 had been reported to the World Health Organization (1) (2), leading to more than 7 million deaths and significant economic and social burden (3-7). While many individuals have fully recovered from the acute phase of SARS-CoV-2 infection, a substantial subset of the population has been experiencing long-term effects, collectively referred to as long COVID or post-COVID syndrome (8, 9).

The Centers for Disease Control and Prevention (CDC) defines long COVID as an infection-associated chronic condition with at least 3 months persistence of symptoms after the initial COVID-19 infection (10). These symptoms often affect multiple organ systems and can range from mild to severe, significantly affecting the quality of life and workability of individuals (11-14). By affecting different organs, the heterogeneity of the long COVID syndrome causes multiple pathophysiologic outcomes, such as organ damage, microvascular dysfunction, and inadequate antibody response among others (15-18). The possible devastating health threats highlight the importance of early diagnosis, highlighting the necessity of early diagnosis to evaluate its potential long-term impact on health even right after the initial infection. WHO defines long COVID as the onset of new symptoms three months after a confirmed SARS-CoV-2 infection, persisting for at least two months and not being attributed to any other condition (1, 19-22).

Long COVID is associated with chronic, persistent conditions that include more general symptoms, such as fatigue, malaise, headache, as well as more specific symptoms that arise from effects on multiple organs (23, 24). The most common symptoms of the condition are respiratory and cardiovascular symptoms, for instance shortness of breath, cough, dyspnea, chest pain, palpitations, arrhythmias, tachycardia, and exercise intolerance among others (25, 26). One fifth of the patient population experience respiratory symptoms with functional limitations (27, 28). The wide spectrum of long COVID manifestation triggers neurological, psychological, and gastrointestinal disorders, with symptoms such as attention disorders, cognitive impairments, anxiety, depression, and loss of appetite (Figure 1) (29-31).

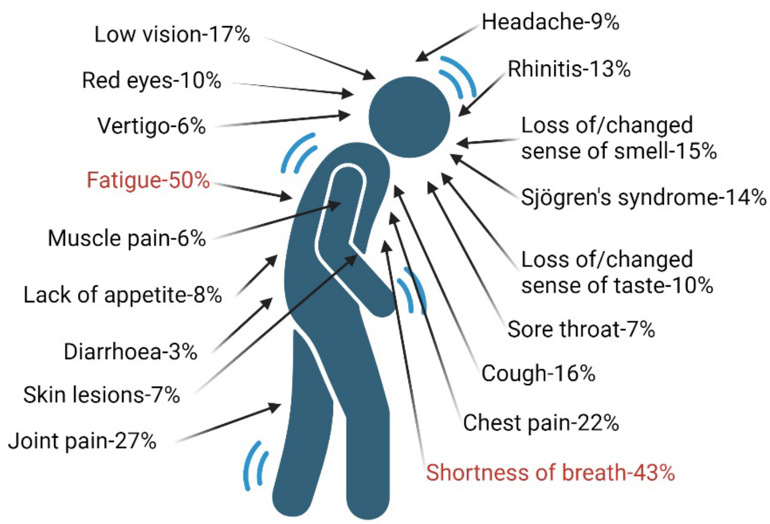


Figure 1: ***The most common symptoms of long COVID syndrome and their prevalence (%).*** The most commonly reported symptoms are fatigue (50%), shortness of breath (43%), joint pain (27%), and chest pain (22%). Other frequently occurring symptoms include e.g., cough (16%), loss, or alteration of smell (15%), Sjögren's syndrome (14%), and rhinitis (13%). Additional manifestations such as muscle pain (6%), skin lesions (7%), and diarrhea (3%) are reported at lower frequencies. Various reported symptoms in connection with the long COVID syndrome highlight the diverse and multisystemic nature of the condition, affecting respiratory, neurological, musculoskeletal, and dermatological functions. The prevalent data shows the significant impact on daily life and the need for a multidisciplinary approach to management and treatment (32).

Long COVID is characterized by several physical and psychological burdens, poor quality of life and social well-being, moreover an inability to work (33-35). These consequences have had a profound economic impact, particularly among working-age adults, because of reduced productivity and increased healthcare costs (36). Given its high prevalence in the working-age population (37-39), optimizing physical functions and improving quality of life and workability through evidence-based symptom management strategies are the main focus of long COVID rehabilitation (40, 41).

1.2. Risk factors of long COVID

People with certain factors have a greater chance of experiencing long COVID including female gender, severity of the initial COVID-19 infection, comorbidities, and vaccination status (42-44).

Gender

Findings suggested that long COVID might be a gender specific syndrome, highly affecting female gender (45), with a disproportionately high prevalence and burden observed among women. Recent studies have indicated that females are not only more likely to report persistent long COVID symptoms, such as fatigue, cognitive impairment, and autonomic dysfunction, but may also experience a longer duration of recovery and more significant disruption to daily functioning compared to males (46-48). These gender differences may be linked to a combination of biological, hormonal, and psychosocial factors, warranting further investigation into sex-specific mechanisms and tailored rehabilitation strategies (42).

Comorbidities

Emerging research also indicates that pre-existing comorbidities significantly increase the risk and severity of long COVID. Comorbidities refer to one or more chronic conditions including cardiovascular diseases (e.g. hypertension), obesity, diabetes, chronic respiratory conditions, or mental health disorders (49). These conditions contribute to prolonged inflammation, immune dysregulation, and organ dysfunction, exacerbating long-term symptoms such as fatigue, cognitive impairment, respiratory distress, and cardiovascular complications (50, 51).

Smoking

Smoking history has been identified as a potential risk factor for the severity and duration of long COVID symptoms due to its impact on lung function, immune response, and systemic inflammation. Several studies suggested that smokers and former smokers may experience more severe and prolonged long COVID symptoms compared to non-smokers. This may indicate that smokers were more likely to experience long-term respiratory complications after recovering from acute COVID-19 infection and smoking was associated with a higher prevalence of fatigue and brain fog, particularly in older adults in long COVID (52). However, there are conflicting reports on whether smoking increases the risk of developing long COVID. Findings suggested that smoking history was an independent risk factor for restrictive lung function abnormalities and persistent dyspnea in older long COVID patients (53, 54). In contrast to the possible higher risks associated with traditional cigarette smoking, an American study analyzing the effect of e-cigarette use on the prevalence of long COVID and found no significance association between e-cigarette usage and long COVID (55). A study on COPD patients found that those with a history of heavy smoking (≥25 pack years) required significantly longer inhaled corticosteroid therapy in long COVID (56).

Lack of COVID-19 vaccination

Recent research indicated that long COVID may be partially preventable as COVID-19 vaccination had been associated with a reduced risk of long COVID, underscoring its role not only in acute infection prevention but also in long-term outcome mitigation (57). Beyond its protective effect against SARS-CoV-2 virus, COVID vaccination may play a role in mitigating severe post-COVID conditions (58).

Severity of initial COVID-19 infection

The severity of the initial COVID-19 infection has emerged as a significant predictor of long COVID outcomes (59). Individuals who experienced severe acute symptoms, required hospitalization, intensive care, or mechanical ventilation were statistically more likely to develop persistent post-acute sequelae, including respiratory, cardiovascular, and neurological complications (60). This association is likely driven by higher systemic inflammation, organ damage, and immune dysregulation during the acute phase (61, 62). However, long COVID is not exclusive to those with severe COVID infection. A notable proportion of individuals with mild or even asymptomatic infections also reported long-term symptoms, suggesting that additional factors, such as host genetics, immune response variability, and pre-existing conditions, modulate the risk (63). A significant number of participants required medical support during the acute phase of SARS-CoV-2 infection, with hospitalization receiving some kind of respiratory assistance such as oxygen therapy, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation (ECMO). Numerous studies investigated the possible consequences of a moderate or severe SARS-CoV-2 infection and the prevalence of long COVID in hospitalized and non-hospitalized patients. A higher prevalence of long COVID was expected in the hospitalized population and co-infections can increase the mortality risk of COVID-19 patients, especially in a hospital setting (64, 65). However, the prevalence of persistent long COVID symptoms was similar in both hospitalized and non-hospitalized groups (66). The reported symptoms were fatigue, chronic pain, anxiety, or depression independently of COVID-19 infection severity (67). Understanding the relationship between initial disease severity and long COVID is essential for risk stratification, patient counseling, and resource allocation in post-acute care settings.

1.3. The impact of long COVID

Long COVID with its persistent, chronic symptoms has been linked not only to higher prevalence of respiratory, cardiovascular complications, but also to psychosocial and mental complications, such as depression and anxiety (68). These conditions exacerbate emotional distress, significantly impairing quality of life and workability, prolonged functional limitations, reduced productivity, and increased absenteeism, further complicating their reintegration into the normal daily life (69). Addressing these health challenges through multidisciplinary care is essential for improving long-term outcomes and an early mental health intervention is crucial to prevent long-term psycho-socio-economical burdens (70). Findings highlighted that COVID-19 survivors who had a history of smoking reported an even worse health-related quality of life, particularly among stroke survivors experiencing long COVID conditions (71).

The prolonged symptoms also affect social well-being, leading to profound economic impact, particularly among working-age individuals (36) (60).

1.4. The role of rehabilitation in long COVID syndrome

The multifaceted nature of long COVID and its wide variety of symptoms highlight the need for comprehensive, multidisciplinary and tailored health management strategies (72). One of the key elements of a symptom releasing approach is therapeutic intervention with a comprehensive long COVID rehabilitation program. Rehabilitation programs, particularly those focused on pulmonary and cardiopulmonary rehabilitation, have been shown to improve physical function, enhance the quality of life, and alleviate some of the most debilitating symptoms associated with long COVID (73, 74). Rehabilitation plays an essential role in restoring wellness and quality of life by improving lung function, increasing exercise tolerance, growing muscle strength and reducing fatigue, which are the most common health concerns in individuals with long COVID (75, 76). The two prominent public health organizations, CDC and WHO, have highlighted the importance of individualized rehabilitation in managing long COVID, recommending patient-centric, multidisciplinary approaches that include physical exercises, breathing techniques, psychological counseling, and cognitive interventions (77). Early identification and timely initiation of rehabilitation interventions can substantially alleviate disease burden and enhance patients' quality of life.

