

# Efficacy of Cardiopulmonary Rehabilitation on Cardiorespiratory Function in Patients with Long COVID Syndrome

Silvia Sarullo,<sup>1,2,3</sup> Cinzia Nugara,<sup>2</sup> Annamaria Lo Voi,<sup>2</sup> Antonino Zarcone,<sup>2</sup> Gabriele Di Francesco,<sup>2</sup> Sergio Bosco,<sup>2</sup> Sergio Carollo,<sup>2</sup> Luigi Mazzara,<sup>2</sup> Francesco Giallauria,<sup>4</sup> Francesco Cappello,<sup>1,3</sup> Filippo M. Sarullo<sup>2</sup>

Department of Biomedicine, Neurosciences and Advanced Diagnostics, University of Palermo,<sup>1</sup> Palermo – Italy

Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital,<sup>2</sup> Palermo – Italy

Euro-Mediterranean Institute of Science and Technology (IEMEST),<sup>3</sup> Palermo – Italy

Federico II University of Naples, Department of Translational Medical Science,<sup>4</sup> Naples – Italy

## Abstract

**Background:** Long COVID syndrome (LCS) refers to persistent sequelae following acute SARS-CoV-2 infection and affects approximately 5%-20% of individuals.

**Objective:** This study evaluated functional capacity limitations in patients with LCS using cardiopulmonary exercise testing (CPET) and quantified the effects of a structured cardiorespiratory rehabilitation (CR) program.

**Methods:** In this prospective observational study, 67 outpatients with LCS completed CPET before and after participation in a supervised CR program. At baseline, patients demonstrated reduced functional capacity, including decreased  $\text{VO}_2\text{peak}$  ( $19.47 \pm 7.86$  mL/kg/min), lower  $\text{O}_2$  pulse ( $10.65 \pm 3.11$  mL/beat), increased  $\text{VE}/\text{VCO}_2$  slope ( $31.26 \pm 7.98$ ), and impaired ventilation ( $\text{VE} = 57.83 \pm 17.37\%$ ). Most participants either did not achieve the anaerobic threshold (AT) or reached it prematurely, although  $\text{VO}_2/\text{work}$  slope values remained within normal limits.

**Results:** After a median 45-day CR intervention, significant improvements were observed in several parameters: resting heart rate decreased by 8.88% ( $p < 0.0001$ ), minute ventilation increased by 30.46% ( $p < 0.0001$ ),  $\text{VO}_2\text{peak}$  rose by 18.85% ( $p < 0.0001$ ), and peak workload increased by 26.82% ( $p < 0.0001$ ). Additionally, 95% of patients achieved AT following CR, with a 16.21% delay in AT onset ( $p < 0.0001$ ). The  $\text{VE}/\text{VCO}_2$  slope showed a modest but significant reduction of 4.03% ( $p = 0.0443$ ).

**Conclusions:** Exercise-based CR substantially improved functional capacity in patients with LCS, demonstrated by increases in  $\text{VO}_2\text{peak}$ ,  $\text{O}_2$  pulse, and ventilatory efficiency. Although these results support CR as a beneficial therapeutic strategy, the underlying pathophysiological mechanisms of LCS remain incompletely understood.

**Keywords:** Post-Acute COVID-19 Syndrome; Cardiac Rehabilitation; Exercise Test; Exercise Capacity.

## Introduction

The Stanford Hall consensus statement for post-COVID-19 rehabilitation (2020)<sup>1</sup> emphasizes the essential role of multidisciplinary rehabilitation for patients recovering from acute SARS-CoV-2 infection. This recommendation is consistent with evidence from previous coronavirus outbreaks, including SARS-CoV-1 (2003) and MERS-CoV (2012), in which acute infections were frequently followed by multisystem sequelae. As with these earlier epidemics, SARS-CoV-2 infection can lead to long-term complications involving

multiple organ systems, particularly the cardiovascular, respiratory, gastrointestinal, musculoskeletal, central and peripheral nervous, and endocrine systems.<sup>2</sup>

After 3 years of global health emergency, the heterogeneous clinical spectrum of COVID-19 has been extensively documented, ranging from critical manifestations (e.g., respiratory failure, septic shock, and multiorgan dysfunction requiring intensive care) to completely asymptomatic disease. This wide variability underscores the need for individualized rehabilitation strategies that address the specific pathophysiological consequences observed in each patient.

Patients with long-COVID syndrome (LCS) are generally defined as individuals who have recovered from acute SARS-CoV-2 infection but continue to experience symptoms in the weeks that follow. Two related conditions are recognized: i) persistent symptomatic COVID-19, in which symptoms last 4-12 weeks after the acute event, and ii) LCS, in which full health has not been restored more than 12 weeks after the first negative antigen test.<sup>2</sup> Approximately 5%-20% of patients

**Mailing Address:** Filippo Maria Sarullo •

Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli

Hospital – Via Messina Marine 197, 90123, Palermo – Italy

E-mail: sarullo.filippo@fbfpa.it, fsarullo@neomedia.it

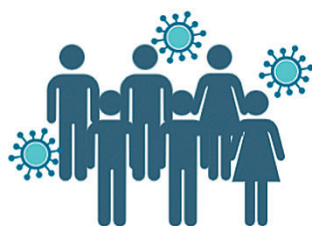
Manuscript received March 04, 2025, revised manuscript July 10, 2025, accepted November 06, 2025

Editor responsible for the review: Lídia Moura

**DOI:** <https://doi.org/10.36660/abchf.20250007i>

**Central Illustration: Efficacy of Cardiopulmonary Rehabilitation on Cardiorespiratory Function in Patients with Long COVID Syndrome**

ABC Heart Failure &amp; Cardiomyopathy



Patients with long COVID syndrome.



Assessment of CPET and classification of cardiorespiratory impairment.



Outpatient cardiorespiratory rehabilitation program and follow-up CPET reassessment.

ABC Heart Fail Cardiomyop. 2025; 5(3):e20250007

CPET: cardiopulmonary exercise testing.

report symptoms after the acute phase, most commonly asthenia, dyspnea, chronic fatigue, and a hyperkinetic heart-rate pattern.<sup>3</sup>

These manifestations appear to arise, at least in part, from alterations in immune function that contribute to the cytokine storm,<sup>4</sup> a process capable of generating systemic inflammation and autoimmune phenomena. Moderate-intensity physical exercise has been shown to modulate immune responses to pathogens, reducing the risk of autoimmune activity, largely through lowering serum concentrations of tumor necrosis factor- $\alpha$  and interleukin-6.<sup>5</sup> Because of its capacity to adjust duration, intensity, and frequency of activity according to each patient's functional status, cardiorespiratory rehabilitation (CR) represents an ideal nonpharmacological intervention in this context.

The present study aims to evaluate the effects of exercise-based CR on functional capacity in outpatients with symptoms related to LCS, using cardiopulmonary exercise testing (CPET) at baseline and after completion of one or more cycles of exercise therapy.

