Study protocol

Study design

This study is a retrospective, single centre study, comparing the rate of improvement in men and women with long COVID-19 syndrome, following the completion of a hybrid PR programme from August 2022 to December 2022. The study flowchart is presented in Figure 1. All patients will have been diagnosed with long COVID-19 based on the persistence of fatigue at least three months following hospital discharge due to COVID-19. Exclusion criteria include participation in another clinical trial, occurrence of myocardial infarction, hospitalisation for unstable angina, stroke, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), implantation of a cardiac resynchronization therapy device (CRTD), active treatment for cancer or other malignant disease, uncontrolled congestive heart disease (NYHA class >3), acute psychosis or major psychiatric disorders or continued substance abuse within 3 months prior to informed consent. No change in the medical treatment will be made during the duration of the PR program. During the first phase of the PR programme, patients will undergo a structured, outpatient, supervised hospital-based PR program for 4 weeks with a frequency of 2 training sessions per week. Following the completion of the first phase patients will undergo 24 home-based tele-rehabilitation sessions for 8 weeks with a frequency of 3 training sessions per week. Assessment will be performed at baseline and following completion of the PR programme and include pulmonary function tests, exercise capacity, daily physical activity levels, functional capacity, peripheral and respiratory muscle strength and quality of life. Informed written consent will be obtained from all patients. The investigations will be carried out following the rules of the Declaration of Helsinki of 1975 and the study was approved by the University Hospital Ethics Committee (Protocol ID-24633).

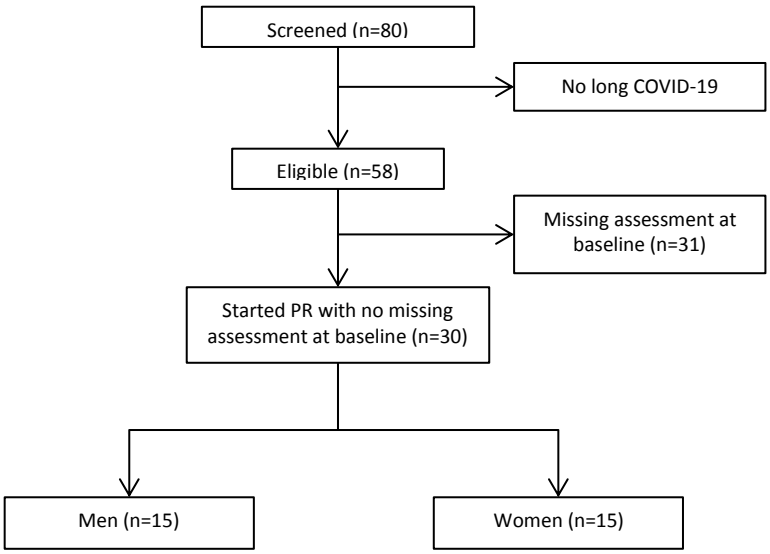

Figure 1. Study flow chart

Respiratory function assessment

Standard spirometry will be performed with a metabolic cart using the "fast inspiratory manoeuvre". Maximum static inspiratory (PImax) and expiratory (PEmax) mouth pressures will be measured with a plastic semi-rigid flanged mouthpiece fitted to a metallic stem incorporating a 3-way tap, manufactured according to the design of Ringqvist. Static lung volumes will be determined by the multiple nitrogen washout technique. The diffusing capacity for carbon monoxide (DL_{CO}) via the single-breath technique will also be determined. Predicted values for spirometry, static lung volumes, and DL_{CO} are from the European Community for Coal and Steel.

Peripheral muscle strength, body mass composition and quality of life

Prior to the onset and following completion of the 3 month hybrid PR program all participants will be assessed for quadriceps isometric muscle strength with a strain gauge Myometer and handgrip strength. Furthermore, body mass composition will be assessed with the method of bio-impedance. Quality of life will be assessed via FACIT, CAT, HADS, SF-36 and the Revised Impact of Events Scale questionnaires.

Incremental cycle-ergometer exercise test

Participants will perform a ramp incremental exercise protocol on the cycle ergometer. The exercise protocol will be as follows: after 3-min of baseline measurements and 3-min of unloaded pedalling, the work rate will be increased by 10-25 Watt every 1-min to the limit of tolerance. During each test, arterial oxygen saturation (SpO_2%) will be obtained by a pulse oximeter connected to the metabolic cart. Blood pressure will be monitored automatically via

a cuff that is connected to the metabolic cart at predetermined time points. The modified Borg 1-10 scale will be used to rate the magnitude of perceived dyspnoea and leg discomfort every 3-min throughout the test and at the end of exercise.

Functional capacity

The 6-min walk test (6MWT) will be performed according to the instructions of the American Thoracic Society, i.e.: the maximum distance walked by each patient on a 20-meter hospital corridor in 6 minutes will be assessed. Intensity of dyspnoea and leg discomfort will be assessed by the modified Borg 1-10 scale, whereas heart rate (HR) and SpO_2% will be recorded at rest and at the end of 6MWT. Moreover, Short Physical Performance Buttery Test (SPPB) will be performed prior and following the completion of the 3-month period.

Daily physical activity

Daily physical activity was assessed for a period of seven consecutive days, one week prior and one week following the completion of the PR program, using a free application installed in the patients' smartphones (Leap Fitness Group). Patients instructed to have their phone in their pocket for as much as possible during the seven day period in order to minimise the data loss.

Exercise training protocol

During the outpatient PR programme, patients will perform supervised exercise training consisting of 30 minutes interval aerobic exercise on electromagnetically braked cycle ergometers at 100% of peak work rate and resistance exercises for the upper body. During each training session dyspnoea and leg discomfort will be recorded on the modified 1-10 Borg scale, whereas HR and SpO_2% will be continuously monitored by a portable pulse oximeter. Based on symptoms of breathlessness and fatigue reported at the end of each exercise session (i.e. both dyspnoea and leg discomfort <4 at the Borg scale), the exercise intensity will be increased by 5-10% of the baseline WRpeak in the next session. The remote 24 home-based PR sessions will be consisted of 30 minutes walking with an individualised target of steps (recorded via the mobile app installed in the patients' mobile phone). The steps, leg discomfort and dyspnoea symptoms will be reported by the patient using a physical activity diary on a weekly basis. The assessors will set new step targets based on the steps and the symptoms reported by the patient. If dyspnoea and leg discomfort are both <4 at the Borg scale the weekly target of steps will be increased by 5-10%, otherwise the target will remain the same.

Statistical analysis

Normal distribution of the data will be checked with the Shapiro-Wilk test. Comparisons of baseline characteristics will be made using independent t-test. Two-way ANOVA with repeated measures will be applied to detect differences between the two sexes across different time points. The LSD post hoc correction method will be used where appropriate. A p value <0.05 is considered significant.