1.5. Challenges in long COVID rehabilitation

Despite the recognized benefits of rehabilitation, several challenges still remain in optimizing rehabilitation programs for long COVID patients. Firstly, there is no one-size-fits-all approach to rehabilitation due to the heterogeneous nature of the syndrome, which affects different patients in different ways (78). While some patients may primarily suffer from respiratory symptoms, others may experience significant neurological, cardiovascular, or psychological issues (79). This variability necessitates tailored rehabilitation programs that reflect the specific needs of each patient. Another challenge lies in the duration and intensity of rehabilitation programs. Although traditional rehabilitation programs often last for several weeks or months, there is growing evidence that shorter, more intensive programs may be equally effective in improving the physical and mental health of long COVID patients (80). The availability of resources and the economic implications of prolonged rehabilitation programs also present barriers to the widespread implementation of such interventions. Thirdly, potential hallmarks of long COVID characterized by symptoms such as fatigue, cognitive impairment, pain, or exercise intolerance, can markedly impair physical fitness. During the evaluations, intervention and treatments, the main aim is to avoid triggering post-exertional malaise (PEM) and post-exertional symptom exacerbation (PESE) (81). Exacerbation may be triggered by active rehabilitation in forms of physical activity, cognitive tasks, or emotional stress. The onset of symptom worsening is variable, it may occur immediately or be delayed after the exertional event, making it challenging to predict and manage. The duration of recovery from PESE is unpredictable, ranging from days to weeks or even months, depending on individual condition and the severity of the exacerbation (82).

1.6. Cardiopulmonary rehabilitation in long COVID

Among the various rehabilitation strategies, cardiopulmonary rehabilitation has emerged as a highly effective intervention for individuals with long COVID, especially those with persistent respiratory and cardiovascular symptoms (83). Cardiopulmonary rehabilitation programs typically include structured exercise programs designed to improve lung function, enhance cardiovascular health, and boost overall physical fitness. Studies have shown that cardiopulmonary rehabilitation can lead to significant improvements in spirometry parameters, exercise capacity, and muscle strength (84). For instance, breathing exercises, resistance training, and aerobic exercises have been found to improve diaphragm strength, maximal respiratory pressure, and lung capacity, thereby alleviating symptoms such as shortness of breath and chest pain (85). Moreover, rehabilitation can have a positive impact on mental health, reducing anxiety, depression, and cognitive impairments (86). The cardiopulmonary exercise test (CPET), a non-invasive method used to assess exercise capacity and pulmonary function, has become an essential tool in evaluating the effectiveness of rehabilitation programs for long COVID patients (87, 88). CPET provides valuable information on functional capacity, exercise-associated pulmonary and cardiac functions among others, and is used for evaluating the severity of dyspnea, exercise intolerance, or exercise-induced hypoxemia and the overall health (89, 90).

2. Objectives

Given the growing importance of rehabilitation in managing long COVID, thus the aims of the thesis are:

(1) to evaluate the effectiveness of our two-week, patient-centered cardiopulmonary rehabilitation program. The program is designed to address the functional limitations and diminished quality of life experienced by individuals with long COVID, with a particular focus on improving exercise tolerance, pulmonary function, overall physical condition and quality of life. The study also seeks to optimize the duration of rehabilitation programs for long COVID patients by examining the long-term effects of short-term intervention. Cardiopulmonary exercise testing (CPET) and other clinical measures, such as the six-minute walk test (6MWT) and quality of life assessments (EQ-5D-3L), were used to monitor patient progress from baseline visit to right after completion of the rehabilitation program, and during follow-up at two and three months.

(2) to predict the need for rehabilitation based on individual functional parameters using a machine learning algorithm, the Random Forest classification model. Machine learning algorithm was used to see whether key parameters of those participating in the rehabilitation programs are able to predict their enrollment in the rehabilitation program compared to a population who did not receive any rehabilitation whatsoever.

The central hypothesis of this study is that a two-week intensive, patient-centered cardiopulmonary rehabilitation program leads to significant improvements in exercise capacity, pulmonary function, and quality of life in patients with long COVID. This study addresses a critical gap in the current understanding of long COVID rehabilitation by focusing on the long-term impacts of a structured, short-term rehabilitation program. As healthcare systems continue to face the long-term consequences of the COVID-19 pandemic, the findings of this study may have significant implications for the development of cost-effective, scalable rehabilitation programs that can be widely implemented to support long COVID patients. Furthermore, the study points out the importance of multidisciplinary, tailored rehabilitation approaches, which are increasingly recognized as key to managing the diverse and complex symptoms of long COVID. By optimizing the duration and intensity of rehabilitation, this research aims to improve patient outcomes while reducing the economic and healthcare burdens associated with prolonged rehabilitation efforts.

3. Methods

Since we had two objectives, we decided to divide the methods into two parts. In the first part, we present the methods of our analysis on the effectiveness of our rehabilitation program, while in the second part we present the methods of the Random Forest classification model.

3.1. Analysis of the effectiveness of a rehabilitation program

3.1.1. Study design and study population

Participants were recruited between 01. April 2021 and 01. April 2022 to participate in the rehabilitation program upon referral from their pulmonologists (Department of Pulmonology, Semmelweis University). Patients at least six weeks after a negative PCR test underwent a comprehensive medical prescreening including a detailed physical examination, laboratory testing, imaging, and PEM/PESE screening. If a patient's medical history, recent results and overall health were adequate to endure a moderately intensive and multidisciplinary rehabilitation program, the participant was considered for enrollment in our study. The study was ethically approved by the Semmelweis University Ethical Committee (Registration Number 160/2021), in accordance with the Helsinki Declaration. Informed consent was obtained from all participants prior to their enrollment.

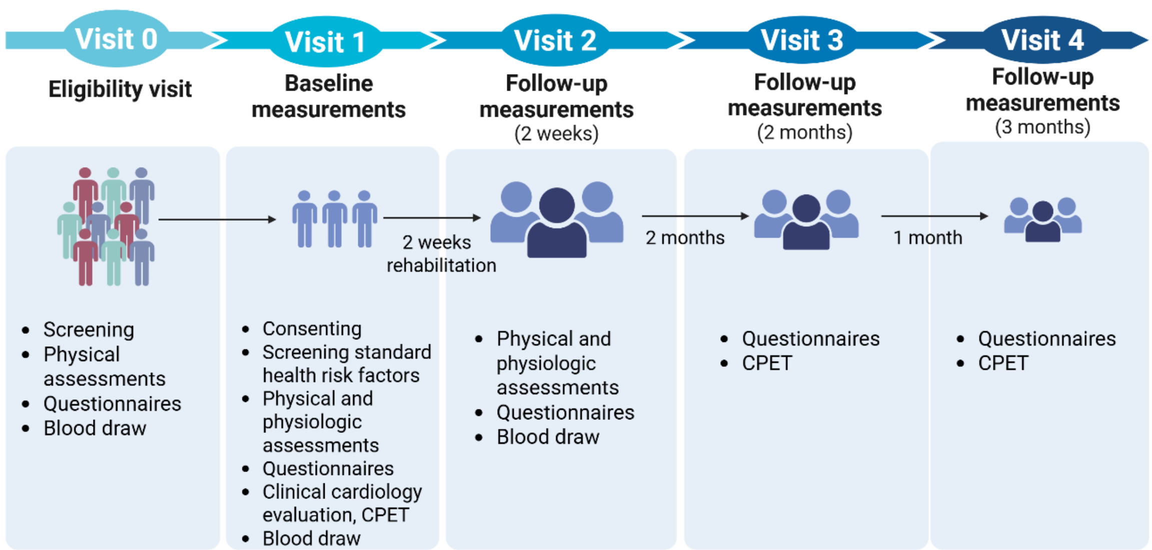
Inclusion criteria for the rehabilitation program are defined as a preexisting COVID-19 diagnosis (nasal swab test confirmed) and/or hospitalization with SARS-CoV-2-infection, persistent long COVID symptoms (≥12 weeks after onset of the acute SARS-CoV-2 infection and cannot be explained otherwise), and understanding oral and written Hungarian language. Individuals with any of the following conditions were excluded from our study: acute mental disorders, organic brain disorders, uncontrolled hypertension (≥140-90 mmHg), uncontrolled diabetes mellitus, unstable cerebrovascular or significant cardiac disease (e.g., heart failure, angina NYHA Class III-IV), severe rheumatic or orthopedic condition or any acute, urgent and/or potentially life-threatening clinical condition (Table 1) (91). Screening process was focusing on the current condition evaluated by numerous medical examinations (including cardiovascular examination), comorbidities according to the recommendation of CDC requirement of Assessment and Testing for Post-COVID Conditions (91) and physical, emotional, and behavioral status. Multi-comorbidities may worsen the severity of long COVID, requiring more focused, patient-centered rehabilitation (92).

Table 1. ***Inclusion and exclusion criteria for our study***

Inclusion criteria	Exclusion criteria
Individual aged 18 years or older	Unstable cardiovascular disease (uncontrolled high blood pressure (>140/90 mmHg), cognitive heart failure, angina NYHA* Class III-IV, etc.)
Required to understand both oral and written Hungarian	Severe rheumatic or orthopedic conditions, which limit freedom of movement
Previously diagnosed and/or hospitalized by SARS-CoV-2 infection	Any contraindication for cardiopulmonary exercise (recent myocardial infarction, severe coronary artery disease, or recent cerebrovascular events)
Persistent long COVID symptoms (e.g., reduced exercise tolerance, dyspnea) ≥12 weeks after onset of the acute SARS-CoV-2 infection	Other conditions: acute or organic mental disorders, untreated diabetes or exacerbation of pre-existing chronic disease
Functional limitations, constant dyspnea at rest or during light exercise	Any life-threatening condition

(NYHA= New York Heart Association, SARS-CoV-2= severe acute respiratory syndrome coronavirus 2)

Participants who met the inclusion and exclusion criteria of having long COVID began their rehabilitation program no earlier than 12 weeks following their recovery from acute SARS-CoV-2 infection. All applicants underwent a further evaluation by a pulmonologist and then took part in the baseline assessment. During the eligibility screening, demographic data, including age, gender, body mass index (BMI), and smoking habits were collected. Additionally, questionnaires (e.g., quality of life [EQ-5D-3L], dypnone scale [mMRC], functional status after COVID-19 [PCFS]), vaccination status, comorbidities, and current, persistent symptoms were documented. By the end of the screening process, a total of 68 patients were involved in the study (Figure 2).