## Methods

### Patient selection and study design

This prospective, observational, single-center study was conducted at the Cardiovascular Rehabilitation Unit of Ospedale Buccheri La Ferla Fatebenefratelli Hospital. The study protocol was approved by the institutional ethics

committee. All enrolled patients were monitored clinically and therapeutically by their referring outpatient team. Participation was voluntary, and patients could withdraw from the study at any time. The study adhered to the principles of the Declaration of Helsinki (1964) and relevant national regulations.

Patients were eligible for inclusion if they met all of the following criteria: i) symptomatic individuals at least 4 weeks after recovery from SARS-CoV-2 infection, defined as the first negative rapid or molecular antigen test; ii) age  $\geq 18$  years; iii) preserved left ventricular ejection fraction (left ventricular ejection fraction [LVEF]  $> 55\%$ ) on echocardiography; iv) absence of acute ongoing conditions (e.g., febrile states, viral or bacterial infections, acute respiratory failure, acute ischemic heart disease, acute heart failure, acute hepatic failure, or acute kidney failure).

Patients were excluded if they met at least one of the following criteria: i) presence of ongoing acute conditions; ii) comorbidities likely to affect CPET performance (e.g., grade III obesity with body mass index [BMI]  $> 40$ , rheumatic diseases, pulmonary fibrosis); iii) congenital cardiomyopathies (corrected or uncorrected); iv) reduced LVEF ( $< 55\%$ ); v) inability to perform CPET, including poor adaptability to a cycle-ergometer test.

### CPET protocol

Cardiovascular, respiratory, and metabolic performance were assessed at baseline and upon completion of the CR

program using a CPET conducted on a cycle ergometer at 60 revolutions per minute (rpm). A ramp protocol was used, consisting of a 2-minute warm-up at a fixed intensity of 10 Watts, followed by an incremental exercise phase in which workload increased every 60 seconds.

Breath-by-breath analysis of exhaled  $O_2$ ,  $CO_2$ , and ventilation volumes was performed by using the Vyntus™ CPX (Vyaire Medical GmbH, UK). Simultaneously, cardiac electrical activity was monitored via 12-lead electrocardiography, humeral blood pressure via sphygmomanometer, and peripheral oxygen saturation via pulse oximetry. Patients were encouraged to continue exercising until muscle exhaustion or until discontinuation criteria were met.<sup>6</sup> The test was considered maximal when the respiratory exchange ratio, defined as the  $VCO_2/VO_2$  ratio, exceeded 1.05–1.10.<sup>7</sup>

The anaerobic threshold (AT), corresponding to the onset of metabolic acidosis due to rising plasma lactate,<sup>8</sup> was determined using the V-slope method based on  $VCO_2$  production,  $VO_2$  consumption, ventilatory equivalents, and end-expiratory gas pressures. The increase in  $VO_2$  relative to workload ( $\Delta VO_2/\text{work slope}$ ) from the first minute of exercise was calculated, as both  $\Delta VO_2/\Delta \text{Work slope}$  and  $AT-VO_2$  reflect muscular efficiency.<sup>9</sup>

Additional parameters included the  $O_2$  pulse ( $VO_2/\text{heart rate}$ ), an indirect marker of stroke volume,<sup>8</sup> and the  $VE/VCO_2$  slope, calculated from warm-up to peak exercise under isocapnic conditions.<sup>9</sup> Peak  $VO_2$  and peak ventilation were obtained by averaging the final 30 seconds of exercise. Predicted  $VO_2$  values were calculated according to sex, ethnicity, age, weight, and height and were expressed as percentages. The percentage of predicted  $VO_2$  was derived using the Wasserman and Hansen equations.<sup>9</sup>

### CR protocol

Patients underwent an interval-based CR protocol composed of four phases: i) warm-up: 10 minutes of gradually increasing intensity up to approximately 60% of  $VO_{2\text{peak}}$ ; ii) intervals: 4 minutes at 85%–95% of  $VO_{2\text{peak}}$ ; iii) relief: 3 minutes at a stable intensity corresponding to 60% of  $VO_{2\text{peak}}$ ; phases 2 and 3 were repeated four times; iv) cool-down: 5 minutes at a stable intensity of 50% of  $VO_{2\text{peak}}$ .

Participants attended the program 5 days per week, totaling 300 minutes of exercise weekly.

### Statistical analysis

Statistical analyses were performed using GraphPad Prism 8.0.1 (GraphPad Software Inc., San Diego, CA, USA). Continuous variables were expressed as mean  $\pm$  standard deviation (SD), or as median for non-normally distributed data. Categorical variables were reported as counts and percentages.

Changes between baseline and the end of follow-up were evaluated using two-way repeated-measures ANOVA. A  $p$ -value  $< 0.05$  was considered statistically significant. Nominal logistic regression was used to examine associations among exercise tolerance,  $VO_{2\text{peak}}$ ,  $AT-VO_{2\text{peak}}$ , resting heart rate,  $VE$ , and  $VE/VCO_2$ . An increase in  $VO_2 \geq 6\%$  relative to baseline

was considered a clinically meaningful improvement, in accordance with prior research.<sup>7</sup>

## Results

### Study population

From December 2022 to December 2023, a total of 74 consecutive patients with LCS were enrolled. Baseline evaluation was performed no earlier than 1.5 months and no later than 6 months after the first negative rapid or molecular antigen test for SARS-CoV-2. Seven patients (9%) withdrew after the initial CPET assessment due to personal or work-related constraints that prevented continuation of the CR. The remaining 67 patients (91%) completed the CR protocol and underwent repeat CPET at a median follow-up of 45 days (range 45–90 days).

Tables 1 and 2 summarize the demographic and clinical characteristics of the cohort. Men represented 52% of the sample ( $n = 35$ ), and the mean age was  $45.74 \pm 14.26$  years. Nine participants (13%) were active smokers. A total of 60 patients (89.55%) had received at least one dose of an anti-COVID-19 vaccine prior to infection with the wild-type virus.

Before infection and its sequelae, 22 patients (33%) reported an active lifestyle ( $> 150$  minutes/week of moderate-intensity or  $> 75$  minutes/week of high-intensity activity, according to the 2011 American College of Sports Medicine position statement).<sup>10</sup> A total of 23 patients (34%) reported a sedentary lifestyle without comorbidities (e.g., overweight or class I–II obesity, hypertension, impaired glucose tolerance/type 2 diabetes mellitus, dyslipidemia, atrial fibrillation), whereas 22 patients (33%) reported a sedentary lifestyle associated with at least one of such comorbidities.

At baseline evaluation, asthenia was the most frequently reported residual symptom ( $n = 58$ ; 85%), followed by fatigue ( $n = 53$ ; 79%) and chest pain ( $n = 30$ ; 45%). All patients were in sinus rhythm, although 3% were receiving antiarrhythmic therapy for a known history of paroxysmal atrial fibrillation. Resting sinus tachycardia was documented in 15 patients (22%).

