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

PhD thesis

Zsófia K. Szarvas, MD

Semmelweis University Doctoral School

Károly Rácz Conservative Medicine Division

Supervisor: **Prof. János Tamás Varga, MD, Phd, DSc**

Mónika Fekete MD, PhD

Official reviewers: Attila Vágvölgyi, MD, PhD and Enikő Bárczi, MD, PhD

Head of the Complex Examination Committee: Prof. Lilla Tamási, MD, PhD, DSc

Members of the Complex Examination Committee: Prof. Mária Szilasi, MD, PhD, DSc and Anikó Bohács, MD, PhD

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1. Introduction

Long COVID is recognized as a chronic, multi-systemic condition, which leads not only to physical limitations but also social and economic burdens, particularly in working-age adults. Persistent fatigue, respiratory symptoms, and psychological distress contribute to diminished work capacity and increased healthcare costs. Mental health complications, especially depression and anxiety, are common and require integrated care strategies. Given the complex nature of long COVID, structured rehabilitation has emerged as a cornerstone of management. Cardiopulmonary rehabilitation improves lung function, exercise tolerance, and quality of life. International guidelines now advocate for individualized, multidisciplinary programs that include physical, psychological, and cognitive interventions. Techniques such as breathing exercises, resistance and aerobic training, and inspiratory muscle training lead to measurable improvements in respiratory parameters, muscle strength, and subjective well-being. Cardiopulmonary exercise testing (CPET) serves as a valuable tool for baseline and follow-up assessment, ensuring safe and effective program delivery.

2. Objectives

This thesis explores the role of rehabilitation in managing long COVID. The primary aim is to evaluate the effectiveness of a structured, two-week, patient-centered cardiopulmonary rehabilitation program designed to improve exercise tolerance, respiratory function, and overall health status. Using cardiopulmonary exercise testing (CPET), six-minute walk test (6MWT), and health-related quality of life assessments (EQ-5D-3L), patient outcomes were measured at baseline, post-rehabilitation, and during follow-ups at two and three months to assess sustained benefits.

A secondary objective is to apply a Random Forest machine learning model to identify whether specific physiological and functional parameters can accurately predict rehabilitation program participation compared to those receiving no intervention. This approach aims to support clinical decision-making and optimize resource allocation.

The central hypothesis is that a short-term, intensive rehabilitation program can lead to significant, long-lasting improvements in patients with long COVID by highlighting the importance of multidisciplinary and individualized rehabilitation.

3. Methods

This study used a two-pronged approach to assess (1) the effectiveness of a two-week cardiopulmonary rehabilitation program and (2) predictive classification using machine learning.

3.1. Evaluation of the rehabilitation program's impact

A total of 68 long COVID patients were recruited between 1st April, 2021 and 1st April, 2022 at Semmelweis University's Department of Pulmonology. Eligibility required ≥12 weeks post-COVID symptoms and a stable clinical condition, confirmed through detailed screening. Inclusion and exclusion criteria ensured safe participation in moderate-intensity rehabilitation.

3.1.1. Intervention

The two-week rehabilitation program included a twice-daily group and individualized exercise sessions tailored to patient needs. Activities involved aerobic and resistance training, inspiratory muscle training, respiratory physiotherapy, and psychological support. Participants were divided into two alternating groups for structured scheduling and personalized supervision.

3.1.2. Data collection and time points

Participants were evaluated at baseline, after rehabilitation, and during 2- and 3-month follow-ups. Parameters included demographic data, questionnaires (EQ-5D-3L), functional capacity (6MWT), cardiopulmonary fitness (CPET) and respiratory function (spirometry).

3.1.3. Statistical analysis

Non-parametric tests assessed changes over time, with $p < 0.05$ considered significant. Analyses were conducted using STATA 14.

3.2. Machine learning model for rehabilitation prediction

To identify which patient characteristics best predict the need for structured rehabilitation, a Random Forest classification model was developed using data from the e-MedSolution database.

3.2.1. Study design

Data were collected from 1st April, 2021 to 1st December, 2022. The study matched 100 participants from the rehabilitation program with 100 age- and sex-matched outpatients who received only a one-time consultation and a home-based rehabilitation plan without supervision.

3.2.2. Variables used

A wide range of physiological and functional parameters were included:

- **Pulmonary Function:** FVC, FEV1, FEV1/FVC, TLCO, KLCO
- **Respiratory strength:** PE_{max}, PI_{max}
- **Oxygenation and performance:** SpO_2, 6MWT distance
- **Subjective measures:** EQ-5D-3L, symptom reports.

3.2.3. Statistical approach

Descriptive statistics (median, IQR for continuous data; counts and percentages for categorical data) were used. Group comparisons were performed with the Mann-Whitney U test and Fisher's exact test with $p < 0.05$ considered significant.

3.2.4. Machine learning method

A Random Forest classifier was trained to distinguish between rehabilitation and outpatient groups using ten train-test splits. The model identified key predictors of rehabilitation need, such as FEV_1, PI_{max}, and SpO_2, offering a potential tool for future triage decisions. Significance was determined at $p < 0.05$.