(BMI= body mass index; CPET= cardiopulmonary exercise test; EQ-5D-3L= European Quality of Life - 5-dimension - 3-level; mMRC= modified Medical Research Council; PCFS= post-COVID-19 Functional Status).

Figure 2: ***The timeline for study design. The study protocol included five sequential visits, beginning with an eligibility visit and followed by baseline and follow-up measurements over two-week and two- and three-month periods.*** Visit 0 (eligibility visit): participants underwent initial screening, physical assessments (e.g. measuring respiratory function test [spirometry], respiratory muscles strength, chest expansion, load capacity, blood pressure, body weight, BMI), questionnaires (quality of life [e.g., EQ-5D-3L] dypnone scale [mMRC], functional status after COVID-19 [PCFS], and blood draw to determine eligibility. Visit 1 (baseline measurements): eligible participants provided consent and completed additional health risk screenings, physical and physiological assessments, clinical cardiology evaluations (e.g., CPET), questionnaires, and blood draw.

Following this, they started a two-week rehabilitation program. Visit 2 (follow-up visit at two-weeks): participants completed a structured 2-week rehabilitation program with active intervention, which was the key active treatment period in the study. After completing the rehabilitation, participants were reassessed with physical and physiological tests, questionnaires, and blood draw. Visit 3 (follow-up visit at two-month): two months post-rehabilitation, participants completed questionnaires and CPET. Visit 4 (follow-up at three-month): a final follow-up visit was scheduled for three months post-rehabilitation, where participants repeated the same questionnaires and CPET (80).

3.1.2. Intervention

Rehabilitation is a multi-faceted process under the supervision of various healthcare professionals, including pulmonologists, rehabilitation providers, cardiologists, physical therapists, dietitians, psychologists, and social workers. Our rehabilitation program included both individualized and group sessions. The tailored program suited the individual's needs, using specially designed exercises and equipment to help patients regain or improve their physical abilities and quality of life. The rehabilitation program involved low- to moderate-intensity exercises to enhance cardiorespiratory function, strengthen muscles, improve quality of life, fitness, and regain work capacity. The rehabilitation program aimed to assist patients with symptomatic long COVID in recovering and regaining not only their physical health but also their mental health in all emotional, psychological, and social aspects (93).

Part of the program was the 30-minutes group exercise sessions twice a day led by a professional physical therapist. These sessions included controlled breathing technique, chest mobility-enhancing and muscle-strengthening exercises with own body weights and dumbbells as well. Low- or moderate intensity individual training with gym bike, treadmill or arm ergometer were assigned according to age, comorbidities, persistent symptoms, and current condition. Patients performed exercises at 60-80% of their maximum capacity, and the duration of exercise gradually increased over time by 15% per week (94).

Twice a day, an inspiratory muscle-strengthening exercise was performed with an inspiratory muscle training device. Providing resistance against inhalation patients inhaled 30 times at 40% of maximum inspiratory pressure. Respiratory muscle training helped participants to master active cyclic breathing techniques and effective coughing techniques. Additionally, they learnt the positive expiratory pressure (PEP) training in tens of repetitions to clear phlegm. Participants were closely monitored during the group and individual training sessions, pulse and oxygen saturation were supervised constantly to avoid dangerously elevated heart rate or oxygen desaturation with mild or moderate hypoxia and maximize the cardiovascular benefits (95).

To ensure a more effective rehabilitation program, participants were divided into two groups. This allowed our professional team to supervise each individual during the training sessions. This structured design integrates medical evaluations, physical rehabilitation, and psychological support, providing a comprehensive recovery framework for participants. Day by day description of our program is displayed in Table 2.

Table 2: ***The detailed program of the two-week long COVID rehabilitation program at Department of Pulmonology, Semmelweis University.*** The rehabilitation program followed a structured two-week schedule, dividing participants into two groups with alternating activities. The first phase consists of registration, orientation, baseline measurements, and blood draw, conducted on Monday for Group 1 and Tuesday for Group 2. Following these initial assessments, cardiopulmonary exercise testing (CPET) and psychological evaluations were scheduled for the next day. Throughout the program, both groups engaged in group and individual exercise sessions, lower limb endurance training, respiratory exercises and training, and psychological consultations, ensuring a multidisciplinary approach to rehabilitation. These activities alternate between the two groups on different days to maintain a balanced schedule. At the end of the second week final assessments were completed, program closure, and report preparation took place. Group 1 completed these procedures on the second Thursday, while Group 2 underwent them on the second Friday (96).

Day of the week	**Group 1**	**Group 2**
Monday	Registration Orientation Baseline measurements Blood draw	
Tuesday	CPET Psychological assessment visit	Registration Orientation Baseline measurements Blood draw
Wednesday	Group and individual exercise sessions	CPET Psychological assessment visit

Thursday	Respiratory exercises and training Psychology consultation	Group and individual exercise sessions
Friday	Group and individual exercise sessions	Respiratory exercises and training Psychology consultation
Monday	Respiratory exercises and training Psychology consultation	Group and individual exercise sessions
Tuesday	Group and individual exercise sessions	Respiratory exercises and training Psychology consultation
Wednesday	Respiratory exercises and training Psychology consultation	Group and individual exercise sessions
Thursday	Final assessments Closure of the program Final report	Respiratory exercises and training Psychology consultation
Friday		Final assessments Closure of the program Final report

3.1.3. Variables

Several key parameters were measured at baseline, and right at the completion of the two-week program. Some of the assessments were repeated during the two- and three-month follow-up visits to detect the mid- and long-term effectiveness of the rehabilitation. The measurements at different time points were as follows:

Baseline assessments:

- Demographic data and medical history, including age, gender, body mass index (BMI), and smoking habits, vaccination status, comorbidities, and current, persistent symptoms.
- Quality of life questionnaire (EQ-5D-3L): assessment of health-related quality of life.
- Dyspnea severity evaluation: modified Medical Research Council (mMRC) dyspnea scale.
- Post-COVID Functional Status (PCFS): evaluation of functional limitations following COVID-19 infection.
- Pittsburgh Sleep Quality Index (PSQI): assessment of sleep quality.

- Respiratory function testing (spirometry): assessment of respiratory capacity and function.
- PI_{max} and PE_{max} measurement: evaluation of maximum inspiratory pressure (PI_{max}) and maximum expiratory pressure (PE_{max}).
- Chest expansion: measuring chest wall mobility.
- Electrocardiographic examination (ECG): analysis of cardiac electrical activity.
- Cardiopulmonary exercise test (CPET): evaluation of the cardiopulmonary system.
- Blood gas analysis: evaluation of arterial blood parameters, including pO_2, pCO_2, pH, standard bicarbonate, and base excess (BE).
- Peripheral muscle strength measurement: assessment of grip strength.
- Exercise tolerance assessment: 6-minute walk distance test (6MWD).

Final assessments:

- Respiratory function testing (spirometry): reassessment of respiratory function.
- PI_{max} and PE_{max} measurement: reevaluation of respiratory muscle strength.
- Cardiopulmonary exercise test (CPET): evaluation of the cardiopulmonary system.
- 6MWD: testing reassessment of exercise tolerance.

Follow up assessment at two- and three months:

- Questionnaires (e.g., quality of life questionnaire [EQ-5D-3L]).
- Cardiopulmonary exercise test (CPET): evaluation of the cardiopulmonary system.

Below is a detailed description of variables that were measured used to measure the effect of our rehabilitation program:

3.1.3.1. Respiratory function test

Pulmonary function test was assessed using computerized spirometer. These tests measured 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 in liters and percentages (IVC (L), IVC (%pred), with Global Lung Function Initiative-defined (GLI-defined) normal spirometry (z-score) (97). Additionally, diffusion capacity was measured using the lung diffusion test, which assesses the transfer factor for carbon monoxide (TLCO).

3.1.3.2. The 6-minute walk test (6MWT)

6MWT measures the distance can be walked in the given time frame on a hard, flat surface. It was used to assess the functional capacity of participants by measuring the distance (m) they walked down the aisle for 6 minutes. This test provides a simple and effective measure of endurance and functional impairment (98).

3.1.3.3. 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) (99).

3.1.3.4. EuroQol 5-dimensional, (EQ-5D - EuroQol-5-dimension questionnaire)

The EuroQol-5D measures the health-related quality of life at three levels (1: least to 3: most) on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D contains the EQ-5D-3L descriptive system with five questions and three answers, the EQ Visual Analogue Scale (EQ-VAS). EQ-VAS has values between 100 (best imaginable health) and 0 (worst imaginable health).

3.1.3.5. Post-COVID-19 Functional Status (PCFS) Scale

The PCFS Scale assesses patient-relevant functional limitations with the help of a score (0-4), where 0 reflects the absence of any functional limitation. Score 1 means symptoms, pain or anxiety are present to an increasing degree but has no effect on activities, score 2 represents a lower intensity of the activities and score 3 accounts for inability to perform certain activities, forcing patients to structurally modify them. Finally, score 4 is reserved for patients with severe functional limitations requiring assistance with activities of daily living (100).

3.1.3.6. Examination of chest expansion

Chest circumference (27) was measured using a measuring tape at the level of the xiphoid process, first at the end of exhalation and then at the end of inhalation. The difference between these measurements represents chest expansion. To ensure a more precise assessment of chest kinematics, the exhalation-inhalation process was repeated three times (101).

3.1.3.7. Oxygen saturation and heart rate

Throughout the rehabilitation program, oxygen saturation and heart rate were monitored continuously using pulse oximetry during both breathing training and exercise sessions. Oxygen saturation and heart rate were measured to ensure that exercise remained within safe limits for each participant.