Mean systolic-diastolic blood pressure values were within normal limits, and 19 patients (28%) were receiving treatment for hypertension. The cohort had a mean BMI of  $26.46 \pm 5.31$  kg/m<sup>2</sup>; 18 patients (27%) were classified as overweight or had class I–II obesity. Nine patients (13%) were receiving therapy for impaired glucose tolerance or diabetes mellitus, and 19 (28%) were on treatment for dyslipidemia.

During acute SARS-CoV-2 infection, 34% of patients required hospitalization, and 30% received anticoagulation with low-molecular-weight heparin. Additionally, 64% received prophylactic azithromycin and 60% were treated with corticosteroids. At admission, high-resolution CT imaging showed unilateral pulmonary foci in seven patients (10.4%) and bilateral pulmonary foci in 30 patients (45%).

Following the acute phase, all participants underwent spirometry. Small airway dysfunction, defined as  $FEF_{50}$  and  $FEF_{75}$  values  $< 65\%$  of predicted,<sup>11</sup> was present in 22% of the cohort, although lung volumes remained within normal limits (Table 3).

### CR and CPET evaluation

All patients participated in a supervised outpatient CR program based on interval training and delivered by a multidisciplinary team including cardiologists, sports medicine physicians, physiotherapists, nurses, nutritionists, and psychologists. The program consisted of a minimum of three treatment cycles (total duration 1.5 months), which could be extended to six cycles (total duration 3 months) if vital parameters (e.g., blood pressure, oxyhemoglobin saturation, heart rate, and cycle-ergometer tolerance) and follow-up CPET indicated insufficient improvement. After a median follow-up of 45 days (range 45-90 days), 37 patients (55%) had completed three cycles and 30 patients (45%) had completed six cycles.

Baseline CPET showed moderately reduced functional capacity, reflected by decreased  $\text{VO}_{2\text{peak}}$  and  $\%\text{VO}_{2\text{peak}}$ , reduced  $\text{O}_2$  pulse, increased pulmonary vascular involvement ( $\text{VE}/\text{VCO}_2 > 30$ ), and reduced VE. In addition, 13% of patients with LCS did not achieve the anaerobic threshold, and

27% showed a premature metabolic shift ( $\text{AT-VO}_2 < 40\%$ ).  $\text{VO}_2/\text{work}$  slope values remained within normal limits.

Table 4 summarizes CPET parameters at baseline and follow-up. At the end of the CR, we observed a reduction in resting heart rate (from  $85.95 \pm 15.67$  to  $78.31 \pm 13.23$  bpm;  $\Delta\% = -8.88\%$ ;  $p < 0.0001$ ) and an increase in ventilation (from  $57.83 \pm 17.37$  to  $75.45 \pm 18.85$  L/min;  $\Delta\% = +30.46\%$ ;  $p < 0.0001$ ). Peak  $\text{VO}_2$  increased from  $19.47 \pm 7.86$  to  $23.14 \pm 7.88$  mL/kg/min ( $\Delta\% = +18.85\%$ ;  $p < 0.0001$ ), accompanied by greater exercise tolerance, as indicated by higher peak workload (from  $91.62 \pm 47.90$  to  $116.19 \pm 45.80$  Watts;  $\Delta\% = +26.82\%$ ;  $p < 0.0001$ ).  $\text{O}_2$  pulse also increased (from  $10.65 \pm 3.11$  to  $12.12 \pm 3.43$  mL/beat;  $\Delta\% = +13.68\%$ ;  $p < 0.0001$ ).

Moreover, 95% of patients achieved the anaerobic threshold after CR, with higher  $\text{AT-VO}_2$  values (from  $15.15 \pm 6.49$  to  $16.91 \pm 6.92$  mL/kg/min;  $\Delta\% = +11.61\%$ ;  $p < 0.0001$ ) and a delayed onset of anaerobic threshold (from  $51.98 \pm 17.25\%$  to  $60.41 \pm 19.33\%$  of  $\text{VO}_{2\text{peak}}$ ;

**Table 1 – Baseline clinical and demographic characteristics of the study population (n = 67)**

| Category                | Variable                                         | Value              |
|-------------------------|--------------------------------------------------|--------------------|
| Demographic Data        | Age, years (mean $\pm$ SD)                       | 45.74 $\pm$ 14.26  |
|                         | Male sex, n (%)                                  | 35 (52)            |
|                         | Vaccinated against COVID-19, n (%)               | 60 (89.55)         |
|                         | Smokers, n (%)                                   | 9 (13)             |
|                         | Active lifestyle, n (%)                          | 22 (33)            |
|                         | Sedentary lifestyle without comorbidities, n (%) | 23 (34)            |
|                         | Sedentary lifestyle with comorbidities, n (%)    | 22 (33)            |
| Anthropometric Features | Height, cm (mean $\pm$ SD)                       | 168.72 $\pm$ 9.24  |
|                         | Weight, kg (mean $\pm$ SD)                       | 75.45 $\pm$ 16.39  |
|                         | BMI, kg/m <sup>2</sup> (mean $\pm$ SD)           | 26.46 $\pm$ 5.31   |
|                         | BSA, m <sup>2</sup> (mean $\pm$ SD)              | 1.86 $\pm$ 0.23    |
| Vital Parameters        | SBP, mmHg (mean $\pm$ SD)                        | 115.17 $\pm$ 14.08 |
|                         | DBP, mmHg (mean $\pm$ SD)                        | 71.67 $\pm$ 9.74   |
|                         | Sinus rhythm, n (%)                              | 67 (100)           |
|                         | Sinus tachycardia, n (%)                         | 15 (22)            |
|                         | HR, bpm (mean $\pm$ SD)                          | 85.89 $\pm$ 16.95  |
| Comorbidities           | Overweight or class I-II obesity, n (%)          | 18 (27)            |
|                         | Hypertension, n (%)                              | 19 (28)            |
|                         | Impaired glucose tolerance or diabetes, n (%)    | 9 (13)             |
|                         | Dyslipidemia, n (%)                              | 19 (28)            |
|                         | AF, n (%)                                        | 2 (3)              |

AF: atrial fibrillation; BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; SD: standard deviation.

## Original Article

$\Delta\% = +16.21\%$ ;  $p < 0.0001$ ). Changes in the  $VE/VCO_2$  slope were smaller, showing a modest but statistically significant reduction (from  $31.26 \pm 7.98$  to  $30.00 \pm 5.50$ ;  $\Delta\% = -4.03\%$ ;  $p = 0.0443$ ).

### CPET results in population subgroups stratified by lifestyle and comorbidities

CPET findings differed significantly across subgroups defined by lifestyle and comorbidity status. Based on physical activity level and the presence or absence of comorbidities, the cohort was divided into three groups: Group A, active individuals who regularly performed  $> 150$  minutes/week of moderate-intensity physical activity or  $> 75$  minutes/week of vigorous-intensity exercise, without comorbidities; Group B, sedentary individuals whose

activity levels were below the Group A thresholds, also without comorbidities; and Group C, sedentary patients with documented comorbidities. Table 5 summarizes the clinical characteristics of such subgroups.