4. Results

4.1. Effectiveness of the rehabilitation program

A total of 68 middle-aged adults (53.5 ± 12.6 years; 29 females and 39 males) with severe and persistent long COVID symptoms were enrolled to our study and completed the two-week

cardiopulmonary rehabilitation. A male predominance was observed in the study population. A total of 41 participants, representing approximately two-thirds of our sample, had a history of smoking, of whom two were current smokers. Most had multiple comorbidities, with hypertension and COPD being the most common. The most frequent symptoms included fatigue, dyspnea, cough, and chest pain.

4.1.1. Short-term effect of the rehabilitation

As a result of this two-week tailored, significant improvements were found in 6MWT, breath holding test, EQ-VAS, and PCFS (Table 1) (1).

Table 1: Changes in functional parameters and quality in short- and mid-term (n=68).

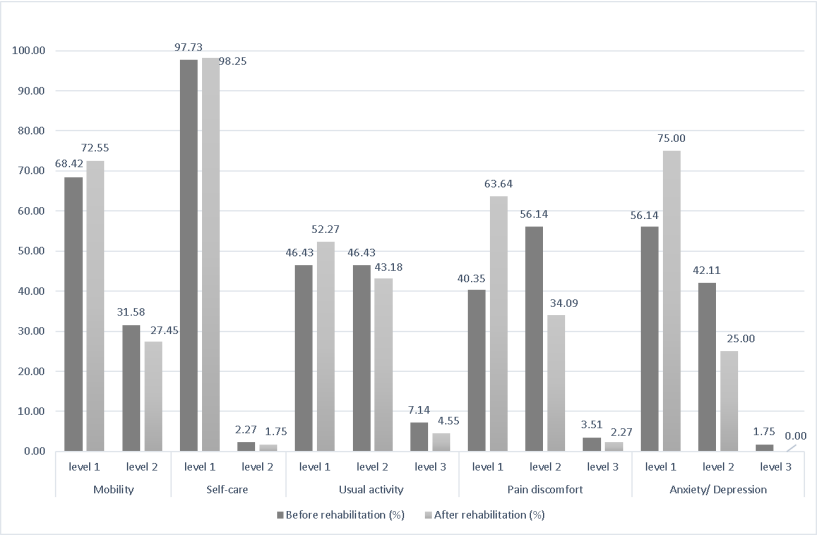
Functional parameters	Before rehabilitation	After 2 weeks rehabilitation	p-value	2 months after rehabilitation	p-value
FEV_1 (%pred) (IQR)	86 (73-103)	91 (80-99)	0.360	91 (80-99)	0.360
FEV_1/FVC (%)	109 (102-113)	108 (102-113)	0.862	104 (100-109)	0.662
PEmax (kPa)	9.7 (7.3-11.7)	4.6 (4.4-4.8)	0.032	9.8 (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

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.

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), in our study we were able to detect positive change in all the five dimensions after the completion of the two-week rehabilitation program. Quality of life significantly improved in all five EQ-5D-3L domains, and the improvements were significant ($p<0.05$) particularly in pain/discomfort and anxiety/depression (Figure 1) (1).

Figure 1: EuroQol-5 Dimensions-3 Level (EQ-5D-3L) questionnaire results before and right after the rehabilitation (n=68).



4.1.2. Long-term effect of the rehabilitation

To objectively evaluate the impact of our intervention on cardiopulmonary fitness, we employed Cardiopulmonary Exercise Testing (CPET) a comprehensive tool that measures respiratory, cardiovascular, and muscular performance during exercise.

We observed a general trend of improvement in multiple physiological parameters, including workload, heart rate response, and ventilatory efficiency. However, statistically significant changes were detected in two key indicators of aerobic capacity: maximal oxygen consumption and oxygen used in one minute per kilogram of body weight (Table 2) (2).

Table 2: The CPET result of 2-month follow-up compared to 3-month follow-up.

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

4.2. Random Forest classification

Using data from 200 individuals (rehabilitation vs. out-patient group), the Random Forest model identified key predictors of rehabilitation need. Both groups were comparable in age, (median 56 years) and sex distribution (57% male and 43%

female), with no significant difference in body mass index (28.75 [25.22-33.11] vs 28.87 [26.48-33.49)]). However, several pulmonary function parameters showed significant differences between the groups, indicating distinct respiratory profiles such as forced vital capacity, FEV1, oxygen saturation (Table 3) (2).

Table 3: 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).

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

The most common 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 ($p = 0.887$) (2).

Highlighting how untreated persistent subjective and objective symptoms affect quality of life, the data collected 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 (2).

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. Our findings indicated that SpO_2, PI_{max}, and FEV_1/FVC ratio had the highest feature importance in Random Forest group classification (2). The model demonstrated good performance in distinguishing between those needing supervised rehabilitation and those managing with home-based care.

5. Conclusions

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 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 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.

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