3.1.3.8. Blood tests

A fasting blood sample was collected at the central laboratory of Semmelweis University (SYNLAB) under clinically stable conditions, fever-free and respiratory infection-free state. The analysis included measurements of D-dimer, C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, high-sensitivity troponin T (hs-TnT), and procalcitonin levels.

3.1.3.9. Cardiopulmonary Exercise Testing (CPET)

CPET was used to evaluate exercise capacity and monitor respiratory and cardiovascular function during exercise. An electronically braked cycle ergometer (Ergoline-900) was used, and the test was performed under the supervision of a pulmonary specialist. Key CPET metrics included maximal oxygen consumption (VO_{2max}), oxygen consumption per kilogram of body weight (VO_2/kg), and the minute ventilation to carbon dioxide production ratio (VE/VCO_2). Continuous electrocardiogram (ECG) monitoring was used throughout the test to ensure patient safety (102).

3.1.4. Statistical analysis

Continuous variables were summarized as medians with interquartile ranges due to the non-normal distribution of the data (as verified by the Shapiro-Wilk test). Categorical data were presented as frequencies and proportions. The Mann-Whitney U test was used to compare continuous variables, while Fisher's exact test was used for categorical variables. Results right after the rehabilitation program and during follow-up were compared to baseline results in order to assess the effectiveness of the intervention and the changes in the patients' condition over time. Statistical significance was set at $p<0.05$. All statistical analyses were conducted using STATA 14.

3.2. Random Forest classification model

3.2.1. Study design and study population

Using e-MedSolution database from 1st April, 2021 to 31st December, 2022 at the Department of Pulmonology, Semmelweis University, we matched participants of our program to age- and sex-matched participants who only received a single medical check-up and a draft of a home-based rehabilitation program without supervision at a 1:1 ratio.

3.2.2. Variables

For this analysis the following variables were used from participants:

- Age (years) (IQR)
- Male/Female (n, %)
- BMI (kg/m^2)
- FVC (L)
- FVC (%)
- FEV_1 (L)
- FEV_1 (ref%)
- FEV_1/FVC ratio
- TLCO (mmol/min/kPa)
- TLCO (%)
- KLCO (L)
- KLCO (%)

- PE_{max} (kPa)
- PI_{max} (kPa)
- SpO_2
- 6MWT distance (m)
- Subjective symptoms
- EQ-5D-3L

3.2.3. Statistical analysis

Continuous variables were shown by medians and interquartile ranges. Categorical data were presented with case numbers and proportions. To analyze 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. A Random Forest classification model was then used to predict the outcome of the rehabilitation program based on key parameters such as FEV_1, 6MWT, and oxygen saturation. The Random Forest model was trained using ten different test-train splits to ensure robust and accurate predictions (103). Significance was set at $p<0.05$.

4. Results

The results of our two objectives are also presented separately, as seen in the Methods parts.

4.1. Analysis of the effectiveness of the rehabilitation program

4.1.1. Baseline characteristics

A total of 68 middle aged adults (53.5±12.6 years of age, 29 female and 39 male), with severe and persistent long COVID symptoms, were eligible to take part in our study. Building on the clinical context, we examined the anthropometric and functional profiles of long COVID patients to identify patterns associated with persistent symptoms. Baseline anthropometric and functional characteristics of our study population are shown in Table 3. The group of 68 individuals had a balanced age distribution with a median age of 53.5 years and a slight male predominance. Pulmonary function, as assessed by FEV_1 and FEV_1/FVC ratio, was within normal ranges. Several laboratory markers, including CRP, D-dimer, IL-6, ferritin, troponin-T, and procalcitonin, were measured to assess underlying inflammation and potential systemic involvement.

Table 3: ***Anthropometric and functional data of long COVID patients (n=68).*** This table presents the general characteristics of a study consisting of 68 participants (104).

Variables	n=68
Mean age (years) (IQR)	53.5 (46.7-62.5)
Male/Female (n, %)	39 (57.35) / 29 (42.65)
BMI (kg/m²)	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 as frequency and percentage; IQR= interquartile range; BMI= body mass index; CRP= C-reactive protein; FEV_1= forced expiratory volume in one second; FEV1/FVC = forced expiratory volume in one second to the forced vital capacity; FVC= forced vital capacity; IL-6= interleukin-6; Troponin-T HS= high-sensitive troponin T).

A total of 41 participants, representing two-thirds of the study population, were former smokers, and two were current smokers. On average, individuals had a smoking history of 21 (13–29) years, with 12 (6-19) cigarettes a day. Medical history showed that most of the enrolled participant had required medical care during the acute SARS-CoV-2 infection as recorded in patients' charts, such as in-patient hospital care (n=38, [55.88%]), sub intensive care (n=4, [5.88%]) and intensive care (n=15, [22.06%]). In 57 hospitalized cases 46 patients needed assisted ventilation as the following: oxygen: n=37 (54.41%), non-invasive ventilation (48): n=11 (16.18%), invasive ventilation: n=6 (8.82%), extracorporeal membrane oxygenation (ECMO): n=2 (2.94%). In our rehabilitation group, cumulative vaccine uptake followed the average national trend in Hungary, ranging from 30% to 65.2% over the study period.

As for comorbidities, hypertension was the most prevalent comorbidity, affecting 47.06% of individuals, followed by chronic obstructive pulmonary disease (COPD) at 38.24%. Other commonly reported conditions included cardiovascular diseases (20.59%), bronchial asthma (19.12%), and diabetes mellitus (17.65%). Mental health-related conditions such as anxiety (10.29%) and depression (2.94%) were among the least common, along with gastroesophageal reflux disease (10.29%) and malignant tumors (8.82%). Musculoskeletal diseases and interstitial lung diseases affected 8.82% and 5.89% of the study population. Notably, only 4.41% of individuals reported having no comorbidities. These findings indicated a high overall burden of pre-existing chronic conditions in the study cohort (Figure 3).

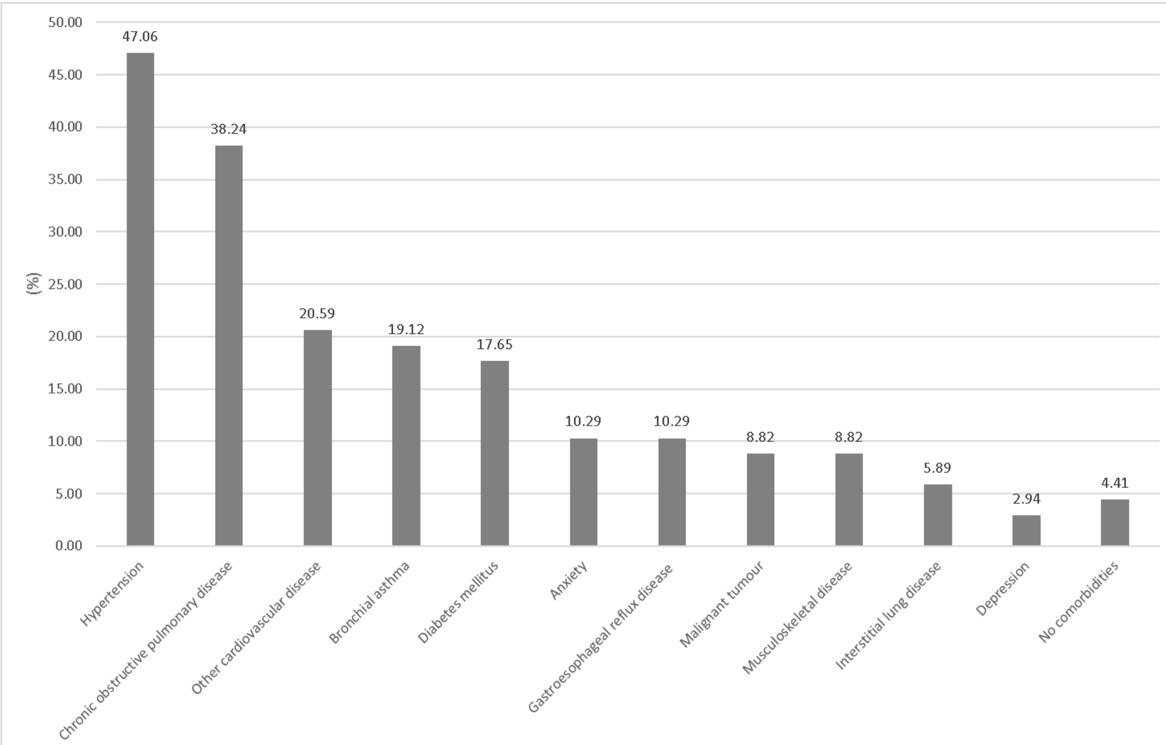


Figure 3: ***Prevalence of different comorbidities in percentage among patients in the rehabilitation group (n=68).*** Regarding pre-existing comorbidities in the rehabilitation group, half of the group had a medical history of hypertension, one-thirds had chronic obstructive pulmonary disease, one-fifths had bronchial asthma, and then one-sixth were previously diagnosed with diabetes mellitus (104).

The most common self-reported subjective symptoms of our patients included reduced performance, fatigue, shortness of breath when climbing stairs, productive cough, dyspnea, rotatory vertigo, chest discomfort (e.g. retrosternal 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, generalized anxiety and depression.

4.1.2. Short-term effect of rehabilitation program

The initial findings of our study demonstrated that the tailored two-week rehabilitation program was effective in improving several functional and quality-of-life parameters in long COVID patients. The breath-holding test showed a statistically significant improvement after two weeks ($p = 0.041$), suggesting enhanced breath control and greater tolerance of respiratory effort. Parallel improvements were observed in dyspnea perception, as measured by the mMRC scale ($p = 0.003$), and in overall functional limitation, as assessed by the PCFS ($p = 0.032$). Quality-of-life assessment using EQ-VAS also improved significantly ($p = 0.015$), indicating a broader benefit extending beyond strict physiological measures.