Comparing CPET values at baseline and follow-up (Table 6), all three population subgroups demonstrated increases in  $VO_{2peak}$ , peak workload,  $O_2$  pulse, anaerobic threshold, and ventilation, along with a reduction in resting heart rate. Notably, improvements in metabolic efficiency were most pronounced in Group C.  $VO_{2peak}$  increased by  $\Delta\% = +29.10\%$  in Group C (from  $13.78 \pm 3.48$  to  $17.79 \pm 4.57$  mL/kg/min;  $p < 0.0001$ ), compared with  $\Delta\% = +11.53\%$  in Group A (from  $26.45 \pm 8.72$  to  $29.50 \pm 8.92$  mL/kg/min;  $p < 0.0001$ ) and  $\Delta\% = +21.57\%$  in Group B (from  $18.24 \pm 4.30$  to  $22.17 \pm 4.49$  mL/kg/min;  $p < 0.0001$ ) (Figure 1, Panel A).

Peak workload also increased in all subgroups: by  $\Delta\% = +16.56\%$  in Group A (from  $128.00 \pm 53.92$  to  $149.20 \pm 52.02$  W;  $p < 0.0001$ ), by  $\Delta\% = +26.78\%$  in Group B (from  $85.74 \pm 32.66$  to  $108.70 \pm 27.00$  W;  $p < 0.0001$ ), and by  $\Delta\% = +48.17\%$  in Group C (from  $61.45 \pm 28.50$  to  $91.05 \pm 35.47$  W;  $p < 0.0001$ ).

The increase in  $O_2$  pulse was greatest in Group A (from  $11.58 \pm 4.43$  to  $13.64 \pm 3.90$  mL/beat;  $\Delta\% = +17.77\%$ ;  $p < 0.0001$ ), suggesting a superior peripheral oxygen extraction capacity in individuals who had a higher fitness level before infection. The increase was  $\Delta\% = +8.77\%$  in Group B (from  $10.37 \pm 2.74$  to  $11.28 \pm 2.65$  mL/beat;  $p < 0.0001$ ) and  $\Delta\% = +14.34\%$  in Group C (from  $10.04 \pm 2.43$  to  $11.48 \pm 2.53$  mL/beat;  $p < 0.0001$ ) (Figure 1, Panel B).

Resting heart rate showed the most pronounced improvement in Group B (from  $89.87 \pm 16.05$  to  $84.78 \pm 13.76$  bpm;  $\Delta\% = -5.66\%$ ;  $p < 0.0001$ ), followed by Group A (from  $83.68 \pm 18.94$  to  $73.23 \pm 9.85$  bpm;  $\Delta\% = -12.48\%$ ;  $p = 0.0018$ ), and then Group C, which exhibited smaller changes (from  $84.14 \pm 10.83$  to  $76.64 \pm 13.36$  bpm;  $\Delta\% = -8.91\%$ ;  $p = 0.0321$ ).

The largest increase in  $AT-VO_2$  was observed in Group A ( $\Delta\% = +15.47\%$ ; from  $19.39 \pm 7.81$  to  $22.39 \pm 7.65$  mL/kg/min;  $p < 0.0001$ ), whereas Group C reached only borderline significance ( $\Delta\% = +55.88\%$ ; from  $8.26 \pm 5.86$  to  $12.88 \pm 4.70$  mL/kg/min;  $p = 0.0354$ ). No statistically significant change was found in Group B ( $\Delta\% = +32.73\%$ ; from  $11.76 \pm 5.89$  to  $15.61 \pm 4.12$  mL/kg/min;  $p = 0.0576$ ).

Similarly, although ventilation increased most prominently in Group C ( $\Delta\% = +39.56\%$ ; from  $51.28 \pm 13.24$  to  $71.57 \pm 19.58\%$ ), this difference did not reach statistical significance ( $p = 0.0968$ ). In contrast, substantial and statistically significant increases were recorded in Group A ( $\Delta\% = +20.13\%$ ; from  $70.49 \pm 16.08$  to  $84.68 \pm 18.89$ ;  $p = 0.0001$ ) and Group B ( $\Delta\% = +35.32\%$ ; from  $51.98 \pm 15.85$  to  $70.34 \pm 15.22$ ;  $p = 0.0014$ ).

Finally, modest but statistically significant changes in the  $VE/VCO_2$  slope were detected in Group B, with a reduction from  $34.13 \pm 7.70$  to  $29.73 \pm 5.34$  ( $\Delta\% = -12.89\%$ ;  $p = 0.0250$ ). This contrasted with the other subgroups: Group A showed an increase of  $\Delta\% = +2.94\%$  (from  $28.57 \pm 7.04$

**Table 2 – COVID-19 infection clinical presentation and LCS-related symptoms in the study population (n = 67)**

| Category                                                     | Variable                            | Value     |
|--------------------------------------------------------------|-------------------------------------|-----------|
| COVID-19 infection clinical presentation and acute treatment | Hospitalization, n (%)              | 23 (34)   |
|                                                              | Unilateral pneumonia, n (%)         | 7 (10,4)  |
|                                                              | Bilateral pneumonia, n (%)          | 30 (45)   |
|                                                              | Cortisone, n (%)                    | 41 (60)   |
|                                                              | Heparin, n (%)                      | 20 (30)   |
|                                                              | Antibiotic, n (%)                   | 43 (64)   |
| LCS-related symptoms                                         | Dyspnea (Borg Scale), mean $\pm$ SD | 5 $\pm$ 3 |
|                                                              | Asthenia, n (%)                     | 57 (85)   |
|                                                              | Fatigue, n (%)                      | 53 (79)   |
|                                                              | Chest pain, n (%)                   | 30 (45)   |

LCS: long-COVID syndrome; SD: standard deviation.

**Table 3 – Spirometry values of the study population at baseline evaluation (n = 67)**

| Category          | Variable                                 | Value             |
|-------------------|------------------------------------------|-------------------|
| Spirometry values | FVC (%), mean $\pm$ SD                   | 96.53 $\pm$ 12.66 |
|                   | FEV <sub>1</sub> (%), mean $\pm$ SD      | 93.55 $\pm$ 14.01 |
|                   | FEV <sub>1</sub> /FVC (%), mean $\pm$ SD | 95.25 $\pm$ 12.39 |
|                   | FEF <sub>25</sub> (%), mean $\pm$ SD     | 88.17 $\pm$ 23.23 |
|                   | FEF <sub>50</sub> (%), mean $\pm$ SD     | 81.53 $\pm$ 25.98 |
|                   | FEF <sub>75</sub> (%), mean $\pm$ SD     | 66.76 $\pm$ 20.71 |
|                   | SAD, n (%)                               | 15 (22)           |

FVC: forced vital capacity; SAD: small airway dysfunction; SD: standard deviation.

to  $29.41 \pm 4.00$ ;  $p = 0.5202$ ), whereas Group C showed a small reduction ( $\Delta\% = -0.50\%$ ; from  $30.97 \pm 8.48$  to  $30.81 \pm 6.89$ ;  $p = 0.1833$ ) (Figure 1, Panel C).