Functional exercise capacity increased notably, with the 6MWT improving significantly after two weeks ($p = 0.031$), reflecting better exercise tolerance and endurance. Respiratory muscle strength also improved, with PE_{max} showing a significant gain ($p = 0.032$), while PI_{max} did not change significantly. These results suggest that expiratory muscle performance may be more responsive to this short-term rehabilitation protocol.

In contrast, several standard pulmonary function parameters remained unchanged across the rehabilitation and follow-up period. No significant changes were found in FEV_1 (% predicted), FEV_1/FVC ratio, PI_{max}, similarly CK, TLCO and KLCO values remained stable, indicating no significant shifts in gas transfer capacity in intrinsic lung mechanics or alveolar-capillary gas exchange capacity within the studied timeframe (Table 4).

Table 4: ***Changes in functional parameters and quality of life before rehabilitation, after two weeks and two months of long COVID rehabilitation (n=68).*** Several functional parameters (6MWT (m), FVC (%pred), IVC (%pred), CK (27), maximal expiratory pressure (PE_{max}), maximal inspiratory pressure (PI_{max}); mMRC; BHT; EQ-VAS; and PCFS) were measured at the beginning and at the end of the program and even at mid-term follow up at two months. As a result of this two-week tailored, complex cardiopulmonary rehabilitation program, we found an improved physical performance, a generally better exercise tolerance, improved respiratory function values and respiratory mechanics parameters with better chest kinematics in our long COVID patients. Moreover, significant improvements were found in 6MWT, BHT, EQ-VAS, and PCFS (104).

Functional parameters	Before rehabilitation	After 2 weeks rehabilitation	p-value	2 months after rehabilitation	p-value
FEV_1 (%pred) (IQR)	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). IQR = interquartile range; 6MWT = 6-minute walk test; CK = chest kinematics; EQ-VAS = EuroQol Visual Analogue Scale; FEV1 = forced expiratory volume in one second; FEV1/FVC = forced expiratory volume in one second to the forced vital capacity; FVC= forced vital capacity; KLCO = transfer coefficient of the lung for carbon monoxide; PE_{max} = maximal expiratory pressure; PI_{max} = maximal inspiratory pressure; mMRC = modified Medical Research Council; PCFS = Post-COVID-19 Functional Status; TLCO = transfer factor for carbon monoxide; p <0.05 means the two indicators were significantly correlated)

Not only improved physical condition but also a better quality of life was measured. EQ-5D-3L questionnaire rates health on five different dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (105), in our study we were able to detect a positive change in all the five dimensions after the completion of the two-week rehabilitation program. According to severity, each dimension is divided into three levels: level 1 indicating no problems, level 2 meaning some/moderate problems and level 3 indicating extreme problems. Following rehabilitation, improvements were detected in all domains. For mobility, the proportion of individuals reporting no problems (level 1) increased slightly from 68.42% to 72.55%, while level 2 decreased. None of the individuals reported level 3 impairment. In self-care, an already high percentage of individuals at level 1 improved from 97.73% to 98.25%, while in level 2 the prevalence dropped from 2.27% to 1.75%. None of the individuals reported level 3 impairment. Usual activity showed moderate improvement, with level 1 increasing from 46.43% to 52.27% and level 3 decreasing from 7.14% to 4.55%. The pain/discomfort domain demonstrated notable changes, with level 1 rising from 40.35% to 63.64% and higher severity levels significantly decreasing. The most substantial and significant improvement was seen in anxiety/depression, where level 1 responses rose from 56.14% to 75.00%, while level 2 decreased from 42.11% to 25%, and level 3 responses dropped to 0%. Overall, the data suggests that rehabilitation had a positive impact across multiple dimensions of health-related quality of life, particularly in reducing severe discomfort and psychological distress (Figure 4).

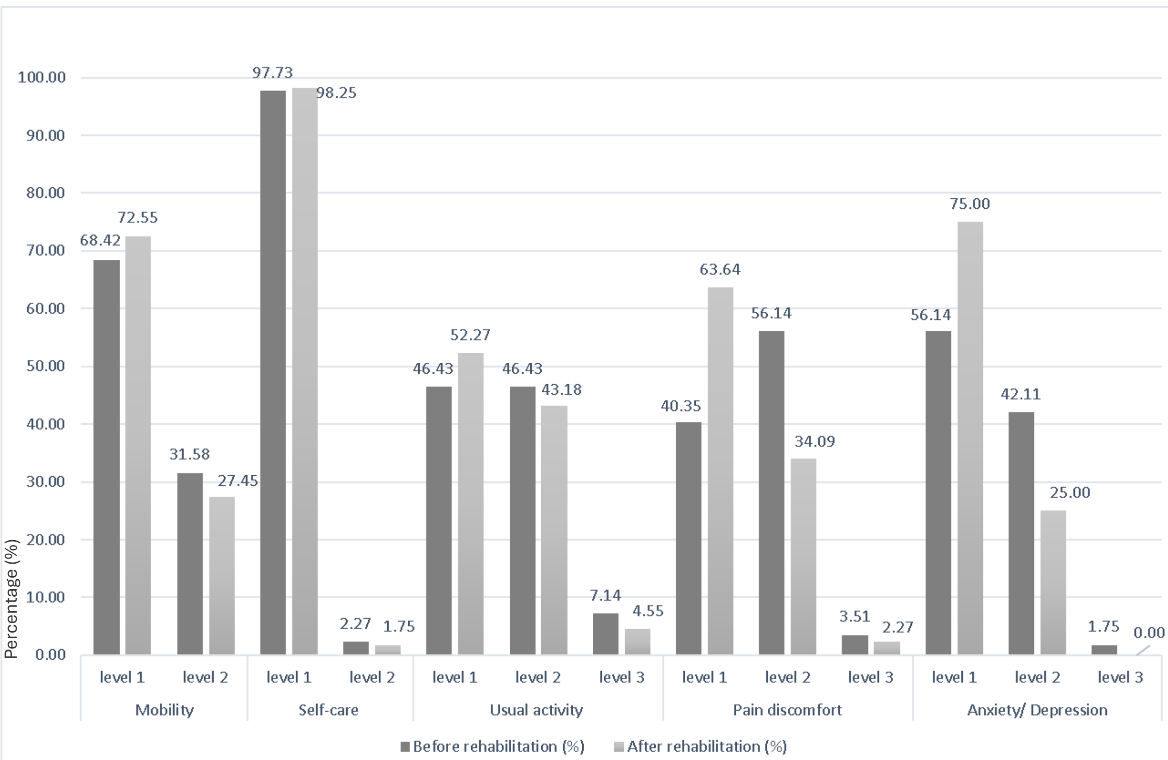


Figure 4: ***EuroQol-5 Dimensions-3 Level (EQ-5D-3L) questionnaire results before and right after the rehabilitation (n=68).*** The bar chart compared five domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression before and after rehabilitation in three levels: level 1 indicating no problems, level 2

meaning some/moderate problems and level 3 indicating extreme problems. In two dimensions (pain/discomfort and anxiety/depression) the improvements were significant ($p<0.05$) (104).

4.1.3. Long-term effect of our rehabilitation program

The initial findings of our study prove that the tailored two-week long rehabilitation was also beneficial after two months of post-rehabilitation. The breath-holding test showed significant improvement after two months of post-rehabilitation ($p = 0.041$) and similar improvement was observed for mMRC dyspnea scale ($p = 0.001$ at two months), PCFS ($p = 0.030$ at two months), EQ-VAS ($p = 0.011$ at two months), and 6MWT ($p = 0.019$ at two months). Our study found no significant changes for the other outcomes (Table 4).

As part of our study, we also investigated the mid- and long-term effects of the rehabilitation by using CPET. A few months after the completion of the patient-centered rehabilitation program, individuals were invited to voluntarily participate in the follow-up CPET assessments. A detectable improvement was found in the three-month follow-up compared to the two-month follow-up. Statistically significant differences were observed in VO_{2max} (ml/min) [1276 (1070–1614) vs. 1429.5 (1191–1871), $p=0.033$] and VO_2/kg (ml/min/kg) [14.6 (11.95–18.2) vs. 16 (12.4–21), $p=0.021$] indicating improved aerobic capacity per body weight. Although peak work rate increased from 106 (82–139) to 121.5 (89–151) and VE_{max} rose from 53.2 (43.3–67.5) to 56.05 (45.5–79.3), these changes approached but did not reach statistical significance ($p=0.084$ and $p=0.052$). Other variables, including HR, HRR, VO_{2max}, VCO_{2max}, VE/VO_{2max}, and VE/VCO_{2max}, remained statistically unchanged over the period assessed (Table 5).

Table 5: ***The CPET result of 2-month follow-up compared to 3-month follow-up.*** A trend toward improvement was observed across most variables; however, statistically significant change was identified only in observed in VO_{2max} (ml/min) and VO_2/kg (ml/min/kg) (80).

Variables	CPET (2-month)	CPET (3-month)	p-value
Peak work rate (WR)	106 (82 - 139)	121.5 (89 - 151)	0.084
HR (1/min)	135 (119 - 155)	141 (120 - 160)	0.948
HRR (1/min)	29 (11 - 51)	26.5 (11 - 43)	0.918
VO_2max (ml/min)	1276 (1070 - 1614)	1429.5 (1191 - 1871)	0.033*
VO_2/kg (ml/min/kg)	14.6 (11.95 - 18.2)	16 (12.4 - 21)	0.021*
VCO_2max (ml/min)	1458 (1212 - 2021)	1696.5 (1363 - 2223)	0.129
VE max (L/min)	53.2 (43.3 - 67.5)	56.05 (45.5 - 79.3)	0.052
VE/VO_2max	40.8 (35.9 - 47.2)	40 (35.9 - 44.5)	0.531
VE/VCO_2max	38.4 (34.6 - 49.2)	40.7 (37.3 - 46.5)	0.291

(Data are presented as median (IQR). IQR = interquartile range; CPET= cardiopulmonary exercise test; HR = heart rate; HRR = heart rate reserve; VO_{2max} = maximal oxygen consumption; VO_2/kg = oxygen used in one minute per kilogram of body weight; VCO_2 = carbon dioxide production; VE_{max} = Maximal ventilation; VE/VO_2 = minute ventilation divided by oxygen production; VE/VCO_2 = minute ventilation divided by carbon dioxide production; p <0.05 means the two indicators were significantly correlated)

In addition to objective clinical measures, patients self-reported significant improvements in severity and frequency of subjective long COVID symptoms were assessed, including but not limited to fatigue, shortness of breath, and cough. At the baseline visit, 49% of participants in our study population reported chronic and recurrent coughing as long COVID symptoms. After the completion of the tailored rehabilitation program filled with individualized breathing training, the prevalence of coughing dropped to 20% at the two-month follow-up and 15% at the three-month follow-up. Similarly, chest pain, which was reported by 30% of the individuals at baseline screening, decreased to 10% by the two-month follow-up and 5% by the three-month follow-up ($p<0.05$). Fatigue and dyspnea also showed significant improvements, with the decreasing percentage of participants reporting severe fatigue dropping from 50% at baseline visit to 25% at the three-month follow-up ($p<0.05$).

4.2. Analysis of the machine learning algorithm model

4.2.1. Descriptive statistics

In our Random Forest classification model, we used the e-MedSolution database to compare the characteristics of long COVID condition in 100 participants with moderate or severe long COVID who underwent the two-week long rehabilitation program (rehabilitation group) and 100 age and gender matched individuals (out-patient group) with mild long COVID symptoms, without debilitating syndromes. Both groups were comparable in age (median 56 years) and sex distribution (57% male, 43% female), with no significant difference in BMI (p=0.504). Significant differences were observed in several pulmonary function parameters: FVC (L) was significantly lower in the rehabilitation group (3.00 L) compared to the out-patient group (3.36 L), p=0.01, FEV_1 (L) and FEV_1 (% predicted) were also significantly lower in the rehabilitation group (p=0.006 and p<0.001), indicating reduced airflow limitation. TLCO was significantly higher in the rehabilitation group (p<0.001), while KLCO (%) was significantly lower (p<0.001). SpO_2 was slightly but significantly lower in the rehabilitation group (p<0.001). Other variables such as FEV_1/FVC ratio, PE_{max}, PI_{max}, and 6MWT distance showed no statistically significant differences between the two groups (Table 6).

Table 6: ***Comparison of anthropometric and functional parameters.*** Data of participants with persistent symptoms of long COVID (rehabilitation group) before their enrollment in two-week pulmonary rehabilitation program (n=100) were compared to patients (out-patient group) from their one-time visit to the outpatient clinic without intervention (n=100). Certain physiological parameters were identified as statistically significant, including FVC (L), FEV1 (L), FEV1 (ref%), and SpO_2 (%) (80).

Variables	Out-patient group n=100	Rehabilitation group n=100	p-value
Age (years) (IQR)	56 (48-68)	56 (47.8-66)	0.881
Male/Female (n, %)	57/43 (57%, 43%)	57/43 (57%, 43%)	N/A
BMI (kg/m²)	28.75 (25.22-33.11)	28.87 (26.48-33.49)	0.504
FVC (L)	3.36 (2.7-4.1)	3 (2.36-3.57)	0.011*
FVC (%)	86 (73.5-96)	86 (69.5-97.5)	0.585
FEV_1 (L)	2.82 (2.27-3.38)	2.51 (1.98-3.06)	0.006*
FEV_1 (ref%)	92 (79.5-104)	84.88 (75.15-89.19)	<0.001*
FEV_1/FVC (%)	106 (102-111)	107 (96.5-112)	0.627
TLCO (mmol/min/kPa)	5.45 (4.49-6.52)	6.87 (5.72-8.54)	<0.001*
TLCO (%)	94.5 (84-110)	90 (74-108)	0.121
KLCO (L)	1.65 (1.41-2.01)	1.6 (1.38-1.9)	0.404
KLCO (%)	111 (88-131.5)	85.5 (75-107)	<0.001*
PE_{max} (kPa)	8.84 (7.25-10.92)	9.8 (7.27-11.68)	0.550
PI_{max} (kPa)	7.41 (5.31-9.86)	7.35 (5.01-10.8)	0.518
SpO_2	98 (97-99)	97 (95-98)	<0.001*
6MWT distance (m)	477 (402.5-502.5)	471 (368.5-534.5)	0.966

(Data are presented as median (IQR); IQR = interquartile range; 6MWT = six-minute walk test; BMI = body mass index; FEV1 = forced expiratory volume in one second; FEV1/FVC = forced expiratory volume in one second to the forced vital capacity; FVC = forced vital capacity; KLCO = transfer coefficient for carbon monoxide; PE_{max} = maximal expiratory pressure; PI_{max} = maximal inspiratory pressure; SpO_2 = blood oxygen saturation; TLCO = transfer factor for carbon monoxide; p <0.05 means the two indicators were significantly correlated).

The most common self-reported subjective symptoms reported in the dataset with different severity of long COVID were shortness of breath, productive cough, dyspnea, and chest pain with retrosternal pressure and reduced physical performance, increased resting heart rate, headache, concentration difficulties, sleep disorders, generalized anxiety and depression. A significant difference (p<0.001) was detected between the two groups. 30% of the rehabilitation group reported destructive chronic chest pain as a leading subjective symptom, while only 8% of the out-patient group reported the same. Productive cough was highly prevalent in both groups, 47% in the rehabilitation group and 49% in the out-patient group. The prevalence of coughing between the out-patient group and the rehabilitation group indicated no statistically significant difference between the groups (p = 0.887) (Figure 5).

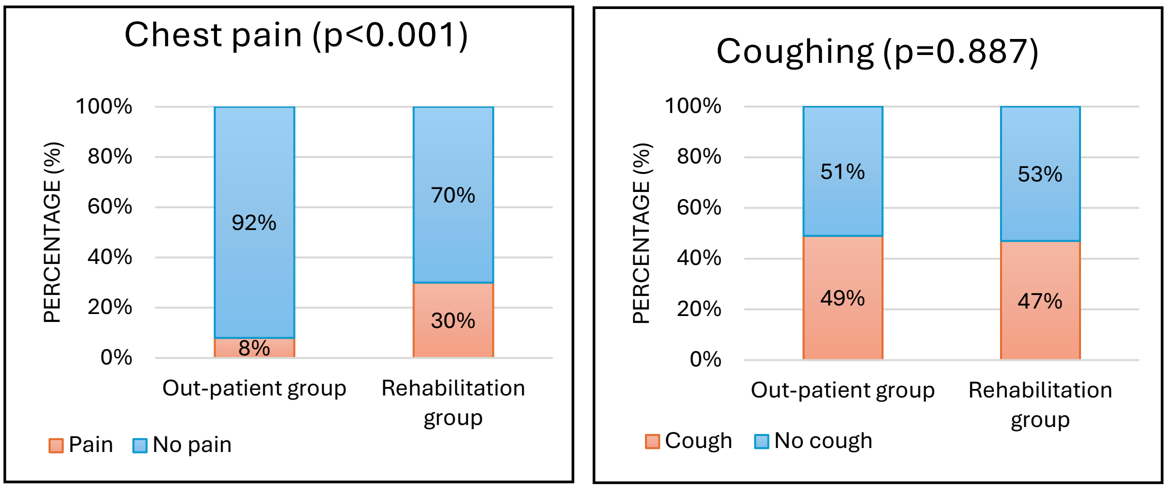


Figure 5: ***The prevalence of the characteristic main symptoms.*** Symptoms were self-reported during the enrollment period, comparing out-patient group (n=100) and rehabilitation group (n=100). The prevalence of chest pain showed a statistically significant difference in the two groups ($p < 0.001$), while the prevalence of coughing was reported equally in both groups (80).

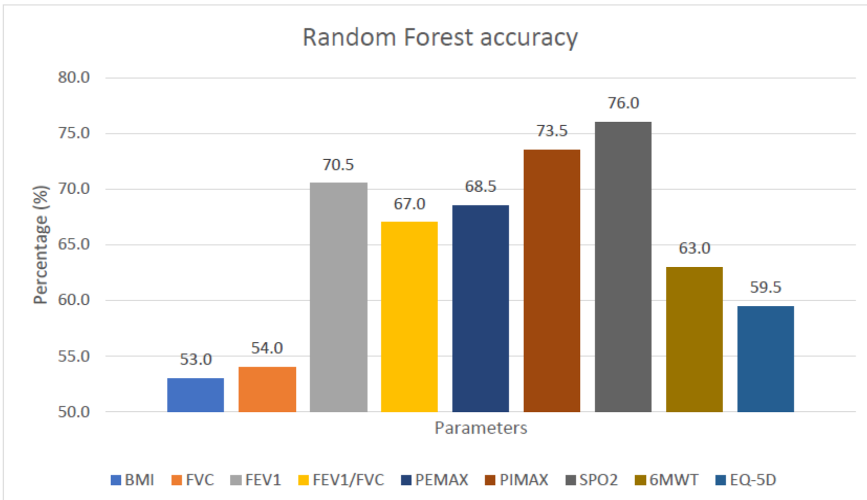
Highlighting how untreated persistent subjective and objective symptoms affect quality of life, the data collected from EQ-5D-3L was used to differentiate the five dimensions of health-related quality of life. Our findings pointed out that more severe subjective and objective symptoms significantly worsened the pain/discomfort dimension (rehabilitation group vs. out-patient group, mean (SD), 1.53 (0.59) vs. 1.72 (0.52), p=0.009, indicating a greater burden of pain in this population (Table 7).

Table 7: ***Presenting the 5 dimensions measured by EQ-5D-3L questionnaire***. Comparing the baseline parameters between the two groups: out-patient group (n=100) and rehabilitation program (n=100). EQ-5D-3L describes quality of life in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Scores represent 1: no problem, 2: moderate problems, 3: extreme problems. Comparison of EQ-5D-3L dimensions between the out-patient and rehabilitation groups revealed no significant differences in mobility, self-care, usual activities, or anxiety/depression domains. However, a statistically significant difference was observed in the pain/discomfort domain, with higher scores in the rehabilitation group ($p = 0.009$). Data are presented as mean±SD. Significance was accepted at $p<0.05$ (80).