## Discussion

This study demonstrated that exercise-based CR improved functional capacity in patients with reduced

**Table 4 – Comparison between case group before and after the cardiorespiratory rehabilitation program (n = 67)**

| Variable                         | Baseline (mean $\pm$ SD) | Follow-up (mean $\pm$ SD) | p-value  |
|----------------------------------|--------------------------|---------------------------|----------|
| VO <sub>2</sub> peak (mL/kg/min) | 19.47 $\pm$ 7.86         | 23.14 $\pm$ 7.88          | < 0.0001 |
| VO <sub>2</sub> peak (%)         | 65.80 $\pm$ 16.02        | 80.22 $\pm$ 16.55         | < 0.0001 |
| Peak load (W)                    | 91.62 $\pm$ 47.90        | 116.19 $\pm$ 45.80        | < 0.0001 |
| O <sub>2</sub> pulse (mL/beat)   | 10.65 $\pm$ 3.11         | 12.12 $\pm$ 3.43          | < 0.0001 |
| VE/CO <sub>2</sub> slope         | 31.26 $\pm$ 7.98         | 30.00 $\pm$ 5.50          | 0.0443   |
| VO <sub>2</sub> /work slope      | 10.33 $\pm$ 2.26         | 10.63 $\pm$ 1.85          | 0.1129   |
| RER                              | 1.14 $\pm$ 0.15          | 1.15 $\pm$ 0.10           | 0.0002   |
| HR rest (bpm)                    | 85.95 $\pm$ 15.67        | 78.31 $\pm$ 13.23         | < 0.0001 |
| HR peak (bpm)                    | 136.74 $\pm$ 29.43       | 145.88 $\pm$ 25.57        | < 0.0001 |
| AT-VO <sub>2</sub> (mL/kg/min)   | 15.15 $\pm$ 6.49         | 16.91 $\pm$ 6.92          | < 0.0001 |
| AT-VO <sub>2</sub> (%)           | 51.98 $\pm$ 17.25        | 60.41 $\pm$ 19.33         | < 0.0001 |
| AT-VO <sub>2</sub> load (W)      | 61.08 $\pm$ 38.71        | 76.28 $\pm$ 38.16         | < 0.0001 |
| No AT-VO <sub>2</sub> , n (%)    | 9 (13)                   | 3 (5)                     | —        |
| Early AT-VO <sub>2</sub> , n (%) | 18 (27)                  | 7 (10)                    | —        |
| VE <sub>max</sub> (%)            | 57.83 $\pm$ 17.37        | 75.45 $\pm$ 18.85         | < 0.0001 |

AT: anaerobic threshold; HR: heart rate; RER: respiratory exchange ratio; SD: standard deviation. A p-value < 0.05 was considered statistically significant.

**Table 5 – Features of the study population subgroups (n = 67)**

| Category                               | Group A (n = 22)   | Group B (n = 23)   | Group C (n = 22)   | p-value  |
|----------------------------------------|--------------------|--------------------|--------------------|----------|
| <b>Demographic data</b>                |                    |                    |                    |          |
| Age, years (mean $\pm$ SD)             | 38.59 $\pm$ 12.25  | 42.13 $\pm$ 12.18  | 56.68 $\pm$ 11.86  | < 0.0001 |
| Male sex, n (%)                        | 12 (55)            | 10 (43)            | 13 (59)            | 0.5695   |
| Smokers, n (%)                         | 4 (18)             | 2 (9)              | 3 (13)             | 0.6578   |
| <b>Anthropometric features</b>         |                    |                    |                    |          |
| Height, cm (mean $\pm$ SD)             | 169.22 $\pm$ 9.47  | 170.00 $\pm$ 10.46 | 166.86 $\pm$ 7.64  | 0.5049   |
| Weight, kg (mean $\pm$ SD)             | 67.04 $\pm$ 15.91  | 74.13 $\pm$ 12.70  | 85.22 $\pm$ 15.68  | 0.0006   |
| BMI, kg/m <sup>2</sup> (mean $\pm$ SD) | 23.21 $\pm$ 3.83   | 25.58 $\pm$ 3.80   | 30.60 $\pm$ 5.36   | < 0.0001 |
| BSA, m <sup>2</sup> (mean $\pm$ SD)    | 1.76 $\pm$ 0.22    | 1.88 $\pm$ 0.25    | 1.93 $\pm$ 0.18    | 0.0413   |
| <b>Vital parameters</b>                |                    |                    |                    |          |
| SBP, mmHg (mean $\pm$ SD)              | 107.95 $\pm$ 10.65 | 115.08 $\pm$ 8.79  | 122.50 $\pm$ 17.84 | 0.0019   |
| DBP, mmHg (mean $\pm$ SD)              | 66.81 $\pm$ 6.46   | 73.78 $\pm$ 9.54   | 74.31 $\pm$ 11.15  | 0.0147   |
| HR, bpm (mean $\pm$ SD)                | 86.45 $\pm$ 24.40  | 87.47 $\pm$ 12.81  | 83.68 $\pm$ 11.26  | 0.7467   |

BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; SD: standard deviation.