Variables	Out-patient group n=100	Rehabilitation group n=100	p-value
Mobility	1.39 (0.51)	1.42 (0.5)	0.567
Self-care	1.15 (0.41)	1.1 (0.3)	0.479
Usual activities	1.56 (0.61)	1.6 (0.62)	0.691
Pain/discomfort	1.53 (0.59)	1.72 (0.52)	0.009*
Anxiety/depression	1.43 (0.57)	1.49 (0.58)	0.213

4.2.2. Results of Random Forest analysis

To explore potential predictive patterns within the data, Random Forest was trained on our dataset with 100 individuals in the rehabilitation group and 100 individuals in the out-patient group, a total of 200 people's dataset. This procedure has the ability to handle mixed feature types and low-dimensional data, to predict the necessity of rehabilitation. Based on the collected data, Random Forest model was able to determine whether the subject belonged to the rehabilitation group or out-patient group. The algorithm includes the following parameters, BMI, FVC, FEV_1, FEV_1/FVC, PE_{max}, PI_{max}, $Sp0_2$, 6MWT, EQ-5D-3L underwent ten runs to ensure a comprehensive assessment of its performance. The classification accuracy of a Random Forest model using various physiological and functional parameters presented in percentage, among all features analyzed, SpO_2 showed the highest model accuracy at 76.0%, followed closely by PI_{max} (73.5%) and FEV_1/FVC ratio (70.5%). Other respiratory measures such as PE_{max} and FEV_1 achieved moderate accuracies of 68.5% and 67.0%, respectively. Functional capacity, represented by the 6MWT, demonstrated an accuracy of 63.0%, while EQ-5D-3L reached 59.5%. In contrast, FVC and BMI showed the lowest predictive accuracies at 54.0% and 53.0% (Figure 6). The median accuracy values were reflected in the mean accuracy, suggesting its reliability as an indicator for assessing the potential need for rehabilitation (106).



(6MWT = six-minute walk test; BMI = body mass index; EQ-5D-3L = EuroQol-5D-3L; FEV1 = forced expiratory volume in one second; FEV1/FVC = forced expiratory volume in one second to the forced vital capacity; FVC = forced vital capacity; PE_{max} = maximal expiratory pressure; PI_{max} = maximal inspiratory pressure; SpO_2 = blood oxygen saturation)

Figure 6: ***Random Forest, a machine learning algorithm, determined an optimal classification model to find reliable predictors for rehabilitation according to participants' performance.*** In Random Forest classification accuracy is commonly defined as the percentage of correctly classified instances compared to the total number of instances in the dataset. It serves as a standard metric for evaluating the performance of classification models. Our findings indicated that oxygen saturation and functional parameters like PI_{max} and FEV_1 had the highest feature importance in Random Forest group classification. The high accuracy percentages of the top three parameters affirm the reliability and generalization capability of our classification model (80).

5. Discussion

A general overview of our main findings showed that the implementation of outpatient rehabilitation programs for patients with long COVID syndrome led to measurable improvements in multiple clinical and functional parameters. Participants commonly reported persistent symptoms such as dyspnea, fatigue, and chest discomfort at baseline visits, which were addressed through tailored and structured rehabilitation interventions. Functional assessments revealed significant gains in exercise tolerance, as reflected by improved 6MWT and CPET parameters. Respiratory muscle strength, assessed through PI_{max} and PE_{max} values, showed moderate improvements following respiratory training. Pulmonary function tests, including FEV_1, remained stable or improved slightly during the rehabilitation period. Patient-reported outcomes also reflected positive progress. Significant improvements were observed in quality-of-life scores (EQ-5D-3L) and functional capacity scores (PCFS), particularly in domains related to mobility, daily activities, and psychological well-being. Dyspnea severity, measured by the mMRC scale, decreased significantly over the course of rehabilitation. Among patients who participated in the two-week structured program at the Department of Pulmonology, Semmelweis University, the multidisciplinary approach combining respiratory physiotherapy, aerobic and resistance exercises, psychological support, and patient education was associated with consistent improvements across both subjective and objective measures (96).

Long COVID has emerged as a major public health challenge, affecting millions worldwide with lingering symptoms. Without effective rehabilitation strategies, long COVID can strain healthcare systems, reduce workforce productivity, and increase disability rates, leading to a significant public health burden (107). An urgent need for rehabilitation programs to manage these long-term effects, enhance recovery, and alleviate economic and healthcare pressures was reported by the European Commission showed the need for integrated rehabilitation programs that address both physical and mental health aspects of long COVID. The report highlighted cognitive behavioral therapy, physical therapy, and nutritional support as crucial components to mitigate long-term disability (108). Long COVID could worsen pre-existing chronic conditions and with the post-exertional malaise which affected a significant percentage of long COVID patients, made standard physical therapy ineffective necessitating tailored rehabilitation programs for high-risk patients, eminently focusing on cardiac and pulmonary rehabilitation programs (109).

When planning pulmonary rehabilitation programs, there are certain factors that should be taken into consideration. Namely, pulmonary rehabilitation programs should be tailored based on patient comorbidities and functional capacity. These tailored programs have shown promising long-term benefits, including improved oxygen uptake, enhanced exercise tolerance, and better overall quality of life (110). Sex differences should also be taken into consideration, as research indicates that men and women with long COVID syndrome responded differently to pulmonary rehabilitation interventions (111). Another key factor to take into consideration is disease severity, as patients with severe respiratory failure needed early mobilization and functional reconditioning to prevent permanent disability (112). Long COVID is often described by decreased cardiopulmonary fitness, reduced exercise tolerance, and quality of life impairments, alongside the sequelae of prolonged immobilization. Survivors of severe COVID-19 are at heightened risk of polyneuropathy, myopathy, and Post-Intensive Care Syndrome (PICS), necessitating comprehensive rehabilitation plan (113).

When planning pulmonary rehabilitations, a key factor is choosing the proper intensity. Our results indicate that low-intensity training can be effective in improving long COVID outcomes. A clinical study by Nambi et al. involving 76 patients with long COVID syndrome assessed the effects of low- and high-intensity aerobic training combined with resistance training. Participants were divided into two groups and engaged in either low- or high-intensity aerobic training for 30 minutes daily over eight weeks. The study revealed that low-intensity aerobic training was significantly more effective ($p < 0.001$) in improving muscle strength and quality of life (114). These findings align with the outcomes of our program, where low-intensity aerobic exercises, conducted on treadmills, stationary bicycles, and rowing machines under professional supervision. Given the elevated risk of cardiovascular events among long COVID patients (115-118), our study prioritized safety through low-intensity, multimodal exercise activities. Despite the lower intensity, our comprehensive program effectively enhanced physical functionality and quality of life (119-122).

To objectively determine the impact of low-intensity physical training on long COVID patients, CPET was utilized. CPET not only measures exercise capacity but also evaluates submaximal and peak exercise responses (123, 124). This non-invasive method provides critical insights into exercise tolerance, functional capacity, and impairments, while also measuring exercise-induced pulmonary and cardiac parameters (125). CPET is particularly valuable in monitoring exertional dyspnea, exercise intolerance, or exercise-induced hypoxemia, enabling a comprehensive evaluation of rehabilitation outcomes (126, 127). Studies utilizing CPET on cycle ergometers found that personalized rehabilitation programs incorporating multicomponent training approaches significantly improve respiratory muscle strength, reduce symptoms such as dyspnea and fatigue, and enhance overall quality of life (128). These findings challenged the notion that longer rehabilitation programs were inherently more effective for long COVID patients (129). Our two-week rehabilitation program also showed sustained improvements in respiratory function and quality of life, as confirmed by CPET assessments conducted two months post-rehabilitation. Our 68 participants who successfully completed the two-week long, tailored rehabilitation program unanimously reported an alleviation of certain, persistent negative symptoms, including shortness of breath, fatigue, chest pain, cough, insomnia, and depression. The positive effects of the rehabilitation program were detectable right at the end of the program with significant improvements in both functional parameters and mental health scores, leading to a noticeable improvement in symptom severity and health status. Even these short-term changes positively influenced the patients' daily activities and their ability to work. No adverse events were observed during the rehabilitation, and all patients completed at least 90% of their rehabilitation program.

Evidence indicates that respiratory muscle training alone is significantly less effective compared to comprehensive rehabilitation strategies, as these relatively simple programs do not include cardiovascular rehabilitation elements, which seemed to be critical for long COVID patients (130). In our study, these exercises, whether conducted individually or in groups, were performed under physiotherapist supervision using equipment such as treadmills, bicycles, or arm ergometers. The patients' exercise tolerance improved markedly during the rehabilitation program, likely due to cardiovascular and musculoskeletal adaptations.

Another key factor to take into consideration is the composition of the rehabilitation team. Multidisciplinary rehabilitation programs have demonstrated significant benefits in improving inspiratory and expiratory muscle strength, endurance, and overall functionality (131-133). Our study also points in the direction that creating an interdisciplinary team of professionals is an effective strategy in managing long COVID patients. Nopp et al. conducted a study on 58 patients with severe long COVID syndrome using an individualized, interdisciplinary rehabilitation program. Their six-week program significantly improved patients' quality of life reduced dyspnea, and also increased walking capacity, similar to our results (134). The positive effect of rehabilitation program on 6MWT for long COVID patients is also corroborated by another study (135).

A final aspect to take into consideration is patient compliance. Patient compliance remained a major challenge following a successful rehabilitation program (136). A significant number of patients resumed work after the completed rehabilitation program, leading to reduced willingness and availability to participate in follow-up visits post-rehabilitation. Strengthening the long-term efficiency of the rehabilitation program would require additional resources, including technical tools (e.g. tablets, apps) and regular follow-up opportunities such as telemonitoring or in person check-ups (137, 138). Telerehabilitation may be a promising alternative for pulmonary rehabilitation (139). A study by Blanco et al. found that strength and breathing exercises delivered via tele-rehabilitation significantly improved fatigue and dyspnea (140). Similarly, Li et al. demonstrated the effectiveness of a six-week unsupervised home-based telerehabilitation program comprising breathing and aerobic exercises, which improved muscle strength and fitness, reduced dyspnea and breathing difficulties (141). However, participants often face challenges returning to regular follow-ups due to prior absences from work during their recovery, further complicating adherence. Long-term follow-up at six months and one-year post-rehabilitation would be ideal but remain unattainable under current resource constraints (142).

By combining these elements, rehabilitation programs could effectively aid patients in improving their functional status, facilitating their return to pre-illness conditions, demonstrating both short-term and long-term benefits (143). These findings are in line with a randomized clinical trial outcome, where a brief outpatient rehabilitation program rooted in cognitive and behavioral approaches significantly improved cognitive and physical function, functional capability and eased long COVID symptoms (144). Generally, even severe symptoms along with significant impairments in physical performance, quality of life, and psychological well-being could be significantly improved through exercise training sessions with a marked reduction in chronic long COVID symptoms, alongside significant improvements in upper and lower limb muscle strength, cardiopulmonary function, perceived physical and mental health, as well as reductions in depression and anxiety (145). A multidisciplinary team is also essential in improving the quality of life of patients and their mental well-being. Considering the psychological benefits, we concur with Demeco et al., who advocate for rehabilitation programs that address both physical and mental health aspects of recovery (146). Our program resulted in significant improvements in quality of life, and not just physical performance and mMRC dyspnea scores (104). A central component of our multidisciplinary rehabilitation program involved empowering participants to learn and practice their tailored rehabilitation exercises at home daily, minimizing the long-term health and economic burdens and maximizing the benefits. This approach developed self-sufficiency, encouraged participants to continue their rehabilitation independently, thus extending the benefits beyond the clinical setting. Multidisciplinary rehabilitation teams play a crucial role in addressing these challenges by alleviating psychological stressors and mitigating feelings of isolation (147). Our team's efforts resulted in marked improvements within two weeks of outpatient rehabilitation, with benefits extending to the three-month follow-up. This extra home-based practice strategy not only enhanced the program's effectiveness but also reduced the costs and logistical challenges associated with prolonged or recurring rehabilitation.

Our study may offer professionals methods on how to identify participants who should be enrolled in rehabilitation programs. Using machine learning techniques, particularly Random Forest models, has become increasingly common in classifying disease severity across various medical conditions. These models are valued for their ability to manage complex, high-dimensional datasets and provide interpretable results. In the context of COVID-19 infection, researchers have developed a Random Forest classifier to categorize COVID-19 patients into distinct severity classes based on clinical and laboratory features, achieving notable accuracy in predicting disease progression (148). In our research, we applied a similar Random Forest machine learning tool to classify long COVID patients based on parameters such as respiratory function, oxygen saturation, and quality of life metrics. Consistent with the recent findings, our model effectively identified key predictors and demonstrated robust performance in distinguishing patients requiring tailored rehabilitation interventions. This alignment may utilize Random Forest models to enhance clinical decision-making and personalize patient care strategies based on patients' individual parameters (149). Random Forest may be a valuable model in the future for supporting pre-rehabilitation enrollment decisions by assigning feature importance scores to variables such as symptoms or physical parameters (150). Notably, among these features, the pain/discomfort dimension of the EQ-5D-3L questionnaire emerged as a significant differentiator between groups, underscoring its relevance role as a critical marker for identifying patients in need of rehabilitation (151).

5.1. Limitation

The study had a few limitations. Our findings in this observational study without a control group might be biased by the natural healing process of patients. Moreover, during the pre-enrollment phase which was designed to screen possible life-threatening conditions such as post-exertional symptom exacerbation and post-exertional malaise, we did not use the DePaul Post-Exertional Malaise Questionnaire. Vaccination status was only partly included as a variable in this study due to the limited mass vaccination availability in Hungary until the first quarter of 2021. While vaccination has been well-documented as a preventive measure against both acute COVID-19 and long COVID, our study could not establish a direct correlation between vaccination status and the severity of long COVID symptoms, primarily due to the transitional period of vaccine availability during the research timeline. However, future studies should further investigate the connection between vaccination, immune response, and rehabilitation efficacy in long COVID recovery. Loss to follow-up was also significant in our study as only 73 of the one hundred patients returned for the two-month follow-up visit, and just 38 showed up at three-month post-rehabilitation. A final limitation is our single-centered study design. Taking this into account, further randomized controlled trials with multicenter enrolment are needed to confirm the results of our study.

6. Conclusion

Our study highlights the significant benefits of tailored pulmonary rehabilitation in improving long-term outcomes for individuals suffering from long COVID. The findings demonstrate that structured, individualized rehabilitation programs effectively mitigate persistent symptoms such as dyspnea, fatigue, and reduced exercise tolerance. Participants in our two-week rehabilitation program reported immediate and sustained improvements in both physical function and mental well-being, with these positive effects persisting for at least two months of post-rehabilitation.

Our study reinforces the importance of multidisciplinary rehabilitation approaches, including psychological support, patient education, and self-managed home exercises to sustain long-term recovery. Given the growing evidence linking chronic inflammation, comorbidities, and smoking history to prolonged long COVID conditions, targeted rehabilitation strategies for high-risk populations, such as smokers, individuals with pre-existing respiratory conditions, and those with persistent neurocognitive impairments should be prioritized.

Our Random Forest algorithm demonstrated promising classification performance to identify predictive patterns associated with the necessity for rehabilitation among individuals with varying physiological and functional profiles. These findings highlight the potential of certain respiratory parameters as reliable indicators and suggest the integration of predictive modeling into clinical assessments to optimize resource allocation in post-acute care settings.

In conclusion, tailored rehabilitation should be a fundamental component of long COVID management strategies, complementing preventive measures such as vaccination. Our findings support the implementation of personalized, evidence-based rehabilitation programs to facilitate recovery, improve quality of life, and reduce the long-term healthcare burden of long COVID. Further research is needed to optimize rehabilitation protocols, explore sex-specific responses to treatment, and integrate technological advancements such as tele-rehabilitation to enhance accessibility and long-term adherence.

7. Summary

Many patients recovering from COVID-19 infection experience persistent symptoms such as cough, dyspnea, chest pain, fatigue, and psychological distress, significantly affecting their quality of life and workability. Despite the growing recognition of long COVID syndrome, complex cardiopulmonary rehabilitation remains underrepresented in clinical practice. This thesis investigates the effectiveness of tailored, multidisciplinary rehabilitation programs in improving functional capacity, respiratory function, and overall well-being in patients with long COVID. Our quasi-experimental study included 68 patients who underwent a two-week complex cardiopulmonary rehabilitation program at the Department of Pulmonology, Semmelweis University. Functional and respiratory parameters, including forced expiratory volume in one second, six-minute walk test, chest kinematics, quality of life (EuroQol-5D, EQ-VAS and PCFS), and the mMRC dyspnea scale, were assessed before, after, and two months following rehabilitation. Results demonstrated significant improvements in six-minute walk test ($p=0.031$), mMRC dyspnea scale ($p=0.003$), EQ-VAS quality of life score ($p=0.015$), and PCFS ($p=0.032$). Additionally, improvements were observed in respiratory function, chest kinematics, and breath-holding time ($p=0.041$), indicating enhanced pulmonary capacity. To further investigate long-term effects, 200 adults with different severity of long COVID were enrolled and categorized into intervention ($n=100$) and control ($n=100$) groups. The intervention group participated in a supervised rehabilitation program, followed by two- and three-month follow-ups, including cardiopulmonary exercise testing. At baseline, significant differences were observed between the intervention and control groups in pulmonary parameters, such as forced vital capacity, forced expiratory volume, and oxygen saturation (all $p<0.05$). Follow-up assessments confirmed sustained improvements in maximal oxygen consumption ($p<0.05$), reinforcing the long-term benefits of rehabilitation. Overall, our findings highlight the effectiveness of a structured, patient-centered rehabilitation program in enhancing functional capacity, respiratory function, and quality of life in long COVID patients. A multidisciplinary, individualized approach may be key to optimizing recovery outcomes, underscoring the need for integrating such programs into long COVID healthcare strategies.

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9. Bibliography of the candidate's publications

9.1 Publications related to the PhD thesis

1. **Szarvas Zsófia**, Fekete M, Szollosi GJ, Kup K, Horvath R, Shimizu M, Tsuhiya F, Choi HE, Wu HT, Fazekas-Pongor V, Pete KN, Cserjesi R, Bakos R, Gobel O, Gyongyosi K, Pinter R, Kolozsvari D, Kovats Z, Yabluchanskiy A, Owens CD, Ungvari Z, Tarantini S, Horvath G, Muller V, Varga JT. Optimizing cardiopulmonary rehabilitation duration for long COVID patients: an exercise physiology monitoring approach. Geroscience. 2024 Oct;46(5):4163-4183. doi: 10.1007/s11357-024-01179-z.

2. **Szarvas Zsófia**, Fekete M, Horvath R, Shimizu M, Tsuhiya F, Choi HE, Kup K, Fazekas-Pongor V, Pete KN, Cserjesi R, Bakos R, Gobel O, Kovacs O, Gyongyosi K, Pinter R, Kovats Z, Ungvari Z, Tarantini S, Horvath G, Muller V, Varga JT. Cardiopulmonary rehabilitation programme improves physical health and quality of life in post-COVID syndrome. Ann Palliat Med. 2023 May;12(3):548-560. doi: 10.21037/apm-22-1143.

3. Fekete, Mónika, **Zsófia Szarvas**, Vince Fazekas-Pongor, Ágnes Fehér, Zsuzsanna Ágnes Jáky-Kováts, József Lukácsovits, Gábor Horváth, Veronika Müller, and János Tamás Varga. "A Poszt-COVID-19 Betegség Tüdőgyógyászati Rehabilitációja." ORVOSTOVÁBBKÉPZŐ SZEMLE 28 (2021): 21–24.

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9.2 Oral and poster presentations related to the PhD thesis

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