## Original Article

**Table 6 – Comparison among study population subgroups before and after the rehabilitation program (n = 67)**

| Variable                                       | Group            | Baseline (mean ± SD) | Follow-up (mean ± SD) | Δ%      | p value  |
|------------------------------------------------|------------------|----------------------|-----------------------|---------|----------|
| VO <sub>2</sub> peak (mL/kg/min)               | Group A (n = 22) | 26,45 ± 8,72         | 29.50 ± 8.92          | +11.53% | < 0.0001 |
|                                                | Group B (n = 23) | 18,24 ± 4,30         | 22.17 ± 4.49          | +21.57% | < 0.0001 |
|                                                | Group C (n = 22) | 13,78 ± 3,48         | 17.79 ± 4.57          | +29.10% | < 0.0001 |
| VO <sub>2</sub> peak (% predicted)             | Group A (n = 22) | 76,82 ± 16,07        | 88.18 ± 17.86         | +14.79% | < 0.0001 |
|                                                | Group B (n = 23) | 60,96 ± 13,60        | 75.52 ± 13.29         | +23.88% | < 0.0001 |
|                                                | Group C (n = 22) | 59,86 ± 12,82        | 77.18 ± 16.02         | +28.93% | < 0.0001 |
| Peak load (W)                                  | Group A (n = 22) | 128,00 ± 53,92       | 149.20 ± 52.02        | +16.56% | < 0.0001 |
|                                                | Group B (n = 23) | 85,74 ± 32,66        | 108.70 ± 27.00        | +26.78% | < 0.0001 |
|                                                | Group C (n = 22) | 61,45 ± 28,50        | 91.05 ± 35.47         | +48.17% | < 0.0001 |
| O <sub>2</sub> pulse (mL/beat)                 | Group A (n = 22) | 11,58 ± 4,43         | 13.64 ± 3.90          | +17.77% | < 0.0001 |
|                                                | Group B (n = 23) | 10,37 ± 2,74         | 11.28 ± 2.65          | +8.77%  | < 0.0001 |
|                                                | Group C (n = 22) | 10,04 ± 2,43         | 11.48 ± 2.53          | +14.34% | < 0.0001 |
| VE/VCO <sub>2</sub> slope                      | Group A (n = 22) | 28,57 ± 7,04         | 29.41 ± 4.00          | +2.94%  | 0.5202   |
|                                                | Group B (n = 23) | 34,13 ± 7,70         | 29.73 ± 5.34          | −12.89% | 0.0250   |
|                                                | Group C (n = 22) | 30,97 ± 8,48         | 30.81 ± 6.89          | −0.50%  | 0.1833   |
| VO <sub>2</sub> /work slope                    | Group A (n = 22) | 10,20 ± 1,46         | 10.61 ± 1.98          | +4.02%  | 0.0002   |
|                                                | Group B (n = 23) | 9,91 ± 2,07          | 10.66 ± 1.58          | +7.57%  | 0.3155   |
|                                                | Group C (n = 22) | 10,92 ± 2,99         | 10.63 ± 2.06          | −2.65%  | 0.3935   |
| RQ (mean ± SD)                                 | Group A (n = 22) | 1,18 ± 0,10          | 1.16 ± 0.07           | −1.77%  | 0.1152   |
|                                                | Group B (n = 23) | 1,09 ± 0,11          | 1.14 ± 0.09           | +4.29%  | 0.0118   |
|                                                | Group C (n = 22) | 1,13 ± 0,20          | 1.13 ± 0.12           | +0.08%  | 0.0188   |
| HR rest (bpm)                                  | Group A (n = 22) | 83,68 ± 18,94        | 73.23 ± 9.85          | −12.48% | 0.0018   |
|                                                | Group B (n = 23) | 89,87 ± 16,05        | 84.78 ± 13.76         | −5.66%  | 0.0001   |
|                                                | Group C (n = 22) | 84,14 ± 10,83        | 76.64 ± 13.36         | −8.91%  | 0.0321   |
| HR peak (bpm)                                  | Group A (n = 22) | 153,60 ± 24,20       | 157.20 ± 20.67        | +2.34%  | 0.0001   |
|                                                | Group B (n = 23) | 139,40 ± 29,19       | 151.40 ± 27.31        | +8.60%  | 0.0001   |
|                                                | Group C (n = 22) | 117,00 ± 23,02       | 128.80 ± 19.27        | +10.08% | 0.0200   |
| AT-VO <sub>2</sub> (mL/kg/min)                 | Group A (n = 22) | 19,39 ± 7,81         | 22.39 ± 7.65          | +15.47% | 0.0001   |
|                                                | Group B (n = 23) | 11,76 ± 5,89         | 15.61 ± 4.12          | +32.73% | 0.0576   |
|                                                | Group C (n = 22) | 8,26 ± 5,86          | 12.88 ± 4.70          | +55.88% | 0.0354   |
| AT-VO <sub>2</sub> (% of VO <sub>2</sub> peak) | Group A (n = 22) | 57,86 ± 18,33        | 68.82 ± 18.74         | +18.94% | 0.0001   |
|                                                | Group B (n = 23) | 42,61 ± 23,31        | 55.96 ± 16.57         | +31.33% | 0.0135   |
|                                                | Group C (n = 22) | 34,64 ± 24,76        | 56.68 ± 20.63         | +63.65% | 0.1339   |
| AT-VO <sub>2</sub> load (W)                    | Group A (n = 22) | 85,18 ± 45,97        | 106.80 ± 39.92        | +25.40% | 0.0001   |
|                                                | Group B (n = 23) | 45,17 ± 28,18        | 67.01 ± 23.91         | +48.35% | 0.5027   |
|                                                | Group C (n = 22) | 28,64 ± 27,09        | 55.45 ± 29.33         | +93.64% | 0.0080   |

|                                  |                  |               |               |         |        |
|----------------------------------|------------------|---------------|---------------|---------|--------|
| No AT-VO <sub>2</sub> , n (%)    | Group A (n = 22) | 0 (0)         | 0 (0)         | 0%      | –      |
|                                  | Group B (n = 23) | 3 (13)        | 1 (4.5)       | –67%    | –      |
|                                  | Group C (n = 22) | 6 (27)        | 2 (9)         | –67%    | –      |
| Early AT-VO <sub>2</sub> , n (%) | Group A (n = 22) | 5 (23)        | 1 (4.5)       | –80%    | –      |
|                                  | Group B (n = 23) | 7 (30)        | 4 (17)        | –42%    | –      |
|                                  | Group C (n = 22) | 6 (27)        | 2 (9)         | –67%    | –      |
| VE <sub>max</sub> (% predicted)  | Group A (n = 22) | 70.49 ± 16.08 | 84.68 ± 18.89 | +20.13% | 0.0001 |
|                                  | Group B (n = 23) | 51.98 ± 15.85 | 70.34 ± 15.22 | +35.32% | 0.0014 |
|                                  | Group C (n = 22) | 51.28 ± 13.24 | 71.57 ± 19.58 | +39.56% | 0.0968 |

AT: anaerobic threshold; HR: heart rate; RQ: respiratory quotient; SD: standard deviation. A *p*-value < 0.05 was considered statistically significant.

exercise tolerance due to late sequelae of SARS-CoV-2 infection, as reflected by increases in VO<sub>2</sub> peak, O<sub>2</sub> pulse, and ventilation.

CPET is a well-established tool for diagnostic assessment, risk stratification, peri-operative and post-operative evaluation, and exercise prescription in both healthy individuals and patients with cardiovascular or respiratory diseases. CPET is therefore considered the gold standard for comprehensive evaluation of cardio-respiratory performance. In July 2020, the American Thoracic Society and European Respiratory Society endorsed its use specifically to assess patients with LCS.<sup>12,13</sup>

As proposed by Kukuc et al. (2020),<sup>14</sup> SARS-CoV-2 may affect multiple organ systems, including the heart, brain, lungs, kidneys, vascular smooth muscle, and skeletal muscle, through ACE2 receptor expression. Although the mechanism of muscle injury remains unclear, both direct cellular damage and transient ischemia have been hypothesized, potentially leading to impaired peripheral oxygen extraction and muscle pain resistant to analgesics. Rinaldo et al. (2021)<sup>15</sup> supported this hypothesis in a cohort of 73 recently hospitalized patients with COVID-19 evaluated with CPET after discharge. Their findings of early AT-VO<sub>2</sub>, reduced workload, low O<sub>2</sub> pulse, and diminished VO<sub>2</sub>/work slope were consistent with physical deconditioning and post-hospitalization syndrome.

Furthermore, Sørensen et al. (2024)<sup>16</sup> reported that spontaneous recovery of functional capacity does not occur at 1-year follow-up in patients with LCS, which suggests persistent circulatory abnormalities and impaired peripheral oxygen extraction as key mechanisms. However, vascular pathophysiology alone may not fully explain the CPET patterns observed in our study population. Only 34% of patients required acute hospitalization, and the VO<sub>2</sub>/work slope, a marker of anaerobic efficiency,<sup>15</sup> showed non-significant improvement ( $\Delta = +17.29\%$ , *p* = 0.1129).

Our working hypothesis was that LCS may be partially driven by autoimmune dysregulation and that moderate-intensity exercise could exert immunomodulatory effects.

This is consistent with the Stanford Hall consensus statement on post-COVID rehabilitation,<sup>1</sup> which recommends early, multidisciplinary rehabilitation within 30 days of the acute phase to optimize functional recovery.

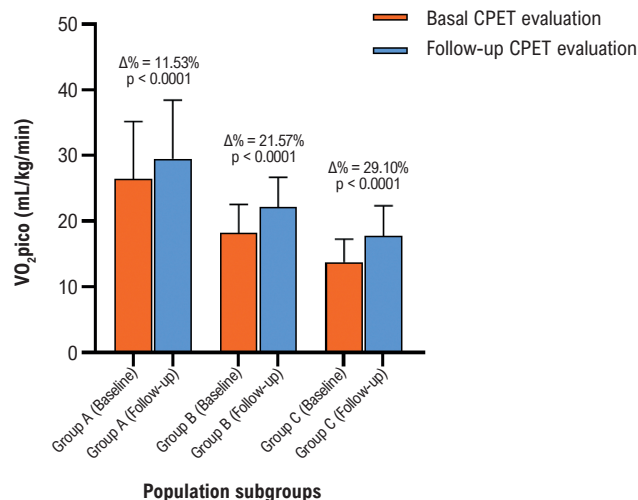
Our findings support these recommendations. CR substantially contributed to functional capacity restoration even in the absence of structural cardiac disease by reducing physical deconditioning and peripheral muscular dysfunction, both frequently implicated in LCS. CPET also proved essential for individualized exercise prescription.

After a 45-day follow-up, significant improvements were observed in VO<sub>2</sub> peak ( $\Delta = +18.85\%$ , *p* < 0.0001), workload ( $\Delta = +26.82\%$ , *p* < 0.0001), O<sub>2</sub> pulse ( $\Delta = +13.68\%$ , *p* < 0.0001), anaerobic threshold ( $\Delta = +11.61\%$ , *p* < 0.0001), and resting heart rate ( $\Delta = -8.88\%$ , *p* < 0.0001). Minute ventilation increased markedly as well ( $\Delta = +30.46\%$ , *p* < 0.0001).

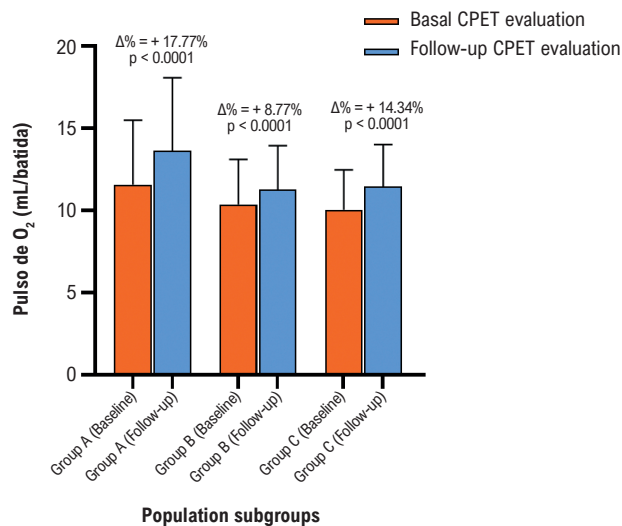
Although VE/VCO<sub>2</sub> typically follows an inverse hyperbolic pattern relative to workload in healthy individuals,<sup>8</sup> our cohort showed a modest yet statistically significant slope reduction ( $\Delta = -4.03\%$ , *p* = 0.0443). Current data do not allow definite distinction between increased pulmonary vascular resistance and respiratory muscle limitations as dominant contributors. Subgroup analysis suggests that the small VE/VCO<sub>2</sub> increase in Group A ( $\Delta = +2.94\%$ , *p* = 0.5202) may reflect improved workload adaptation, whereas the slight reduction in Group C ( $\Delta = -0.5\%$ , *p* = 0.1833) may reflect simultaneous influences of workload accommodation and persistent vascular abnormalities attributable to SARS-CoV-2-related microvascular injury.

This interpretation is compatible with evidence from Bonaventura et al.<sup>17</sup> demonstrating endothelial dysfunction during acute SARS-CoV-2 infection, as well as post-mortem studies confirming widespread endothelial injury.<sup>18</sup> Endothelial dysregulation appears central to both acute and post-acute SARS-CoV-2 pathophysiology, and pre-existing conditions such as hypertension and diabetes mellitus may further exacerbate microvascular impairment and systemic inflammation.<sup>18</sup> In patients with LCS, these comorbidities

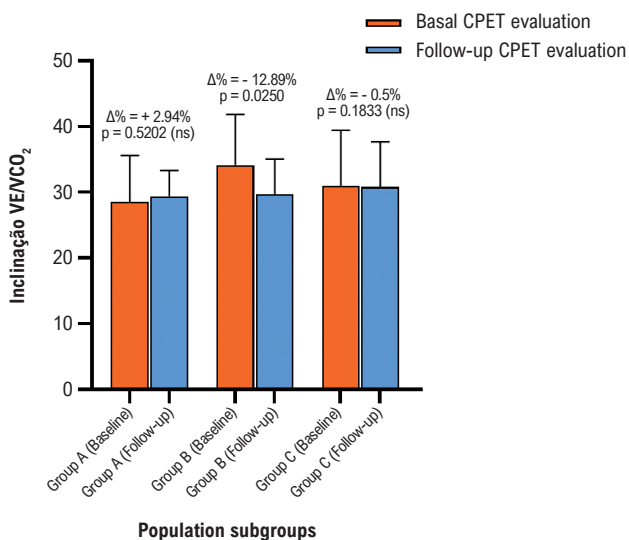
### Panel A VO<sub>2</sub>peak variations



### Panel B O<sub>2</sub> pulse variations



### Panel C VE/CO<sub>2</sub> variations



**Figure 1** – Variations at follow-up in population subgroups.

may attenuate the beneficial effects of exercise and slow symptom resolution and functional recovery.

Future prospective studies in larger LCS cohorts, with extended follow-up intervals ( $\geq 6$ -12 months) and detailed inflammatory profiling, will be necessary to confirm these observations and further clarify the underlying mechanisms.

### Limitations of the study

The principal limitation of this study is the absence of a control group, which ideally would have included SARS-CoV-2-naïve individuals voluntarily participating in a structured CR program. Several practical constraints prevented the establishment of such a comparator group: i) limited clinical capacity, which was prioritized for patients with LCS or other cardiorespiratory conditions; ii) the considerable time commitment required from participants (1 hour/day, 5 days/week for at least 6 weeks); and iii) the substantial personal financial costs associated with program participation.

Additionally, a potential selection bias must be acknowledged. Because successful CPET completion was part of the inclusion criteria, individuals unable to finish the test were excluded from the study, which may have led to underrepresentation of patients with more severe functional limitations.

### Conclusions

This prospective observational study demonstrates that CR is an effective nonpharmacological intervention for LCS, a condition that may involve immune dysregulation and systemic inflammation. Because of the immunomodulatory properties of moderate-intensity exercise, CR not only alleviated persistent symptoms but also produced significant improvements in functional capacity across subgroups with differing baseline fitness levels.

Meaningful enhancements were observed in  $\text{VO}_2$  peak, anaerobic threshold, exercise tolerance (reflected by increased

peak workload and more frequent attainment of anaerobic glycolytic transition),  $\text{O}_2$  pulse, and ventilatory efficiency.

Although these findings are encouraging, the underlying pathophysiological mechanisms driving LCS remain incompletely understood. Additional studies with extended follow-up and more comprehensive biological characterization are warranted to further refine therapeutic strategies and support full functional recovery in this population.

### Author Contributions

Conception and design of the research: Sarullo S, Nugara C, Sarullo FM; Acquisition of data: Sarullo S, Nugara C, Lo Voi A, Zarcone A, di Francesco G, Bosco S, Carollo S, Sarullo FM; Analysis and interpretation of the data: Sarullo S, Nugara C, Giallauria F, Cappello F, Sarullo FM; Statistical analysis: Sarullo S; Writing of the manuscript: Sarullo S, Nugara C, Giallauria F, Sarullo FM; Critical revision of the manuscript for content: Sarullo S, Nugara C, Lo Voi A, Zarcone A, di Francesco G, Giallauria F, Cappello F, Sarullo FM.

### Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

### Sources of funding

There were no external funding sources for this study.

### Study association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Palermo 1 under the protocol number 150109. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

### References

1. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall Consensus Statement for Post-COVID-19 Rehabilitation. *Br J Sports Med*. 2020;54(16):949-59. doi: 10.1136/bjsports-2020-102596.
2. Roma. Istituto Superiore di Sanità. Indicazioni ad Interim sui Principi di Gestione del Long-COVID. Rapporto ISS COVID-19 n. 15/2021. Roma: Istituto Superiore di Sanità; 2021.
3. Rajan S, Khunti K, Alwan N, Steves C, MacDermott N, Morsella A, et al. In the Wake of the Pandemic: Preparing for Long COVID [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2021.
4. National Institutes of Health. COVID-19 Treatment Guidelines: Clinical Spectrum of SARS-CoV-2 Infection. Bethesda: National Institutes of Health; 2021.
5. Zheng Q, Cui G, Chen J, Gao H, Wei Y, Uede T, et al. Regular Exercise Enhances the Immune Response Against Microbial Antigens Through Up-Regulation of Toll-Like Receptor Signaling Pathways. *Cell Physiol Biochem*. 2015;37(2):735-46. doi: 10.1159/000430391.
6. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise Standards. A Statement for Healthcare Professionals from the American Heart Association. Writing Group. *Circulation*. 1995;91(2):580-615. doi: 10.1161/01.cir.91.2.580.
7. Corrà U, Agostoni PG, Anker SD, Coats AJS, Leiro MGC, Boer RA, et al. Role of Cardiopulmonary Exercise Testing in Clinical Stratification in Heart Failure. A Position Paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(1):3-15. doi: 10.1002/ehf.979.
8. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med*. 2003;167(2):211-77. doi: 10.1164/rccm.167.2.211.
9. Wasserman K, Hansen JE, Sue DY. Normal Values. In: Weinberg R, editor. *Principles of Exercise Testing and Interpretation*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 160-82.

10. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise. *Med Sci Sports Exerc.* 2011;43(7):1334-59. doi: 10.1249/MSS.0b013e318213fe1b.
11. Xiao D, Chen Z, Wu S, Huang K, Xu J, Yang L, et al. Prevalence and Risk Factors of Small Airway Dysfunction, and Association with Smoking, in China: Findings from a National Cross-Sectional Study. *Lancet Respir Med.* 2020;8(11):1081-93. doi: 10.1016/S2213-2600(20)30155-7.
12. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation.* 2016;133(24):e694-711. doi: 10.1161/CIR.0000000000000406.
13. Bai C, Chotirmall SH, Rello J, Alba GA, Ginns LC, Krishnan JA, et al. Updated Guidance on the Management of COVID-19: From an American Thoracic Society/European Respiratory Society Coordinated International Task Force (29 July 2020). *Eur Respir Rev.* 2020;29(157):200287. doi: 10.1183/16000617.0287-2020.
14. Kucuk A, Cure MC, Cure E. Can COVID-19 Cause Myalgia with a Completely Different Mechanism? A Hypothesis. *Clin Rheumatol.* 2020;39(7):2103-4. doi: 10.1007/s10067-020-05178-1.
15. Rinaldo RF, Mondoni M, Parazzini EM, Pitari F, Brambilla E, Luraschi S, et al. Deconditioning as Main Mechanism of Impaired Exercise Response in COVID-19 Survivors. *Eur Respir J.* 2021;58(2):2100870. doi: 10.1183/13993003.00870-2021.
16. Sørensen L, Pedersen CL, Andersen MJ, Oestergaard LG, Schiøttz-Christensen B, Sperling S, et al. Cardiopulmonary Exercise Testing in Patients with Long COVID. Evaluating Functional Capacity and Exercise Limitations. *CHEST Pulmonary.* 2024;2(2):100036. doi: 10.1016/j.chpulm.2024.100036.
17. Bonaventura A, Vecchié A, Dagna L, Martinod K, Dixon DL, Van Tassell BW, et al. Endothelial Dysfunction and Immunothrombosis as Key Pathogenic Mechanisms in COVID-19. *Nat Rev Immunol.* 2021;21(5):319-29. doi: 10.1038/s41577-021-00536-9.
18. Barone R, Gammazza AM, Paladino L, Pitruzzella A, Spinoso G, Salerno M, et al. Morphological Alterations and Stress Protein Variations in Lung Biopsies Obtained from Autopsies of COVID-19 Subjects. *Cells.* 2021;10(11):3136. doi: 10.3390/cells10113136.



This is an open-access article distributed under the terms of the Creative Commons Attribution License